EMANUEL SYNDROME

A GUIDE FOR families & caregivers



Stephanie Rese, RSW

with Melissa Carter, MD, FRCPC, Murney Rinholm, BEd, and Joanna Holmes, BSc (Hons), MSc Booklet design: Jessica Mandujano

E M A N U E L S Y N D R O M E . O R G

EMANUEL SYNDROME A GUIDE FOR families & caregivers

The content of this guidebook is not a substitute for medical advice and intended for informational purposes only. You should always seek professional advice for medical concerns.

This book is dedicated to all the families around the world, raising children with Emanuel syndrome.

Photographs: *Thank you* to the many parents around the world who shared photos of their children for this guidebook.

Stephanie Kese

- founder of Chromosome 22 Central



EMANUELSYNDROME.ORG © CHROMOSOME 22 CENTRAL, INC. 2022 WWW.C22C.ORG "A bend in the road is not the end of the road. Unless you fail to make the turn." - Helen Keller

TABLE OF CONTENTS

Welcome to our parent guidebook for Emanuel syndrome	5
What is Emanuel Syndrome?	6
How common are balanced 11;22 translocations and Emanuel syndrome?	8
How did Chromosome 22 Central begin?	8
Who is Dr. Beverly Emanuel?	10
Dr. Beverly Emanuel	11
What are children with ES like?	13
Do children with ES have a common appearance?	14
What is the life expectancy for a person with Emanuel Syndrome?	15
Why are some children differently affected than others, both medically	
and developmentally?	15
Receiving the Diagnosis	16
What do we do first?	17
The 11q;22q Translocation	19
Pregnancy, Miscarriage and Infertility	22
Reproductive Options	24
Balanced 11q;22q Translocation & Cancer Risk	25
Congenital Anomalies and Medical Issues	27
What types of problems should my doctor screen my child for?	28
Common Issues	28
Appearance	28
Cleft palate	28
Cardiovascular issues	29
Gastrointestinal / Feeding issues and the Digestive System	31
Neurological issues	32
Functional neurological findings	32
Structural neurological findings	32
Seizures	33
Infections and immunity	35
Genital and Anal Differences	35
Respiratory issues	36
Urinary system	37
Vision, Eyes	38
Ears and Hearing	39
Musculoskeletal / Orthopedic issues	40



EMANUELSYNDROME.ORG

TABLE OF CONTENTS

	43
Dental	43
Skin issues and differences	44
Prenatal concerns and findings	45
Growth and Development	45
Perinatal	45
Development	45
Behaviour	46
Physical Development	48
Puberty	48
Intellectual Development	49
Developmental Stages	49
What to expect in the newborn stage	51
What to expect the first year and early infancy	54
The School Years	54
Transition to Adulthood	57
Treatment	58
Considerations for undergoing medical procedures	59
Occupational Therapy	59
Physical Therapy	61
Speech and Language Therapy/Pathology	61
Assistive Devices	62
Music Therapy	63
Engaging your child in the world	64
Respite Care	69
Palliative, Hospice and End of Life Care	70
Losing a child	70
Awareness	71
Research	73
Raising the Goddess of Spring	75
Becoming your child's advocate	77
Connect	78
Contact	79
Glossary of terms	80
References	83



EMANUELSYNDROME.ORG

WELCOME TO THE PARENT & CAREGIVER GUIDEBOOK FOR EMANUEL SYNDROME



We know that if you are reading this, you have a lot of questions about your child, and maybe yourself, if you are a t(11;22) carrier.

Whether you are new to this journey or have been on it for a long time, you have found a community that will help you understand what you need to know and offer you support. We are sure you have a lot of questions. We are available to talk to on Facebook, or by email or phone. You just have to reach out.

Before you dive in, we want to tell you that our website and Facebook group are maintained by parents just like you, living all around the world and raising children with Emanuel syndrome, so know that you are among friends. Actually, we are more like family.



Since 1996, we have learned of several hundred children with Emanuel syndrome and are aware of hundreds of carriers of the balanced t(11;22). Much of the information in this guide has been obtained from information collected from our families, published medical reports, as well as results from a 2009 study on children with Emanuel syndrome and t(11;22) carriers by Dr. Melissa Carter and colleagues.



Our children are amazing! If you have ever read a medical article on Emanuel syndrome, you will not read that some of our children have some reading ability and can do very basic math...have learned to skip rope, dribble basketballs, ride horses with assistance and even have earned a yellow belt in Taekwondo!

WHAT IS EMANUEL SYNDROME?

A syndrome is typically defined as a set of findings that characterize a condition. Our children are usually diagnosed, however, after a positive genetic test indicating the presence of an extra small "derivative" chromosome made up of parts of chromosomes 11 & 22. Having this extra chromosome leads to the common features that are typically seen in the majority of children with ES, and which may include a small jaw (micrognathia), cleft palate, heart defects, ear differences, skin tags, kidney and genital abnormalities, and most significantly, intellectual and physical impairments. It is important to know that not all children with Emanuel syndrome have exactly the same features. Some children may have fewer physical or medical issues, but all will experience delays in their intellectual development.

Our children have been said by some parents to resemble each other because of characteristic facial features, which although can vary, may include a broad nose, a longer upper lip (philtrum), low set ears, smaller chin, and deep-set eyes.



WHAT CAUSES EMANUEL SYNDROME?

Emanuel syndrome is caused by the presence of an extra derivative chromosome, which is made up of the top part of chromosome 22 and the bottom part of chromosome 11. Typical individuals have 46 chromosomes, but individuals with Emanuel syndrome inherit this extra derivative chromosome, which gives them 47 chromosomes in total – one too many. This is much like how individuals with Down syndrome have an extra chromosome 21 – a trisomy 21. A trisomy is three copies of a whole chromosome or part of a chromosome.



Chromosomes come in pairs, and these pairs are numbered from 1 to 22 along with a pair of sex chromosomes - either two X chromosomes (for a female) or an X and a Y chromosome (for a male). When a baby is conceived, he or she inherits one set of chromosomes from each parent. In the case of 11/22 balanced translocation carriers, to produce a child who has Emanuel syndrome, either their egg or sperm would have had to contain the derivative chromosome.

Thus, in ES, a part of chromosome 22 is present three times instead of the usual two times, from the very top, or "p" arm, down to the long "q" arm, to the breakpoint identified as 22q11.2. Part of chromosome 11 is also present three times instead of the usual two times, from the 11q23.3 section down to the end.

Having too much or too little genetic material (such as a missing or extra part of a chromosome) very often results in birth defects. Since balanced carriers have the correct amount of genetic material that has simply switched places, they develop normally. If the chromosomes are the blueprint for how cells form, problems with the chromosomes are like faulty blueprints that cause cells (and therefore the tissues and organs that cells make up, such as the brain and heart) to develop abnormally.

Individuals with Emanuel Syndrome will have a karyotype that reads:

47, XX (or XY), +der(22),t(11;22)(q23.3q11.2), mat (or pat)

A karyotype is basically a word map that describes a person's chromosomes.

47 – indicates that there are 47 chromosomes (a normal complement is 46)

XX - indicates if it is a female (XY if it is a male)

+der(22) - indicates that there is an extra (+) "derivative chromosome" (der) present, and the number in the brackets indicates which chromosome is involved (based on the centromere, which holds the p and q arms together – NOT on the larger piece of chromosome)

t(11;22) - refers to the two chromosomes involved in the translocation

(q23.3;q11.2) - refers to the breakpoints involved on each chromosome



The karyotype will be followed by "mat" if the extra chromosome was inherited from the mother (maternal) or "pat" (paternal) if it was inherited from the father. In rare instances, the child may also inherit the balanced translocation as well as the extra chromosome.

Karyotypes that were done before the mid-1990s may show different breakpoints on these 2 chromosomes, but Dr. Emanuel's research has since shown that the breakpoints are almost always the same, so older reported karyotypes that differ are presumed to be inaccurate now. They were done with the best technology available at the time.

HOW COMMON ARE BALANCED 11;22 TRANSLOCATIONS AND EMANUEL SYNDROME?

Balanced translocations have been estimated to occur in approximately 1 in 500 people; however, it is the t(11;22) translocation that is known to be the most common reciprocal translocation in humans. The prevalence of the t(11;22) translocation in the human population is not truly known, which one researcher attributes to the lack of large-scale chromosomal studies on healthy individuals (Ohye, 2014).

Reciprocal translocations happen when part of one chromosome changes parts with another chromosome and are typically "balanced" in that nothing is missing or added. Parents with a balanced translocation can have children with an unbalanced translocation. In the case of the t(11;22), it results in a child having an extra derivative chromosome made up of parts of 11 and 22 together.

While the t(11;22) translocation itself is considered to be relatively common, there are not so many children known in the world with the unbalanced version, known since 2004 as Emanuel syndrome. Between published cases and members of our group, we know of about 1000 people with ES.

A paper on the theoretical prevalence of Emanuel syndrome from a group of Japanese researchers suggested it may occur in 1 out of every 110,000 births, but we really do not know how many people with ES are living in the world (Ohye, 2014). Our group knows of several hundred people, and we know that there are several hundred cases noted in medical journals. Emanuel syndrome is considered a rare disorder.

HOW DID CHROMOSOME 22 CENTRAL BEGIN?

In 1995, Maia was born to Stephanie and Martin, in Alberta, Canada. Stephanie had four previous miscarriages and no knowledge that she was a **t(11;22) carrier**. Maia was identified at three months of age, as



having unbalanced 11/22 translocation, or as it was then known,

supernumerary der(22) syndrome and Stephanie was subsequently identified as a carrier.

Stephanie went on a search for others. In 1996, a group of 17 families came together who had children with what they suspected was the same condition (then



known as **supernumerary der(22) syndrome**) and created *The International 11;22 Translocation Network*. She then discovered the work of Dr. Beverly Emanuel and they met for the first time in Philadelphia in the year 2000.



The natural evolution of the group came to be inclusive of all chromosome 22 disorders and was renamed Chromosome 22 Central after so many families found the original website and had children with different chromosome 22 disorders, but no place online to call home. Stephanie's husband answered a call from a family in Israel one day, handed her the phone and stated, "It's like chromosome 22 central around here!"

The name stuck.

Our organization supports families in over 40 countries who have members with various chromosome 22 disorders, but our core group of members stemmed from families raising children with what is now known as Emanuel syndrome.

Articles on the unbalanced 11/22 translocation (a.k.a Supernumerary Der(22) syndrome) date back to the 1970s. Even earlier reports in the 1960s and early 1970s describe some cases of "trisomy 22," a distinct condition that was confused with der(22) syndrome in the early days of chromosome analysis. Punnett et. al., (1973) is one such report. While not able to be conclusive due to the limited technology of the time, these reports likely describe children with the unbalanced t(11;22) translocation, now known as Emanuel syndrome.

Historically, the medical literature has offered many different terms for this disorder. Families found it difficult to connect with each other because of the different names given to their child's condition. Many of the clinical symptoms seen in our children are also found in children who have trisomy 11q. The condition was reported by many different names through the years including:

- Trisomy 11q
- Partial trisomy 11q
- Unbalanced 11/22 translocation
- Cat Eye syndrome
- Trisomy 22
- Partial trisomy 22
- Partial trisomy 22q
- Partial trisomy of 11 & 22
- Trisomy 11/22
- Incomplete trisomy 22
- Supernumerary der(22),t(11;22) syndrome
- Supernumerary der(22) syndrome
- Der(22)t(11;22)
- Supernumerary chromosome derivative (22)
- Chromosome 11;22 translocation

All of these reports were about children who shared a similar phenotype - observable physical features - which included findings like low set and abnormally shaped ears, cleft palates, small jaws, heart defects and other common physical findings, along with a extra derivative (22) chromosome.





WHO IS DR. BEVERLY EMANUEL?

While numerous reports have been published about t(11;22) and the unbalanced syndrome, one researcher, Dr. Beverly Emanuel, a geneticist at the Children's Hospital of Philadelphia/University of Pennsylvania Medical Centre, has been consistent in her work on the subject. Several of our group members have participated in her studies. She and her colleagues were the first to describe the mechanism by which the chromosomes of a t(11;22) carrier get wrongly sorted into egg and sperm cells so that the extra derivative chromosome ends up causing problems. Dr. Emanuel's laboratory has studied the DNA sequence of the derivative chromosome and discovered that all individuals have identical pieces of chromosome 22 and chromosome 11 switch places.

Chromosome 22 is particularly prone to rearrangement because of DNA sequences called PATRRs (palindromic AT-rich repeats) found along the q arm. This area is also involved in the development of other chromosome 22 disorders, including **Cat Eye syndrome**, the more common **22q11.2 Deletion syndrome**, and the **22q11.2 Microduplication syndrome**. It has also been involved in a recurring translocation with chromosome 8.

The name given to the disorder in 2004, **Emanuel syndrome**, was chosen by our parent group to reflect the consistent contributions of Dr. Beverly Emanuel. Her long-standing dedication to research on t(11;22) dates back to the early 1970s and continues to this day. Her research has been invaluable in helping us understand why this translocation happens. This work, along with her support of our efforts to get information out to the public, made it easy for our group to want her name be given to this relatively rare condition. The term "Emanuel syndrome" was welcomed as a unifying name for our families, and is being adopted by the medical community as new articles are published using this name.

If you visit our website, you can see a video presentation from Dr. Emanuel from our awareness day in 2021, outlining her many years of work on the 11/22 translocation.

Prior to Dr. Emanuel's involvement, this condition did not even exist as an entry in the National Library of Medicine's database, "Online Mendelian Inheritance in Man" (OMIM), which is a database of human genes and genetic syndromes. At our group's request, this entry was added to OMIM in November of 2004, with the ID number 609029. It was our first step in getting this condition not only named, but properly recognized.

In 2007, Dr. Emanuel and colleagues wrote an article for GeneReviews, an expert-authored database of genetic conditions, also through the National Library of Medicine. Emanuel syndrome did not have an entry prior to this time. The new entry offered families current information on genetic counselling as well as an overview of the condition.

You can find the links for these articles on our website, emanuelsyndrome.org.

The largest study ever conducted on people with Emanuel syndrome was done in 2009, titled Phenotypic Delineation of Emanuel Syndrome (Supernumerary Derivative 22 syndrome): Clinical features of 63 individuals, by Melissa T Carter, Stephanie A St. Pierre, Elaine H Zackai, Beverly S Emanuel, and Kym M Boycott. It was published in the August 2009 edition of the American Journal of Medical Genetics. It was a landmark paper that gave current and accurate information about the condition, which was something that had been lacking. This paper was invaluable in getting information to families and their treatment providers.

Between 2009 when this paper was released, and 2022, there have been more than 50 new articles released describing cases of Emanuel syndrome. Our group continues to try to keep up with the latest information in order to get it into the hands of our families, as well as the information we gather from being in touch with each other.





On November 22, 2010, our group held its first **Emanuel Syndrome Awareness Day** Campaign, which helped spread awareness through the cyber world. We recognize this date, "11/22", each year for continued awareness. We have graphics on our website that you can use for this special day.

In between these milestones, we have had opportunities to meet other members in special C22C "family reunions". We have tried our best to educate each other and the public about this rare chromosome disorder.







DR. BEVERLY EMANUEL

Dr. Emanuel's original article from one of our group's first newsletters in 1996 was written before we had the condition named. The article in its original format:

By Dr. Beverly Emanuel, The Children's Hospital of Philadelphia

In order to talk about the Supernumerary der(22) Syndrome, first we need to step back and describe some terminology. This is so that everyone reading this will begin on the same footing. As you may know, a syndrome is really a collection of findings that has been seen recurring over and over again in patients. For example, one group of associated features actually includes: a heart problem; malformed ears with pits or tags; small chin; and a high arched or cleft palate. Syndromes are often named after the person or persons who first described the collection of findings. Once an underlying cause is identified, the name may be changed to reflect the specific chemical

abnormality, chromosome difference, or gene change that caused the problem. Here, in the case of the Supernumerary der(22)t(11;22), the name reflects the chromosomal change.

Genes are made up of a chemical called DNA and they are housed within larger structures called chromosomes. Most people have 23 pairs of chromosomes (46 total), with one of each pair coming from the mother and the other from the father. Chromosomes are numbered 1 through 22; the 23rd pair are called sex chromosomes because they determine a person's sex (male or female). The chromosomes are found in every cell in the body. Cells are so small that they, and the chromosomes they contain, can only be seen by observation with a microscope.



Since genes are housed inside the chromosomes, they themselves can't be seen at the microscope, but they can be measured by using special "molecular" tests. A good way to think about chromosomes and genes is to compare them to a train. A train has a number of box cars just as a chromosome has a number of stripes or bands. We can see the box cars when we look at a train, just as we can see the chromosomes and their band patterns when we observe them at the microscope. We cannot, however, see the packages inside the box car without first opening the door. The same is true for a chromosome - the genes are the packages inside.

When a baby is conceived with either too much or too little chromosomal material, birth problems or birth defects can occur. This may include a whole extra chromosome, as in the Supernumerary der(22)t(11;22) syndrome (an extra "derivative" 22 chromosome), a whole missing chromosome as in Turner syndrome (a missing X), a piece of material missing or extra, or a complex rearrangement of chromosomal material. When chromosomal material is missing or extra, genes are generally missing or extra. Since genes are the blueprint of the body, when they are deficient or duplicated, the body's blueprint changes, frequently leading to birth problems and learning differences.

So again you ask, what is the 11;22 translocation and the Supernumerary der(22) Syndrome?

In 1980, working at the Children's Hospital of Philadelphia in the U.S.A., we (Dr. Elaine Zackai and I) described the 11;22 translocation. At about the same time, the t(11;22) was also described by a consortium of European scientists. People who carry the 11;22 translocation have a very small piece of chromosome 22 (22q11 -> qter) transferred to chromosome 11 and a small piece of chromosome 11 (11q23 -> qter) transferred to 22 (thus, it is called a translocation). Chromosomes are divided into two parts, the top part being called the "p"or short arm and the bottom part called the "q" or long arm. Thus, the 22q11 -> qter and 11q23 -> qter designation tells everyone who works in genetics that the area transferred or translocated starts at a very specific spot on the "q" arm of chromosomes 11 and 22 and goes to the end ("ter" or terminus) of the "q" arm. It is very important to know the location of a moved piece of chromosomal material in order to make some general comparisons between individuals. This is because if two children have different parts of the same chromosomes extra it would be like comparing "apples to oranges" to compare them to one another. Most often when there is a chromosomal rearrangement or translocation they are not exactly alike.

However, with the t(11;22), we suspect that the story is different. The 11;22 translocation is appears to be the only translocation which seems to have recurred over and over again, creating numerous carriers. The points of chromosome exchange appear to be at the same spots on 11 and 22 in all instances. Several hundred families with what appears to be the same rearrangement have been described in the scientific literature. Carriers of the t(11;22) are themselves normal, but come to the attention of the geneticist or pediatrician subsequent to the birth of a child affected with the +der(22) syndrome who has the derivative (22) or rearranged chromosome 22 as an extra chromosome. Occasionally, translocation carriers are discovered upon being studied for multiple miscarriages or infertility. Patients with the +der(22) syndrome (or the extra chromosome) have distinctive features which can include tags or pits in front of their ears, abnormally shaped ears, a cleft or high arched palate, a small chin, a heart defect, mental retardation and sometimes genital abnormalities in the male.

Geneticists have long been interested in understanding the mechanisms and results of chromosomal rearrangement. Chromosomal rearrangements or translocations are the result of DNA rearrangements at the molecular level. Translocations are one of the major categories of structural chromosomal alterations. The mechanisms by which they are generated are largely unknown. Balanced translocations, i.e. those in which there is no microscopically visible loss of genetic material are amongst the most common of these rearrangements accounting for roughly 0.2% of structural abnormalities. In general, the chromosomal change is presumed to occur during the formation of either the egg or sperm which created the first person with the rearrangement in a family. Then, that person carries the change in every cell of his or her body and



is capable of passing the change to his/her children. It can be transmitted either as a balanced rearrangement or as an extra chromosome as in the Supernumerary der(22) Syndrome.

The cellular events which end in chromosomal rearrangement or translocations, especially those like the recurrent t(11;22), remain to be elucidated. Understanding the molecular basis of this translocation may serve as a model for understanding the mechanisms involved in creating other translocations. Thus, efforts to map the elusive constitutional t(11;22) translocation breakpoint are progressing. For example, we have already determined that a major portion of the DNA which surrounds the region of the breakpoint on chromosome 22 is duplicated several times on chromosome 22. This duplication which is normally present on every chromosome 22 may make this chromosome more prone to engage in rearrangements. The determination of the exact size of the duplication, number of copies and their location is currently under investigation. Further, the relationship between having a translocation, especially an 11;22 translocation, and how chromosomes separate during formation of egg and sperm, is not clear and has not been well studied. These are some of the studies we are currently pursuing in our laboratory research.

Further, our research team includes several geneticists who specialize in identifying genes, how they work, and why they cause problems when they are extra or changed. We hope to provide the scientific community with new information about the genes which reside in the duplicated pieces of chromosomes 11 and 22. We also try to understand how genes influence each other. When there is a supernumerary der(22), many genes are extra but probably not all of them play a role in causing the symptoms associated with the duplication. Thus, additional studies will be necessary to understand the role that each of the genes plays in the cause of the complex and variable symptoms which are seen in the children with the Supernumerary der(22) syndrome. Our research studies will enable us to determine if these problems are caused by the duplication of several genes, or by many duplicated genes. Further, most individuals with the Supernumerary der(22) syndrome have a duplication of the same exact pieces of chromosomal material but they do not all have the same symptoms. Perhaps other factors play a role in who develops which symptoms. Much more work needs to be done and this is our job for the future. We welcome your participation in our research efforts and thank you for all of your interest. TOGETHER, we will begin to understand the t(11;22) and the Supernumerary der(22)t(11;22) syndrome.

WHAT ARE CHILDREN WITH ES LIKE?

Some of our members wanted to tell other parents that above all, it is possible for our children to have a meaningful, happy life. They are happy; they will smile, giggle, show affection, and feel loved, like any other child.

Often, when a parent hears their child has a diagnosis of Emanuel syndrome, they are not given a very human picture of what it will be like to parent their child beyond what to expect medically or developmentally. Yes, it will be difficult some days. Your child will face challenges, but they will also just love being your child and you will love them. Some of our parents have felt that when given the diagnosis they were offered a very grave picture of the future. We want to give you the peace of mind that our children are very much loved, feel love and express love. They will learn at their own pace, will bring joy to their families, and have lives worth living.



"One of our first questions was what kind of life would she have beyond the medical aspect. We wanted to know if she would have the ability to feel happy. If she would be able to experience love. The genetics doctor painted a very horrible picture. One told us we couldn't count on her living even for the year. But if he had told us that she would be able to smile, laugh, love, and be happy then it would have been a lot easier to handle." "Every giggle, belly laugh and smile reminds me that the things that irritate me are so trivial. This child has endured more pain and obstacles in her life than I will ever see yet she has a simple joyous outlook that I will never fully grasp. She is trusting, kind and loving. Isn't that what we all want our children to be?"

"After 10 days in the NICU, we finally got to bring her home. She had learned how to eat from the Haberman Feeder bottle, if we held her and squeezed the nipple. She still looked kind of funny, but in a lot of ways she was just like any other newborn baby. The next morning we bundled her up and brought her to Target. As she lay there sleeping in her car seat in the shopping cart with her winter hat on, I remember thinking that no one else had any idea that she wasn't just... a regular baby."

"Our son is doing very well. He is now 3 months old. He focuses well, holds his neck nicely and his muscle tone is very strong. He does the "walking reflex", all something the doctors told us he would never do. He eats a lot. He still gets milk from breast. He is a strong fighter and he really wants to show us that he is here. He wants to play and "talk". He has some very good sounds. He has discovered his hands. He looks at them and smiles, puts his hands in his mouth and hits the toys hanging from the activity blanket. He stands on his feet when we hold him, he holds his neck. At the moment we have a very lively, happy little boy. "

"My child has taught me how precious life is and how the things I go through are nothing compared what she went though. She has had 3 surgeries in her first year and yet, she is able to smile and bring joy to our life. Whenever things get tough, I look at her and see how she can be happy and it makes me take things in a much more positive way."

DO CHILDREN WITH ES HAVE A COMMON APPEARANCE?

Some of our children appear to resemble each other, and often are labelled by medical professionals as being "*dysmorphic*". This term can be upsetting to parents, but basically is just a medical way of suggesting the presence of a genetic syndrome. Some of our children have deep-set eyes, lower set ears, and a longer upper lip (referred to as "*philtrum*") which may give many of them a common appearance. Many of our children have smaller feet. Our children also seem to have longer, tapering fingers.

When we did our study in 2009, a specialist who looks at the differences in children with genetic conditions was unable to pinpoint a specific "look" for our children, however, most of the parents in our group are able to see these similarities. We find it quite remarkable to see how many of our children look alike. In fact, photo recognition technology can even help diagnose ES (Liehr et. al., 2017).



WHAT IS THE LIFE EXPECTANCY FOR A PERSON WITH EMANUEL SYNDROME?

This is one question often asked by new families because sometimes, they are given a limited picture for their child's future. It is not an easy question to answer, but it often will have to do with what kinds of medical issues your child may face. It is true that some of our children have passed away in early life or even before they were born, especially if they faced life-threatening medical issues such as severe heart defects or congenital diaphragmatic hernias.

We cannot predict how long your child may live, but we can state that we are aware of people who have Emanuel syndrome who are in early and mid-adulthood. At the present, we know of people with Emanuel syndrome living more than 50 years. That is incredible to many of us who had children diagnosed even just 25 years ago and were given very bleak outcomes.

We have several adults living with ES in our online support group. Based on the fact that genetic testing was not very common many years ago, it is impossible for us to say that there are no older cases that we may not be aware of. They may have been given a different name for the diagnosis many years ago and are not aware of the change in name. We now know that long-term survival for people living with ES is possible.

WHY ARE SOME CHILDREN DIFFERENTLY AFFECTED THAN OTHERS, BOTH MEDICALLY AND DEVELOPMENTALLY?

It is not yet possible for us to know why some children will present with certain medical problems or birth defects, while others do not, or why some will learn to speak and walk, and others not. As with any syndrome, or even just people in general, there is a wide spectrum. Most people will fall somewhere in the middle. There will be some that do very well, and others, not so well. Just like in our society – we have some people who can be exceptionally gifted and others with learning disabilities, even with a normal complement of chromosomes.







"Seeing this picture of my son hitting a piñata at a birthday party honestly made me teary-eyed! I wish I could go back in time and tell the terrified me when he was born (and quite a while after), how despite all the hardship there will be even more joy. Gosh, our kids are so amazing!"

RECEIVING THE DIAGNOSIS

For some of you, the diagnosis of ES did not come immediately. Sometimes, children with ES are identified as having something else first, such as having a cleft palate, experiencing feeding or breathing issues, or finding a heart defect; things that lead to further investigations and the underlying diagnosis of ES.

Any parent will tell you it feels like the world stops for a bit. We all know how you feel. Here are a few comments from the book, *Raising the Goddess of Spring* from other parents:

"When my son was diagnosed, I wanted to know everything I could and no doctor knew about this. The information there is available at the c22c.org web page was very useful. I printed the whole list of what is mostly seen in our kids and marked the things my boy had, so whenever I go to a new doctor (that used to be quite often) I was the one who knew most of the information on ES and I carried a copy of the list to show. I also carry a copy of the 2009 study on the natural history of ES. I made a written follow-up of all the medical issues my son has faced because there are so many that you can sometimes forget."

"It is important to take the time for yourselves and your baby. Not all parents will react the same way, but take time to understand what the diagnosis will mean for your family. Give yourself time. Time to cry, time to grieve. You were expecting a healthy child, and learning that this child will face challenges is incredibly overwhelming and emotional. You may need to grieve the healthy child you were expecting. It is not something you can just get over in a day."

"There is no denying that anytime a baby is brought into a family, things change. It is at best, a stressful and exhausting time. When your child is born and given a rare diagnosis and may possibly have serious medical problems to deal with, this only adds to that stress. You will need to be prepared for possible medical procedures, the time required to take your child to therapies, and sometimes needing to learn a new skill that other parents do not need to know, to be able to take the best care of your child. You will need to be prepared to discuss the diagnosis with other members of your family, friends, and sometimes strangers. This can be a difficult thing to do about something that you don't always understand

immediately yourself. It was not just you expecting to have a healthy child, but anxious grandparents, uncles and aunts, young cousins and family friends."

WHAT DO WE DO FIRST?

Catch your breath. Take some time to accept the news you have been given. Learn everything you can about this condition as you will become your child's advocate. The process of learning about ES may help you feel better. You will see that many others are on the same journey as you.

"We have always been 'go-getters', achievers and just folks who know what they want and work hard to get it. With our daughter, we were quick to realize that 'fixing' ES is not going to happen. So the feeling of helplessness of trying to change this for your baby was really tough ... but instead of focusing on 'fixing' her, we fixed ourselves and how we view the situation ... it makes having her around a true blast!"

As ES is so rare, the people who will surround your child will likely have never heard of Emanuel syndrome. Tell them about our website. Or share a copy of this guidebook. *Other parents have shared:*



"Our daughter has changed our lives in so many positive ways. The day I found our daughter had ES was the worst day of our lives. It was like losing the daughter we thought we were going to have. I couldn't live without the friends that I have made online. I appreciate the support, prayers, and love. Finding out our daughter had ES was the worst day, the day she was born was the best!"

"When my son was diagnosed, I wanted to know everything I could and no doctor knew

about this, so the information there is available at the c22c.org web page was very useful. I printed the whole list of what is mostly seen in our kids and marked the things my boy had, so whenever I go to a new doctor (that used to be quite often) I was the one who knew most of the information on ES and I carried a copy of the list to show. I also carry a copy of the 2009 study on the natural history of ES. I made a written follow up of all the medical issues my son has faced, because there are so many that you can sometimes forget."

"We met with a doctor about the results of a blood test that had come back from the Mayo Clinic, regarding our daughter. The doctor told us that she had Emanuel Syndrome. He laid some different colored markers out on the table, removed some of the caps and tried to demonstrate how her chromosomes are arranged. I said it was fascinating and my wife burst into tears. The doctor gave us a print out on Emanuel Syndrome. It said things like "severe retardation". It was hard to believe, hard to comprehend. We had never heard of this syndrome. How could we have a baby who might never walk or talk, or "thrive"? It seemed like this meant she would probably just lay around in bed forever."

"You have to learn that your child has Emanuel Syndrome, and you have to feel anxious, lost, sad, angry. You feel that your life collapses. All these feelings are normal and I felt them too. Your life is not over, but it will be different than you imagined. Having a child with Emanuel Syndrome means you do not always have the same concerns as other parents. I sometimes feel the impression of not living on the same planet as some. But, I'm a mom first. My life with my daughter is like a mountain stream. There are quiet moments, joy, laughter, hope and moments of tumultuous doubt, discouragement, and anxiety. My daughter has taught me an essential quality: patience."

"After I had my son he was not able to come home with me. He remained in NICU for 15 days. He had jaundice quite badly. His bilirubin levels were so high that he was going to need a blood transfusion if

they did not decrease. Thankfully they did!! So when I went to the hospital to take him home, the doctor felt that he needed to talk to me...I guess inform me of his diagnosis. He said that my son would never put right and left together; don't expect him to play baseball and he probably won't even know who you are. Then he had the nerve to tell me that he didn't think his condition was compatible to life. I sat there and listened to him, wishing that he would hurry it along so we could go. I guess I wasn't giving him the response he was looking for. So he asked me if I understood. I told him yes, I understand. I hear everything your saying but it's not up to you and I believe that he's going to be alright. Well, my son is able to put left and right together. He can throw a baseball, toy and whatever else he decides to pick up (lol) and he most definitely knows who I am! My son is doing over and beyond what they said he would. "

"I regret the moments I entertained the idea that she wasn't going to be a baby. She loves to swing, be bounced, look at lights and hear music, just the same as any other baby."

"The sound of her first cries will never leave me. I think I knew then before I had even really seen her that something was wrong. She sounded more like a kitten then a newborn. I can still see her eyes wide, huge and blue.....she was struggling to get air into her tiny lungs. I remember holding her in my arms the first time, watching her trachea completely sink into the back of her neck, she was pulling so hard to try to breathe. She would attempt to cry in between breaths and it was again, like a kitten. Her limp body, the blue around her lips, the extra skin on her face, the monitors beeping that she wasn't getting enough air.

The look on my husband's face. Seeing everyone else's faces filled with worry, not just my family members, but the doctors and nurses. There was no mistake....something was very wrong. Where was the healthy 8 lb baby girl I was supposed to be having? My head was spinning while I desperately tried to act like I was happy in front of everyone. I mean what kind of mother would I be if I showed them all how sad I was right now? I recall the nausea hitting me hard when I realized that something was very wrong with this baby in my arms. I wanted to put her down and run out of there. I wanted to run away from this awful reality. These images will never leave me. I will carry them always. They have made me who I am. They have strengthened me."

When you are ready, connect with our families. Visit our website for the links to our online group. We are easily accessible to talk on the phone, on the Internet, or communicate by email or on Facebook. Remember, there is no timeline to process this. There are a lot of us here to help you.

"I couldn't live without the friends that I have made online. I appreciate the support, prayers, and love. Finding out our daughter had ES was the worst day, the day she was born was the best!"

"The most important thing you can do is to get connected with other families. We all have different stories and our kids present in a uniquely different way, but when you are told by every medical professional you come in contact with that they have never seen a child with your child's diagnosis it becomes a very lonely, scary, discouraging road and having someone who truly understands the isolation is a powerful thing."

"This journey can be a hard one but you don't have to walk it alone. This child who has been entrusted to you will also put you in the path of those who you may have never met. Our life is much richer because of it."

What you can do right now:

- **Feel** what you will.
- Accept that this is a confusing and difficult time for the moment.

PAGE 18 OF 95

- **Take** the time you need, but don't isolate yourself for too long.
- **Maintain** a sense of normalcy. Keep routines that are important. Lots of things will change, but not everything has to.
- **Don't** place limits for the future or think too far ahead. There are children with ES who do far more than was thought possible when the disorder was first identified.
- **Take** one step at a time. You don't need to figure everything out right away.
- **Request** information from us, from your doctors.
- Learn all you can.
- Write down your questions.
- **Reach out** to family, friends, our group members. There are so many of us here to help you when you are ready.
- **Realize** that things you read on paper even in this guidebook and in medical reports, don't give the true story of what your child's life will be like. On paper, many of our children seem to have so many challenges! But they are far more than you can imagine! You are going to be celebrating holidays, achievements, milestones and family time just like a typical child. There is going to be laughter, joy, fun, and you will love them immeasurably.

THE 11Q;22Q TRANSLOCATION

Carriers of the balanced t(11;22) are considered to be normal in every respect, except for the challenges they can face when trying to have a baby. It is not something you (or your parents) could have prevented. It is usually passed down through the generations, but may not be identified until a carrier has difficulties with infertility, repeat miscarriages or has a child diagnosed with Emanuel syndrome.



Stephanie and Julia visiting together in England -

both t(11;22) carriers who met because of their children.

There are different types of translocations, however, the t(11;22) is known as a reciprocal translocation. It is the most common recurring reciprocal translocation seen in humans. A reciprocal translocation means that there is a two-way exchange of information between these two chromosomes. Nothing is missing and nothing is extra, thus making a carrier of this translocation "balanced" in terms of genetic information.



Translocations are a relatively common occurrence (1 in 500 people are estimated to have one) and there is nothing you did to make it happen.

Translocations can occur between any chromosomes. It happens in unrelated families, from various ethnic backgrounds. It can be found going back several generations in some families. It also has been found, rarely, to happen spontaneously in some carriers.

When a carrier is identified and neither of their parents has the same translocation, it is called *a de novo occurrence*. Dr. Beverly Emanuel and colleagues have done studies that show that this specific translocation can sometimes be found only in the sperm of normal males (no other cells are affected by the translocation) and thus they can go on to have children who can be 11/22 carriers, and their children, in turn, have a risk of having a child with Emanuel syndrome.

HOW DOES THE BALANCED TRANSLOCATION HAPPEN?

Most people with this translocation have inherited it from one of their parents. You may not have known about this being passed down from generation to generation. It is a completely random event; there is nothing you can do to stop it from being passed on, and there is nothing that makes passing it on more likely.



Graphic provided by Dr. Beverly Emanuel

How did it happen in the first place? Many generations back, likely in a male relative's sperm, chromosomes 11 and 22 switched q arms. These two chromosomes have something in common; they both have PATRRs (palindromic AT-rich repeats) in their DNA sequence, which makes them prone to breakage in that area. If a chromosome breaks, it often latches on to another broken chromosome end nearby. The two ends fuse together and become a new chromosome – which we call a "derivative." The derivative chromosome can be passed on to future offspring, and it can also cause problems with how chromosomes segregate – that is, how they are divided up during the process of making eggs and sperm. This is why some balanced translocation carriers have trouble conceiving a pregnancy, and how you can end up with a pregnancy in which the baby has an unbalanced karyotype.

In November 2021, Dr. Emanuel did a virtual talk about the history of the t(11;22) and her work. You can view this on our YouTube channel.

CARRIER AND PRENATAL TESTING

When one carrier of the t(11;22) is identified, there may be other family members who are tested and identified as carriers. It is almost always the case that one of their parents is a carrier of the translocation as well. It will be important once a carrier is found in the family to make other family members aware of their own chances of being a translocation carrier. If a carrier has other children who do not have Emanuel syndrome, it will be important information for them when they reach the age of reproduction, and testing to determine if they are carriers is recommended.



I HAVE OTHER HEALTHY CHILDREN. WHAT ARE THE CHANCES THAT THEY CARRY THE BALANCED TRANSLOCATION?

Siblings of children with Emanuel syndrome have a 50% chance of inheriting the balanced translocation from the carrier parent, and 50% chance of having normal chromosomes.

WHAT TEST IS USED TO DIAGNOSE THE 11;22 TRANSLOCATION AND EMANUEL SYNDROME?

A test called a chromosomal analysis (or G-banded karyotype) will reveal the balanced translocation and the extra derivative chromosome. Essentially, it is a picture of the chromosomes in a single cell of an individual. To get this test, your doctor orders a blood sample to be sent to a special laboratory called a Cytogenetics lab.



Cousins with ES - both their mothers, who are sisters, carry the t(11;22).

Testing to identify Emanuel syndrome is also done using fluorescence in situ hybridization (FISH) and chromosomal microarray analysis.

New and novel approaches such as Next Generation Phenotyping (NGP - Face2Gene) using computer-aided facial dysmorphology analysis are starting to show promise, especially for patients living where there is limited access to newer genetic approaches, but are not yet in common use (Liehr et. al., 2017).

WHAT TESTING IS REQUIRED TO DIAGNOSE A FETUS WHEN PREGNANT?

When you are between 10 and 12 weeks gestation, you can have chorionic villus sampling (CVS) or amniocentesis when you are at least 15 weeks pregnant. These procedures take a piece of the placenta (for CVS) or some cells from the amniotic fluid surrounding the baby (for amniocentesis), and a chromosome analysis is performed on these cells in the lab. Based on these results, you will know whether or not the baby has the extra chromosome that causes Emanuel syndrome.

Some people who are already facing fertility issues are reluctant to have one of these procedures because they slightly increase the risk of having a miscarriage. It is possible to get hints about whether or not the baby has ES based on ultrasound, but it is not nearly as accurate. Also, by the time the ultrasound shows abnormalities (if at all – most pregnancies will have normal ultrasounds), it may be too late to have a pregnancy termination, if that is your wish.

Pregnancy termination (also called abortion) is not an option that everyone will consider. However, if you choose to have prenatal testing by CVS or amniocentesis, and the baby is affected, you will be offered termination if it is legal in your area. If you wish to have a pregnancy termination and it is not legal in your area, you can ask your doctor to refer you to another state or country for the procedure.

PAGE 21 OF 95



In Canada, most major hospitals offer termination of pregnancy up to 22 weeks.

Carter et. al., (2009) found in a study of 63 cases, that less than 20% of congenital anomalies are found by ultrasound before birth, suggesting that a normal prenatal ultrasound cannot exclude a diagnosis of ES.

PREGNANCY, MISCARRIAGE AND INFERTILITY

AM I AT RISK FOR COMPLICATIONS DURING PREGNANCY?

Carter et. al. (2009) found that out of 63 female carriers studied, approximately 80% had no complications during the pregnancy with their child with ES. The reported complications that did occur included intrauterine growth restriction (small baby) in 24%, decreased fetal movement (18%), oligohydramnios (too little amniotic fluid) in 16%, vaginal bleeding (11%), breech presentation (14.5%) and prematurity 9.5%). Most mothers did have completely normal pregnancies.

WHAT RISKS DO I HAVE IF I BECOME PREGNANT?

FEMALE CARRIERS

Most of the literature we have seen up to now gives the following statistics for carriers; If you are a female carrier of the t(11;22):

in you are a remain carrier of the ((11,22).

- you have an approximately 5-6% chance of having a child with Emanuel syndrome for each pregnancy conceived
- you have an approximately 55% chance of having a child who carries the balanced translocation for each pregnancy conceived
- you have a 23-37% chance of having a miscarriage for each pregnancy conceived

MALE CARRIERS:

- you have an approximately 2-5% chance of having a child with Emanuel syndrome for each pregnancy conceived
- you have an approximately 40% chance of having a child who carries the balanced translocation for each pregnancy conceived
- you have a 23-37% chance of your partner having a miscarriage for each pregnancy conceived

In our 2009 study of t(11;22) carriers who have a child with Emanuel syndrome (Carter et. al., 2009), we noted the incidence of miscarriage for those families to be higher. These findings cannot be considered as official risks, as there is a bias in how we obtained the figures (we didn't survey all carriers, only carriers who have accessed the website). In order for us to do a more complete study on true risks for t(11;22) carriers, a

scientific study with a control group would need to be performed. Keeping that in mind, for the purposes of this guide we will share the results of the carriers surveyed.

Our study counted 66 female carriers and 5 male carriers, all of whom had at least one child with Emanuel syndrome, with a total of 297 pregnancies. Out of that number:

For Females: 66 female carriers had 277 pregnancies.

Of those 277 pregnancies:

- 57 pregnancies resulted in a liveborn infant with Emanuel syndrome,
- 138 of the pregnancies were lost to miscarriage or selective abortion; (approximately 50%), and
- The remaining pregnancies produced a healthy child who had either a normal karyotype or the balanced translocation (30%)

For Males: 5 carriers partners had 20 pregnancies:

- 1 of the children was born with Emanuel syndrome (5%)
- 10 of those pregnancies were lost to miscarriage or selective abortion (50%)
- The remaining pregnancies produced a healthy child who had either a normal karyotype or the balanced translocation (45%)

As this was not a scientific study of carrier pregnancy outcomes, we did not separate miscarriage and abortion outcomes during the study. They are listed together now only to indicate a negative outcome of the pregnancy. While the outcomes are not definitive risks, they do show that there can be a significant chance of having a child with Emanuel syndrome or losing a pregnancy to miscarriage.

There are t(11;22) carriers in our group who have had more than one natural child born with Emanuel syndrome. We also know of a few pregnancies that resulted in the birth of twins both affected by Emanuel syndrome and one instance of twins where only one of the children was affected with Emanuel syndrome.

Most often, in about 90% of the cases of Emanuel syndrome, it is determined that the mother is the carrier of the balanced t(11;22). Carriers will have some eggs/sperm that will be completely normal – ie – not affected by either the balanced translocation or have the derivative chromosome present, but some of the eggs/sperm will contain the extra chromosome that results in Emanuel syndrome. It is theorized that, for parents of a child with ES, women are more frequently found to be the carrier because sperm carrying the extra chromosome may be less able to fertilize an egg than normal sperm. However, women's eggs, no matter if they carry the extra chromosome or not, seem to have equal chances of being fertilized.

Many members in our group who carry the t(11;22) have had experience with multiple miscarriages, periods of infertility, and some know what it is like to lose a child. There are even families who have had more than one child born with Emanuel syndrome. No matter what you are going through, there will be someone for you to talk to who understands all of these heartbreaks and frustrations. There are also a lot of success stories and people who can give you hope as you build your family.



Twins with ES

PAGE 23 OF 95

REPRODUCTIVE OPTIONS

If you are a carrier of a balanced 11;22 translocation, you may experience reproductive challenges. Women or men can carry the t(11;22), either in their eggs, or sperm. You will want to ask yourself (and your partner) many questions about what being a carrier will mean as you plan to have children and you will want to talk to your doctor or genetics counsellor to ensure you have a complete understanding of your options. Are you prepared for the possibility of raising a child with disabilities? Are there ways you can ensure you have a child who is not affected by Emanuel syndrome? There are many things to think about. If you are newly diagnosed, this can be a very overwhelming thing to learn.



Sisters with ES

Many of our carriers have healthy children - some naturally, some by the use of reproductive technically (preimplantation genetic diagnosis with invitro fertilization). Some have chosen to adopt.

Many factors will affect your decision to have more children. Some carriers make the decision to have a natural pregnancy and rely on prenatal testing to determine if the unborn child has Emanuel syndrome. They can then make the decision to continue the pregnancy or to terminate. Some carriers know ahead of time that their child has Emanuel syndrome, and they were better prepared before their child's birth about what to expect

before their child's birth about what to expect. Others may choose preimplantation genetic diagnosis – a special procedure where the egg or sperm is taken out of the carrier parent and can be tested to ensure that it is either balanced or unaffected before being implanted into the mother. There has been some success with this method of reproduction.

Carriers may opt to use donor eggs or sperm implanted through in vitro fertilization (IVF). Some health insurance plans will cover this procedure. Unfortunately, the success rate of achieving a pregnancy by IVF is lower than we would like.

Unfortunately, it is not covered by most health insurance plans and is quite expensive.

There are many carriers in our support group who have tried all of these ways to have more children and have tried naturally as well. Whatever option you choose will be right for your family, and will be based on your own personal views. Talking to other carriers as well as your genetic counsellor or family physician will help you and your partner decide which route is best for you.

The book *Raising the Goddess of Spring* contains stories of people in our support group who have experienced the challenges of being a carrier of a chromosome translocation, and some who have pursued alternative ways to grow their families, in the chapter *Reproductive Considerations*.

You can talk to other members of our group about their experiences. Please join us on Facebook.







If you are not ready to share with others yet, send us a private message at c22central@gmail.com. C22C's founder and the current president both have first-hand experience with the t(11;22).

Founder of C22C, Stephanie, a carrier of a balanced 11/22 translocation, experienced several miscarriages and chose adoption. She writes about this in her book.

Whatever choice you make, there is likely someone in our group who has walked that path and will be able to talk with you.

BALANCED 11Q;22Q TRANSLOCATION & CANCER RISK

To date, despite previous studies that referred to a greater risk of breast cancer for balanced t(11;22) carriers, no medical risks have been definitively confirmed in carriers. The study by Dr. Melissa Carter and colleagues in 2010 analyzed 80 pedigrees and found that the risk of breast cancer was



not increased over the general population. The study did find a higher incidence of melanoma and esophageal cancer, but this would have to be investigated further to prove any true correlation. The number of people in this study was too small to confirm a statistically significant correlation, meaning that the findings may have occurred strictly by chance.

Those of you who have been a part of our group for a period of time will be aware of past articles which have suggested a link between breast cancer and being a carrier of the 11/22 translocation. Below are references regarding this. While our own study with Dr. Melissa Carter in 2010 showed there was no increased risk, breast cancer is common enough and women should be aware of this risk and perform regular self-screening and mammograms as suggested by their physicians. A 2019 study did find there was an increased risk for breast cancer and suggested increased breast cancer surveillance for female carriers.

There have been other papers that suggest a link between the t(11;22) and the risk for developing cancer, but more research is needed to confirm any definitive connection. The papers that we are aware of that explore this connection are:

Carter, M. T., Barrowman, N. J., St Pierre, S. A., Emanuel, B. S., & Boycott, K. M. (2010). Risk of breast cancer not increased in translocation 11;22 carriers: analysis of 80 pedigrees. *American Journal of Medical Genetics*. *Part A*, *152A*(1), 212–214.

Doyen, J., Carpentier, X., Haudebourg, J., Hoch, B., Karmous-Benailly, H., Ambrosetti, D., Fabas, T., Amiel, J., Lambert, J. C., & Pedeutour, F. (2012). Renal cell carcinoma and a constitutional t(11;22) (q23;q11.2): case report and review of the potential link between the constitutional t(11;22) and cancer. *Cancer Genetics*, *205*(11), 603–607.

Jobanputra, V., Chung, W. K., Hacker, A. M., Emanuel, B. S., & Warburton, D. (2005). A unique case of der(11)t(11;22),-22 arising from 3:1 segregation of a maternal t(11;22) in a family with co-segregation of the translocation and breast cancer. *Prenatal Diagnosis*, *25*(8), 683–686.

Lindblom, A., Sandelin, K., Iselius, L., Dumanski, J., White, I., Nordenskjöld, M., & Larsson, C. (1994). Predisposition for breast cancer in carriers of constitutional translocation 11q;22q. *American Journal of Human Genetics*, *54*(5), 871–876.

Schoemaker, M. J., Jones, M. E., Higgins, C. D., Wright, A. F., UK Clinical Cytogenetics Group, & Swerdlow, A. J. (2019). Mortality and cancer incidence in carriers of constitutional t(11;22)(q23;q11) translocations: A prospective study. *International Journal of Cancer*, *145*(6), 1493–1498.

Wieland, I., Muschke, P., Volleth, M., Röpke, A., Pelz, A. F., Stumm, M., & Wieacker, P. (2006). High incidence of familial breast cancer segregates with constitutional t(11;22)(q23;q11). *Genes, Chromosomes & Cancer, 45*(10), 945–949.

CONGENITAL ANOMALIES AND MEDICAL ISSUES

According to Carter et. al., (2009), congenital anomalies are seen in nearly 90% of all children born who have ES. These can commonly include heart defects, cleft palates and renal malformations.

It is also common for children with ES to have what are known as "dysmorphic features". While the facial "phenotype" or "look" is variable, some common features are seen.

WHAT TYPES OF PROBLEMS SHOULD MY DOCTOR SCREEN MY CHILD FOR?

Generally, your doctor should do a general physical on your child, but specifically, he or she should screen for the following or make referrals for:

Palatal Evaluation - for cleft palate

Heart defects – an echocardiogram (an ultrasound of the heart) should be done once in infancy;

Ear problems – all children with developmental delays and/or frequent ear infections should have their hearing tested regularly by an audiologist; children with frequent ear infections should be referred to a paediatric Ear, Nose and Throat (ENT) doctor for consideration of drainage tubes:

Vision – have your child's vision assessed by an optometrist or ophthalmologist who specializes in children:

Orthopedic issues - specialist to check for hip, spine and other possible orthopedic problems;

Neurology - EEG if suspicious of seizures;



Feeding and swallowing tests: To check for palate problems, intestinal malformations, gastroesophageal reflux and/or airway issues; **Aspiration** is seen in a large number of children as well;

Kidneys – malformations can be seen on an abdominal ultrasound; if urinary tract infections are an issue, a VCUG (voiding cystourethrogram) should be performed to check for reflux:

A few of our children with ES have been reported as having **hypothyroidism**.

Gastrointestinal Evaluation - (reflux, structural glanomies)

Urological Evaluation - for malls (crysotchidism, micropenis)

Developmental services - early intervention or infant development specialist, speech therapist, physiotherapist and occupational therapist assessments;

Genetic counseling - for other family members to screen for carrier status; and

Failure to thrive - can sometimes be seen in children who have poor feeding due to hypotonia, craniofacial differences, cardiac or gastrointestinal malformations



We have not listed every possible medical issue – but we have listed the major ones. Some children may have a unique feature not seen in any other child with ES.

Another important thing to remember is that even though your child may have a general screening and things seem stable, our children are full of surprises. Make sure that you follow up and go for regular health checkups. Some serious health issues that may not have been present at birth may show up later in life. It is important not to let your guard down as a parent. It is not our advice that you panic about everything, but be conscious that your child may develop health issues and trust your instincts. You will learn what is normal for your child and if something seems out of the ordinary, it doesn't hurt to get it checked out.

Go to our website and download our infographic on what to screen for to share with your medical professionals.

COMMON ISSUES

A P P E A R A N C E

Some of our children, as mentioned previously, appear to resemble each other, and often are labelled by medical professionals as being "*dysmorphic*" which is basically defined as someone having an atypical appearance.



Some of our children have deep-set eyes, lower-set ears, and a longer upper lip (referred to as **"philtrum")** which you can see clearly here when Maia was a baby.

Some features seen in the faces of people with ES may include:

- Hooded eyelids
- Ptosis (drooping upper eyelids)
- Deep-set eyes
- Upslanting palpebral fissures (the opening between the eyelids)
- Low hanging columnella (the bridge of tissue that separates the nostrils at

the nasal base)

- Micrognathia (a smaller than typical jaw
- Facial asymmetry/Hemifacial microsomia

CLEFT PALATE

A cleft palate is an incomplete closure of the roof of the mouth during the development of the fetus. Cleft palate is sometimes seen in conjunction with **Pierre Robin Sequence**, a combination of cleft palate, small jaw (micrognathia) and a downward, displacement of the tongue (which is further back in the airway than normal, and referred to as **glossoptosis**.) Cleft palate is seen in approximately 50% of children with Emanuel syndrome. It can be full, affecting both the hard and soft palate, or just the soft palate. This is a picture of Maia, who had a complete cleft palate. You can see in the photo she is missing the palate.



A cleft palate is an incomplete closure of the palate (the boney part at the top of your mouth) and/ or the soft palate (the soft part at the back of the mouth) and uvula (the 'dangly bit' at the back of the mouth.

Cleft palates can lead to problems with feeding and, if combined in Pierre Robin Sequence, difficulties with breathing as well. Cleft palates are repairable with surgery, which usually takes place around 1 year of age. Some of our children have less serious forms of clefting, seen as submucous clefts, or bifid uvulas (where the uvula – located at the back of the throat – appears to be split in two.) Some children may have very high arched palates. **Cleft lip** is not typically seen, but has been reported by Luo, 2017.





Micrognathia (a smaller than normal jaw) is very common and can be seen as part of Pierre Robin sequence. Some children with ES in our group have undergone treatments called jaw distraction surgery (Mandibular Distraction Osteogenesis (MDO)) to improve the symptoms associated with having a very small jaw.

Maia - note the recessed jaw

Other less common findings can include:

- High arched palate
- Uvular hypoplasia / Bifid uvula

"Kieren was diagnosed late with both plagiocephaly and brachycephaly. Due to this, wearing two cranial reshaping braces/helmets only provided minimal repairs. Having testosterone shots may have also jumpstarted the plates closing. But the main goal of having his eyes come back into alignment was reached. As always, Kieren met this with sass and fierce objection."



CARDIOVASCULAR ISSUES

The 2009 study our group participated in reported that about 57% of children with Emanuel syndrome will have some form of heart defect, and about half of those will require surgical repair. Many of the heart issues did not affect life expectancy. Some of the more common heart defects found in our children are:

- Atrial Septal Defect or ASD (most common: seen in 45% of children with a heart defect)
- Ventricular Septal Defect or VSD (13% of those with a heart defect)
- Patent Ductus Arteriosus or PDA (11% of those with a heart defect)



- Pulmonic Stenosis (6% of those with a heart defect)
- Total Anomalous Pulmonary Venous Return or TAPVR (3% of those with a heart defect)
- Tetralogy of Fallot
- Coarctation of the Aorta

There have been other more rare heart differences reported in the medical literature as well. A few instances of hypertension have also been reported (Carter et. al., 2009). A cardiac assessment would be an expected evaluation for all children with ES.

"Finding out my 13-month-old daughter was going to need open heart surgery is by far the scariest thing I have ever experienced. I feel like I have held it together quite well through finding out she has Emanuel Syndrome and that I am the carrier, not that I didn't have breakdowns and disappointments and adjustments through it all, but that I was able to pull myself together within a respectable amount of time. I can honestly say I was an emotional mess."

"Aedyn was born with an ASD (atrial septal defect) and was monitored by a pediatric cardiologist from birth. At 2 1/2 months, an additional heart defect was discovered - pulmonary valve stenosis. Because he had been born prematurely and was quite small, the goal was to get him to a bit more normal newborn baby weight before having this addressed in the cath lab. So at 3 1/2 months, he had a balloon procedure to help "pop" the valve open more so it wasn't so narrow. We were informed that as he grew, he would very likely need this procedure done again maybe several times. To date, Aedyn is 10 years old and his cardiologist describes him as the "poster child for a balloon procedure" and has not needed any more intervention since 3 1/2 months old. For the type (size) of ASD he had, we were told that would be addressed at around age 4 or 5. His heart has continued to manage this well and has never needed the ASD addressed. Both issues are doing well! When the doctor said we could move to annual appointments I cried it was so overwhelmingly positive! We had not expected he would do this well! Currently, he sees his cardiologist every 2 years or so. His doctor said he would normally feel comfortable discharging him with how well his heart is doing, but since Emanuel syndrome is "always a wild card" we all feel more comfortable with periodic check-ups."

Several of our group member's children have undergone heart surgery to correct their defects, either through a procedure called heart catheterization, or open-heart surgery. Most have done well after their surgery. Most of the heart abnormalities seen in children with ES are correctable with surgery.

"Phoenix had a coarctation repair at just 5 days old. His recovery was amazing. He had a drain in for 3 days. He also has a small VSD right at the bottom that has not caused symptoms but is monitored yearly.



He also has a bicuspid aortic valve which also is non-symptomatic at present. He will be with cardiology for life."

GASTROINTESTINAL / FEEDING ISSUES AND THE DIGESTIVE SYSTEM

Feeding problems with children with ES are common. Some children have problems with coordination of the



muscles involved in swallowing, which can cause choking or **aspiration** of food or liquids into the lungs. For these children it may be unsafe to eat food orally, and therefore they may be on a soft or pureed diet, or may need to have a **gastrostomy tube** (a tube implanted into the stomach).

The majority (75%) of our children have issues with **drooling**, which is likely secondary to hypotonia in the facial muscles. Some of the children in our group have used treatments with medication or surgery to control drooling if it becomes severe. Talk to your doctor if you are concerned.

Many also have ongoing problems with **constipation** and require the use of laxatives or stool softeners. You will want to make sure this is one area that

gets under control quickly and you should speak to your pediatrician about bowel regimes.

Some of our children experience **gastroesophageal reflux (GERD)** and require antacid medication. Some children require surgery called a **fundoplication**.

"It was discovered during a swallow study that Phoenix suffers from reflux. He has been on antacid medication since birth. Phoenix drools constantly and needs several bibs per day. He does not swallow his secretions."

Some of our children have been born with a severe defect called a **diaphragmatic hernia**. This is a defect or "hole" in the muscular wall that separates the lungs and heart from the abdomen, which allows the contents of the abdomen to enter the chest cavity. This can cause serious problems with breathing and stress on the heart. It requires surgery to repair.

A recent paper reviewing congenital diaphragmatic hernia and Emanuel syndrome is **Adams et. al., 2021.** This paper reviews medical and surgical interventions offered to patients including surgical repair and ECMO support (extracorporeal membrane oxygenation). This allows the blood to bypass the heart and lungs to allow them to





heal.

Other types of hernias such as belly button (umbilical) or groin (inguinal) can also exist, but these are typically not life-threatening.

A condition called **intestinal malrotation** has also been seen in some of our children. This is a twisting of the intestines or bowel and can cause obstructions, which may require surgical treatment.

Some of our children have experienced **liver differences**, including reports of biliary atresia or liver lobe agenesis.

There have also been **gallbladder issues** seen, including reports of gallstones.

NEUROLOGICAL ISSUES

Children with ES can experience both functional and structural neurological differences. Functional neurological issues have to do with the nervous system and how the body receives signals from the brain, for example when someone experiences seizures. Structural issues are things such as differences in how the brain develops, or if there are malformations or injuries.

FUNCTIONAL NEUROLOGICAL FINDINGS

Hypotonia

The most common neurological problem, seen in over 60% of children with ES, is a condition called hypotonia, which means low muscle tone. It has been reported in many published cases and also reported by many of our members. This affects the development of motor skills and can cause children to have hyperflexible joints, problems with drooling, feeding and poor posture. If your child has hypotonia, early physiotherapy is essential to help your child reach their full potential. Children with hypotonia will be later in reaching their milestones such as lifting their head, rolling, sitting up and walking.

"Phoenix has low toned muscles, especially in the upper limbs. He gets tired very easily from doing daily tasks. He attends therapies several times a week to build up his strength and keep the pathways of the muscles firing to the brain."

STRUCTURAL NEUROLOGICAL FINDINGS

- *Microcephaly* (smaller than usual head) is seen in children with ES
- Ventriculomegaly (enlargement of the ventricles of the brain)
- Brain atrophy (loss of brain cells)
- **Absent or hypoplastic corpus callosum** (the corpus callosum is the band of white matter that connects the two hemispheres of the brain)
- White matter abnormalities
- **Dandy-Walker Malformation** (a brain malformation that involves a partial or complete absence of the area between the cerebellar hemispheres and a cyst that forms near the base of the skull) has been reported in several publications as well as our members.
- Chiari Malformation (structural defects of the cerebellum)
- *Hydrocephalus* (an abnormal accumulation of cerebrospinal fluid on the brain)



"Phoenix was diagnosed with hydrocephalus as a result of Chiari 1 malformation of the brain and skull at 1 year of age. He had a VP shunt placed and will have one for life. After discharge from surgery Phoenix's shunt malfunctioned. He suffered some damage to the brain and lost most of his fine motor skills. He gets regular MRIs to check there are no new changes to the spine and skull."

TETHERED SPINAL CORD

A tethered spinal cord is a treatable condition. It occurs when the tissue around the spine is attached to the spinal cord, and this can impact the ability of the spinal cord to move freely. It can cause pain and other symptoms, and typically, surgery is used to treat it.

Signs of a tethered spinal cord might include things such as issues with bowel or bladder control, issues with walking, a lump in the lower back, or a sacral dimple (a small dimple at the base of the spine) among other signs. Tethered spinal cords can be discovered by doing an MRI of the spine.

Sacral dimples are a common finding in our children, and are common in general, and are not always associated with a tethered cord.

There are cases reported of children with Emanuel syndrome having a tethered spinal cord:

"Chiara was born with a sacral dimple, which was discovered by MRI to be a tethered spinal cord. At age 4 she had a laminectomy to release it - we couldn't be sure if it was interfering with walking and toileting, so decided the benefits outweighed the risks. Hospital stay for about 4 days, this was when we figured out that morphine keeps her awake and agitated. The picture is of surgery site 2 days out, stitches inside staples outside, also you can see where they placed the epidural."

SEIZURES

Seizures are seen in almost half of people with ES. Some of them are grand mal seizures, and some are partial seizures. There are many different types of seizures seen in our children. Some of our children have seizures that are serious and difficult to control. Many of our children require medication to control their seizures.

A seizure is best described as a sudden abnormal electrical discharge in the brain.

Seizures can look very different depending on where in the brain the electrical discharge is occurring. Doctors classify seizures into types based on what they look like. Here are some common examples:

Generalized tonic-clonic seizure – the whole body convulses, and the child loses consciousness. He may wet himself or bite his tongue. This type of seizure used to be called "**grand mal**" seizures, because they look scary when they are happening! They are also very tiring – afterwards, the child will want to sleep.

nside







Absence seizure – these can be very subtle, as consciousness is only lost for a second or two. Usually, the only noticeable sign that a seizure is happening is the person pauses what they are doing and may flutter their eyelids. These used to be called "petit mal" seizures.

Complex partial seizure – this type is variable. Usually, the child appears to be awake, but they are not responsive when you talk to them. One or more parts of the body may move in a repetitive way (for example, lip-smacking or hand wringing). They usually last between 30 seconds to 2 minutes, and when the seizure is over, the child feels tired and does not remember it happening.

Infantile spasms – like the name suggests, this type of seizure occurs only in infants, and it does literally look like a spasm. The whole body jerks either forward (like a sit-up) or backward. . The child appears to be awake and may not seem disturbed by the seizure. They can happen alone or in clusters (several in a row).

Febrile seizures – These are typically generalized tonic-clonic seizures that occur when a child (usually between 6 months and 3 years of age) is mounting a fever, or when the fever is starting to break.

Epilepsy is simply the term used to describe the tendency to have seizures. A child who had a single febrile seizure does not have epilepsy unless he or she continues to have seizures once the fever has gone away.



Epilepsy usually begins in childhood or adolescence. Some children who have epilepsy grow out of it by the time they reach adulthood.

If your child has a seizure for the first time, they should be checked out in the hospital emergency room right away. The doctors will do a CAT scan to make sure there is no bleeding in the brain causing the seizure. A neurologist will usually see the child as well, either in the emergency room or as an outpatient.

An electroencephalogram (EEG) will be done to see if there is a specific location in the brain that is prone to seizure activity. Depending on the type of seizure, the age of the child, and the results of the EEG and CAT scan (or MRI scan), the doctor may decide to put your child on medication. Anticonvulsant medications (for example: valproic acid, phenobarb, lamotrigine, and carbamazepine) can help prevent further seizures from happening, but they all have side effects. It can take awhile to get the right balance of medication type

and dose while avoiding side effects.

Epilepsy.com is a great parent-friendly website for further information on seizures.

"My daughter did not show any signs of seizures or neurological problems. She was two years old before we had a neurological workup. She had other pressing problems and the neuro appointment kept being pushed to the back burner. At the appointment, she had an EEG that came out fine. I was even proud when they told me that her EEG was "normal for a child of her age" and that her brain waves were not considered "slow". They scheduled a 48-hour EEG and an MRI for the following month just to be on the safe side. We were told it was just a precautionary measure and she seemed fine. Less than two days later she had her first (and so far only) massive seizure on my living room floor. It was 3:15 am and I felt like the wind had been knocked out of me. She ended up in the PICU on a ventilator for three days. When we arrived at the hospital they performed an MRI of her brain. It revealed a thin corpus callosum, mild hydrocephalus and mild cerebral atrophy. I was told that the combination of these three brain abnormalities put her at higher risk for seizure activity. They are still unable to tell me why she never had seized before that day and what caused the seizure to happen that day. She has been on medication for her seizures. Since starting the medication she has not had any seizures and her EEG's have all come back normal."

INFECTIONS AND IMMUNITY

Some children with ES have challenges with poor immunity and/or may experience frequent infections.

One of the most common health issues in our children is overwhelmingly recurrent middle ear infections (*otitis media*). Many of our children have had to have placement of ear tubes, multiple times.

Recurrent chest infection/pneumonia and sinusitis are also seen frequently.

Other health issues can be *urinary tract infections* and *thrush*.

There are a few (about 20%) who have reported low *immunoglobins,* a condition that can leave them more susceptible to infection. Some of our children have received special intravenous treatments to help improve their immunity.



"Phoenix has low levels of IGA & IGG. IGA antibodies play a major role in protecting us from infections of mucosal surfaces. Including tears, saliva, colostrum, genital, respiratory and gastrointestinal secretions. IGG is associated with infections of the ears, nose and lungs.

Phoenix has only had a couple of infections in the chest and ears. He has not needed any immunoglobulin therapy as his levels have stayed stable."

"Christy was born July 1986. She had chronic pneumonia from about 8 months old. Even though her labs showed low immunity to pneumonia, doctors also evaluated how often she was hospitalized. At age 4, IVIG therapy was started every two weeks and lasted about 8 months and then her own immune system took over. She did not have any side effects from it. She was healthy, began to eat and was no longer considered 'failure to thrive'. The feeding tube was removed and best of all she no longer experiences pneumonia and she is now 35. She does have low IGA and has issues with sinuses but nothing major. Medication is dosed as a toddler as her body can only handle low doses."



GENITAL AND ANAL DIFFERENCES

It is not uncommon for children with Emanuel syndrome to have genital or anal differences, or differences in their reproductive system.

Males with ES may have **undescended testicles (cryptorchidism)** or an **abnormally small penis** (**micropenis**). Undescended testicles may come down on their own within a few weeks of birth. If not, they must be brought down surgically into the scrotum.

There are also reports of **hypospadias** - where the opening of the urethra is not located at the tip of the penis.

Other less common or unique findings have included:

atresia), where the opening to the anus is missing or blocked. Urgent surgery is

There are also reports in the medical literature, and among group members, of incidences of **Hirschsprung's Disease**. This is a condition where missing nerve

cells in the muscles of the colon make it difficult to pass stool and result in

A smaller percentage of people with ES (about 15%) may be born with **imperforate anus (also called anal**

• Abnormal testes / hypoplastic scrotum

required to repair this when the child is born.

• Ambiguous genitalia

blockages.

- Hypoplastic labia majora and minora
- Duplication of the uterus and vagina
- Bilateral hydrocele
- Rectovaginal fistula
- Hypoplasia of the uterus
- Single ovary

RESPIRATORY ISSUES



Several children with Emanuel syndrome have been reported to have breathing issues. This is due to more than one factor. Breathing issues have sometimes kept our children in the hospital at birth until their issues resolve or are treated so that they can be managed at home. Some of these breathing issues result in lifetime challenges and can impact them more significantly when they become ill, especially with respiratory issues, or if they need surgery and require intubation. Some of these issues are:

Pierre Robin Sequence is a common finding in children with ES. The combination of cleft palate, small jaw and tongue displaced towards the back of the throat (glossoptosis)has been a problem for many of our members.

Other reasons for breathing issues that are not as common in children with ES

include:

Aspiration: When food or liquid (even saliva) is breathed into the lungs, instead of being swallowed, which can cause serious problems such as pneumonia.

Tracheomalacia (floppy airway).

Laryngomalacia (floppy larynx which can cause noisy breathing).

"Evyn was referred to an ENT at her 2-week checkup and diagnosed with laryngomalacia at 1 month old. The sound of her breathing was terrifying! We were followed closely by the ENT and made the decision to hold off on a trach because it slowly improved. At 2 years old, her breathing is almost completely "normal." What a scary time though! My best advice is to trust your momma gut!"






Some individuals with ES require a **tracheostomy** to help them breathe. But that doesn't stop them from smiling!

Many of our children have issues with drooling, which is due to low muscle tone. This can lead to aspiration, which in turn can cause pneumonia. Excessive drooling is also known as **sialorrhea**.

URINARY SYSTEM

Many children with ES have problems with their kidneys. These essential organs develop in the womb and because the ES DNA road map does not always match the norm, small, malformed or single kidneys are often seen.

Kidney differences are quite common, seen in over 35% of our children. Some children have been born with only one kidney, known as unilateral *renal agenesis*.

Others have reported that their kidneys were abnormally small) or did not function well.

Some have **vesicoureteral reflux**, which is when urine from the bladder travels in the wrong direction up towards the kidneys via the ureters. It must be treated and monitored to prevent permanent damage to the kidneys.

Other kidney differences we know about in kids with ES:

- Hypoplasia of kidneys
- Recurrent UTIs
- Hydronephrosis
- Chronic renal insufficiency
- Hydrouereter

An evaluation of your child's kidneys should be a routine part of their evaluation shortly after birth.

The kidney's job is to filter toxins from the body and dispose of them in the urine. They also secrete hormones to help make red blood cells and to keep the right amount of minerals (electrolytes) in your blood. It is worth mentioning that an absent kidney from birth (renal agenesis) is not uncommon in the general population and in many cases the second kidney can compensate. However, sometimes a small solitary kidney cannot successfully rid the body of toxins or produce enough urine and this condition is called renal failure. There are five stages of kidney failure which is determined by a blood test called the eGFR test.

The symptoms of kidney failure may not be obvious without testing. Fatigue, shortness of breath due to excess fluid buildup, skin irritation, nausea, swelling in the ankles, feet and hands, high blood pressure, and changes in urination. A basic metabolic panel blood test will help your doctor to diagnose, and it is recommended that all young children with ES have an abdominal ultrasound to screen for small or absent kidney, even if there are no symptoms at birth.



One of the standard tests in the metabolic panel is the creatinine level. Creatinine is a waste product produced by muscle tissue that is normally filtered through the kidneys. When this level is high, it means that this waste product is not being adequately processed out of the body. This level is often used as a baseline. Later testing can use this baseline (along with the eGFR) to indicate whether the kidney function is worsening or not.

Treatment involves many factors as poor kidney function affects other body systems. High blood pressure is a very common symptom that is treated with medication. Since another function of the kidney is to help make red blood cells and balance the minerals in the blood, poor kidney function can affect bone health. Osteoporosis is a complication that needs to be carefully monitored in an ES child with poor renal function. Calcium and mineral supplements are often needed. The parathyroid function should also be checked and Vitamin D supplements may be prescribed.

Fluid balance in a child with poor renal function is tricky. The kidneys may need extra fluid to assist with flushing toxins from the body but if the kidney is not able to process a lot of fluid, the fluid will build up in the cells or sometimes in the space between the cells (interstitial fluid) where it will cause swelling particularly in the feet, ankles and hands. Often the fluid will build up in the lungs which can cause pneumonia and breathing difficulties. So there can be a fine line where enough fluid is given to flush the kidney but not so much that it builds up in the tissues. In a hospital setting, they will weigh the diapers or use a catheter in the bladder to determine if the amount of fluid intake matches the output of urine to help calculate the correct amount. A dietician can also help to make calculations.

Later stages of renal failure are treated with a procedure called dialysis which mechanically removes the toxins from the body. There are two main methods: Hemodialysis runs the patient's blood through a machine via a venous access port and peritoneal dialysis pumps dialysis fluid into the peritoneal cavity (space in your abdomen) and this fluid is run through a machine to remove the waste. Peritoneal dialysis can sometimes be done at home.

In the final stages of renal failure, some families may be asked to consider a transplant. Your hospital transplant team will evaluate for eligibility but generally speaking, due to immune deficiencies and/or frequent lung infections, ES patients are not great candidates for transplant which requires immunosuppressive drugs for life to prevent organ rejection.

VISION, EYES

While most of our children do not have problems with

vision, *nearsightedness* (myopia) can be seen in children with ES. So can *strabismus*, which is a problem where one or both of the child's eyes will drift inward or outward. Other less common eye differences (including single case reports) have been seen:

- **Astigmatism** (differences in the curvature of the cornea)
- **Glaucoma** (abnormally high eye pressure which can affect the optic nerve)
- **Duane syndrome** (an eye disorder that limits horizontal eye movement)
- **Nystagmus** (involuntary, rapid and repetitive movement of the eyes)
- Ptosis (drooping upper eyelid)
- Hyperopia (farsightedness)
- **Epicanthal folds** (skin fold of the upper eyelid covering the inner corner of the eye)
- Microphthalmia (eyes that are smaller than usual)



- Esotropia (eyes with a tendency to turn inward)
- Iris coloboma (a hole or defect in the iris of the eye which may affect vision)
- Optic nerve atrophy (may cause changes in vision)
- Nuclear sclerosis (cloudiness in the eye)
- Conjunctival lipodermoid (growths found under the conjunctiva)
- Cataracts
- Retinal angiopathy (a disease of the retina)

Regular ophthalmology assessments are recommended for people living with ES.



"We had no clue that Joaquin had poor eyesight but are so glad his OT suggested he get an eye exam because we found out he is pretty moderately farsighted. We were amazed at how the optician was able to perform the exams while also making Joaquin comfortable. Now we just have to work at keeping them on!"

"Aedyn has been followed by an ophthalmologist since he was in the NICU. We have been able to do some non-surgical interventions that have worked well for Aedyn and have been able to avoid surgery. When he was younger we did patching for a period of each day to help address his eye-crossing. We paired this with various activities like his time in the stander, etc. When he needed a slight prescription and he got glasses, we also were able to add some prisms to that prescription that helps as well. With each recent eye exam, we have been able to reduce the number of prisms in his prescription. With regular monitoring and some diligence with therapies and guidance with his activities at school, we have consistently seen improvement over the years and hardly ever see any crossing now. Aedyn is 10 years old and wears glasses for school, computer activities, therapies, etc."



EARS AND HEARING

Some of our children can be born with ear differences – which might present as tiny pits or tags on the ears, and some children have been born with malformed or even missing ears (known as *microtia*). Some of our children have ears that are lower set, smaller than usual, or even have differences in the inner ear which can impact their hearing.

Hearing loss is very common in children with ES, affecting about 75% to some degree. Hearing loss can be anywhere from mild to profound, including complete deafness.

In some cases, the hearing loss is due to fluid behind the eardrum (**conductive hearing loss**), but it can also be **sensorineural**, caused by damage to the inner ear or nerves involved in hearing. For those with conductive hearing loss, ear tubes to relieve the pressure behind the eardrum has improved hearing in some cases.

Children with sensorineural hearing loss may benefit from hearing aids, and some children with ES have had cochlear implants.



"When Steven was just over two months old, we noticed that he was not responding to sound while we attended a local parade. We tested this ourselves by banging pots while he was awake or asleep, and he didn't even flinch. Later we had his hearing tested and it was discovered that he had very little hearing – if any at all."



"Phoenix failed his first hearing test at 3 days old due to glue ear. He was fitted with a bone conductor until he could get grommets (ear tubes) at 6 months of age. He is now nearly 4 and has had 4 sets of grommets. He has extremely narrow ear canals."

MUSCULOSKELETAL / ORTHOPEDIC ISSUES

Orthopedic and musculoskeletal differences/ issues are common in children who have ES. The following are the more common findings:

Hips: Half of our children have problems with their hips. This can be as mild as *hip dysplasia*, or as significant as *hip dislocation*. Some of our children have required surgery to repair hip problems.



"Joaquin was diagnosed with mild developmental hip dysplasia at 18 months. He wears a hip brace every night for bed. It doesn't bother him and it doesn't limit his mobility - he can roll around, sit up, and scoot while wearing the hip brace."

"Kieren was diagnosed at almost a year with left hip dislocation. It had been out since birth most likely. Extreme

bracing was attempted at first. But—he wasn't able to handle it. He had started to become intolerant to his formula, he had frequent stooling, and wouldn't sleep with the brace. He had also begun to stand. In the end, we wore a Pavlik Harness (used for infants!) because with his hypotonia he couldn't 'unvelcro' himself. So without surgery and with minimal "bracing" Kieren's hip was fixed."





"Aedyn was born with hip dysplasia and monitored by an orthopedic surgeon and hip ultrasounds since birth. At age 6 months, when his bones had developed enough to see on x-ray, it appeared he needed to have this addressed and was referred to another orthopedic specialist at a university medical center. Because he was so small and developmentally delayed, doctors thought that even at 7-8 months he was still a good candidate for a Pavlik harness. He used the harness 24 hours a day for about 3 months. Then was fitted for a different type of bracing that he wore overnight only for another year or so. The overnight bracing was actually quite easy for him and for us and just continued to give him extra help with positioning while he slept to help the ball form in the socket better. Daily weight-bearing (stander, gait trainer, etc.)

also helps with this. Aedyn is currently 10 years old and has not needed surgery to further address this."

"It was discovered much later on that Phoenix had hip dysplasia on the left hip. He has yearly orthopedic X-rays and reviews. Currently, his hip is sitting 1/3 of the way out. They will do surgery when it gets to 2/3. They prefer to wait as long as they can to do surgery due to growth they may need to repeat the surgery if it is done too young."



About half of our children have ankle instability, which is often associated with hypotonia. Often a physiotherapist or doctor will prescribe ankle-foot orthoses (ankle braces) to help with stability once the child starts to walk.



"Joaquin wore AFO's (Ankle Foot Orthotics) because of his flat feet and also because he has foot pronation (where the inside of the foot curves out instead of in). When we were talking with his orthotist and former PT about what type of orthotic would be best for Joaquin we decided to go with the AFO's, over the shorter SMO's, they went up his calf so they help provided him with some stability while standing. He graduated to SMO's after a year and a half and now has liners."

Many of our children have smaller feet than typical. For example, Maia, Stephanie's daughter who is an adult, has feet that are children's size 11

"Phoenix has tiny feet and small heels. He also has hypermobility in his joints including his ankle. He has had AFO'S since 1-year-old. He gets 1-3 pairs a year depending on growth. They help him stand and be supported through the foot and ankle.". **Kyphosis** and **scoliosis** (changes in the curvature of the spine) are also fairly common (about 30% of children). Some have had the conditions seriously enough to require bracing or surgical intervention. Of the parents who have talked about their children who have had the surgery, while they acknowledge the challenges for recovery, they remark about how tall and straight their children's backs are following surgery, and how it improved their quality of life.

"Myah wore the Milwaukee brace. She was supposed to wear it 23 hours a day, only off for 1 hour to bath, etc. without it. She could only tolerate it for short periods of time, I don't think we ever got to more than 2 hrs total in a day. The doctor finally agreed that quality of life was more important at this age and we would deal with surgery later in life. The goal of the brace was not to fully correct scoliosis but to prolong the age when surgery would be needed. The doctor did not want to perform surgery on a child less than 10 yr old. Myah is 12 and we are going for surgery April 2022."

Joint contractures (where muscles or joints are tightened) and *torticollis* (tight neck muscles that affect movement of the neck) have also been reported.

Some of our children have been noted to have an extra pair of ribs, or club feet. Instances of children with loose joints / hyperextensible fingers and toes have been seen as well.

Other less common findings seen in our children that have been reported in the literature include:

- Flat feet
- Rocker bottom feet
- Clubfeet
- Delay in bone age/growth
- Dislocatable radius & ulna (forearm)
- Shoulder joint subluxation
- Proximally implanted thumbs
- Coxa valgus (malformation of the femur)
- Clavicle deformities
- Clinodactyly (abnormally bent or curved fingers)
- Vertebral fusion
- Sprengel deformity (shoulder blade is too high on one side of the body, affecting movement)
- Contractures, hypoplasia in fingers and toes
- Different sized feet

"As Damian became older he didn't want to walk. He sat on the floor, we didn't know what happened. Took him to the doctor, because we didn't know what was going on. And one day we realized he has his feet of different sizes and we had been buying his shoes for the small foot!







DENTAL

Dental anomalies are commonly seen in our children. Baby teeth are typically late to appear. Teeth can come in crooked and crowded and may appear abnormally shaped. Sometimes this is because of a smaller than usual jaw.

Some of our children are missing a few adult teeth – with no teeth to come in behind the baby teeth that fell out.



It is not uncommon for our children to have enamel defects, which may make them prone to getting cavities, or to require dental surgery to have extra teeth removed, or baby teeth removed that did not become loose and fall out on their own. Most articles published on ES, as well as members of our parent group, report these common findings.

"Maia had teeth that came in with enamel defects. She also was missing some adult teeth as shown on an x-ray. Some of her baby teeth didn't come out and had to be removed. Her teeth are not lined up properly."

Within our group, our shared experience is that our children can be challenging to examine for routine checkups or cleanings or to obtain radiographs. Often, it can be a risk to sedate our children for a thorough dental examination. Some parents have been able to arrange a dental assessment or radiographs when a

child has to be sedated for a different procedure, for example when ear tubes are being placed.

As our children are unlikely to express pain in the mouth due to an infection or cavity, regular dental care, including assessment, cleaning and obtaining radiographs, is recommended.

SKIN ISSUES AND DIFFERENCES

Some of our children have been found to have increased nuchal fold / excess neck skin. This is something that can be seen in children who have chromosome abnormalities

and might be something that is identified on an ultrasound.

"This is Shelby as a newborn and a bit older. It was basically the first thing they noticed that was abnormal on my ultrasounds. They were convinced she had Turner Syndrome. She grew into her skin fairly quickly. You can't even tell now."





Sometimes children with ES may be born with skin tags or pits on parts of their body. We often see them near the ears or mouth. These tags can be removed surgically if they are bothersome. This little guy is Blade and he has them on each side of his face. They are expected to be removed when he has surgery to fix his cleft palate.







"We were offered plastic surgery but the pits aren't deep enough to cause trouble and the tags we just see as part of her. In fact, when trying to explain to a friend's little girl years ago some of Lucy's differences I said she had 'extra bits' (meaning chromosomes). A few months later it transpired she thought it was her ear tags, that all Lucy's needs were due to them! Quite cute really."



Ear pits.

PRENATAL CONCERNS AND FINDINGS

Carter et al (2009) reported that most women expecting children with ES (81%) did *not* report any pregnancy complications However, there were instances of:

- Intrauterine growth restriction
- Decreased fetal movements
- Oligohydramnios
- Breech position
- Vaginal bleeding
- Prematurity

While the majority of cases of ES are not diagnosed prenatally, there have been a handful of articles that have identified various prenatal findings including:

- Increased nuchal fold thickness / excess neck skin
- Head and facial malformations
- Diaphragmatic hernias
- Heart malformations
- Brain malformations (especially Dandy-Walker malformation seen in several reports)
- Kidney malformations
- Intestinal and bowel anomalies



This is a 3D ultrasound image that shows an ear tag.



GROWTH AND DEVELOPMENT

Children with Emanuel syndrome will have issues with growth and development. In this section, we will talk about their physical and cognitive development, as well as look at how they develop from birth to adulthood.

Just remember that what you read doesn't tell the whole picture of who your child will be. Things may sound scary or difficult when you read that your child will experience delays, but remember that these things will be only a part of who your child is.

PERINATAL

For mothers carrying children with ES, the frequency of pregnancy complications is low, as is prematurity. The most commonly seen complication, occurring in 24% of cases is intrauterine growth retardation and birth weights are typically low (Carter, et. al., 2009).

DEVELOPMENT

Every child with Emanuel Syndrome will have global developmental delays. Some parents have asked us what causes our children to have developmental and speech delays. This is due to the extra genes our children carry. It affects the normal development of the brain, and this affects every area of development. The first area of developmental delay that parents typically notice is in the area of gross motor skills – the process of learning to sit, stand and walk independently.

"Every milestone is HUGE because your child has worked harder to get there than typical children do. Feel free to celebrate in a big way. My husband and I cried when our daughter pulled herself across the floor for the first time at around the age of 4."

IF MY CHILD DOES NOT HAVE A LOT OF MEDICAL ISSUES, DOES THAT MEAN HE WILL DO BETTER DEVELOPMENTALLY?

This question has been asked by more than one parent. Medical issues do not predict how well your child will develop. Some children have very serious, lifethreatening medical issues but they sometimes do better cognitively than others who have had relatively few medical problems. This is not something we are able to predict.



BEHAVIOUR

Behaviour problems are not common in our children. Only a small percentage have been reported to have anxiety issues, episodes of agitation or self-harm/self-injurious behaviour. Some of the children have required medication to treat these issues. Some children have exhibited self-stimulating behaviours such as rocking.

If you are concerned about behavioural issues, you can talk to your doctor about a referral to a behavioural therapist.

PHYSICAL DEVELOPMENT

Children with ES will generally experience differences in how they grow and develop. Many of our children do not typically reach physical developmental milestones such as sitting, standing or walking, at the same rate as compared to children who do not have ES.

The majority of our children do not reach a normal adult height and weight. Many are on the lowest end of the spectrum for both height and weight typical for their age. Some of the children may have small, underdeveloped feet and hands. Many of our children at some point have been given the label "failure to thrive".

Past medical reports on Emanuel syndrome have suggested that bone growth in our children is delayed.

In Carter et al., (2009), 50% of the individuals reported were below the 3rd centile for weight, and 73% of individuals reported their height as below the 3rd centile. Having growth below the 3rd centile is also noted



At age 27, Maia is not much heavier than our German Shepherd - who is about 70 lbs. She is more the size of an eightyear-old girl with tiny feet. Even with AFOs, her shoes are a child's size 1.

in several other reports.

Fine motor and self-help skills are also significantly delayed in the majority of our children. Most children require help for dressing and feeding, beyond the age when they are infants. About 40% of children at a developmentally appropriate age were able to use a spoon or fork appropriately.

"When my son was a baby I was comparing him to other kids I saw and asked their age to realize how behind he was. I don't know if other parents have done this, but it is not a good thing to do. As they grow the differences become more evident. You will find a way to face this."

About 20% of our children with ES are fully or partially toilet trained. Some of our children are toilet regulated – which means they are taken to the bathroom at regular intervals.



WILL MY CHILD LEARN TO WALK?

The majority of children with ES do learn to walk, but the age at which they achieve this may be delayed. Most of our children are able to learn to walk with assistance (using a walker), or independently. Of those who use walkers, they are usually around age 5. There have been some children who did learn to walk independently even earlier than this. (Carter et. al., 2009).

For some of the children who do not learn to walk, or who are able to walk with support but still have limited mobility, you will likely at some point require a wheelchair, or specialized stroller. This doesn't mean your child has to use it exclusively – but for longer trips it can be helpful so he doesn't tire out, or fall and injure himself. The idea is to maximize your child's experiences, not to admit defeat!





Joaquin started using a gait trainer at 2 1/2, graduated to a Nimbo walker at 4 years old, and started walking independently at 6 1/2

"What should you expect? They will tell us, as time goes by. Each of them has their own potential and no doctor or no other professional like an Occupational Therapist or Physiotherapist is to tell you your child will never do this or that. This gets you down to hear there are so many things they will not do, and they are so smart, always surprising with a new milestone. Our son was not going to live....but he is 9 now. He was not going to walk....but he learned to walk on his own, at 6 or 7 and he does it very well. He was



never going to tell when he wanted to go to the bathroom... but he has learned his own way to tell us and is learning to be regulated very well. He was never going to do many things and you should see the many things he is able to do ... he has a preference lately for making big, big messes!"

It may be hard to look into the future, but there may be a time when you need to make home modifications, such as adding a wheelchair ramp if your child does not learn to walk well, or making a larger bathroom to accommodate a bathtub lift. You may need to modify a vehicle to accommodate a wheelchair or special seating arrangement. These are concerns we will mention briefly, only for the purpose of financial planning. Some of the parents wished they had thought about those things sooner and thought it was worth mentioning, so families



would be able to plan better when moving homes, or to save money for equipment that might not be covered. Some of our families have thrown fundraisers to raise money for modified vehicles or home renovations. Depending on which country or state you live in, some financial grants may be available for these things. When and if you need this, your child's therapist will be able to point you in the right direction.

PUBERTY

In the majority of girls with ES, menstruation does occur. This has happened anywhere from age 9 to 18, with the majority of girls starting between ages 11-13. There have been two reports of girls who reached adulthood and did not have any menstruation (Carter et al., 2009).

"Every milestone is HUGE because your child has worked harder to get there than typical children do. Feel free to celebrate in a big way. My husband and I cried when our daughter pulled herself across the floor for the first time at around the age of 4."

Keep in mind that children with ES will develop differently, even though they have the same diagnosis. While there are some children who do not develop independent mobility, there are some children with ES who are walking independently even in early childhood. And while most of our children are small, there are some who reach an average adult size when fully grown. There is a lot of variability with growth.

INTELLECTUAL DEVELOPMENT

Most people with ES have intellectual disabilities that are considered in the severe to profound range. People experiencing this level of intellectual disability require daily supervision and support, relying on others for most basic needs such as feeding, toileting and mobility. They may understand speech but have limited ability to communicate with words. They will not be able to live independently as adults.

This is very hard to hear as a parent, but there are so many things you can do to help your child develop to the best of their abilities. And, our group members will be with you every step of the way.



It will be important for parents to explore other options for their children to be able to express themselves, maximizing all opportunities for learning and teaching alternative ways to







EMANUELSYNDROME.ORG

communicate.

Your child's speech and language therapist will help you decide on the best ways to help your child communicate.

As parents creating this guide, we know how you are feeling if you are reading this information for the first time. We know how hard this is to read. Be assured that you will be celebrating so many successes with your child and be amazed by them. We are all going to be cheering along with you!

DEVELOPMENTAL STAGES



As our children go from birth to adulthood, they will have some unique considerations. We hope this general overview of these stages of life will be helpful.





Newborn



Ages 1 - 3



School Years



Adulthood

WHAT TO EXPECT IN THE NEWBORN STAGE

"If your baby has a NICU stay, GET A SOCIAL WORKER! Find out about all the available services and have them place the 0-3 referrals. It will save a lot of research and time after you get out of the hospital. The first years are incredibly hard. Birth to

two years old was the hardest and a lot of it was spent in survival mode. Give yourself, your partner, and your family a lot of grace. My son had an 8-week NICU stay, 17 doctors for follow-ups, and 9 surgeries in his first 18 months of life. As hard as it was, there was still so much joy! The firsts are different, but they are so much



richer! You learn to appreciate all the small stuff and in those "small things" find so much more to be grateful for."



This stage is going to be one of learning for you as a parent, and one where you begin to assess, along with your doctor/pediatrician, what issues your child may have. You may experience some anxiety as you begin to let the diagnosis sink in, and as you learn about challenges your child may face.

It is common for many of our children to not go home from the hospital immediately after birth, and some of our children face some medical issues that require extended hospitalizations.

Some of the most common reasons our children have been kept in the hospital following birth were complications related to hypotonia, problems with feeding, requiring surgery to correct things such as heart defects or hernias, requiring oxygen therapy, or treatment for jaundice.

Other problems that have been seen include seizures, infection, or problems with breathing due to a narrower than usual airway, often in combination with the condition **Pierre Robin sequence** - a condition in which the tongue is

displaced towards the back of the throat, along with a smaller receded chin and a cleft palate. Despite the fact that some of our children have had difficulties with feeding after birth, some mothers have successfully breastfed their children.

"We did not get my daughter's diagnosis until she was almost 7 months old and because of that had a slightly different experience than some other families in that we didn't have doctors telling us what our child would not be able to do. When she was in the NICU for the first week of hier life and was having trouble latching on for breastfeeding we were told that it was simply because she had a high arched palate and to keep trying. Because of this I struggled with my daughter for one month trying to train her to latch on properly. For fifteen minutes prior to feeding her with a bottlel would put her on my breast alsmost every time she ate. It was a long and frustrating battle as I thought I was making my daughter associate feeding with negativity because she would cry the entire time before giving her the bottle. We had some successes early on, maybe once every few days, she would latch on for an entire feeding, but them we would go back to fighting with her. That being said, miraculously at a few days after her one month birthday she figured it out and from that point until her 9 month birthday I was able to breastfeed my daughter. I am thankful because I did not have people discouraging me because I might have given up. I know that many of our children have feeding issues and that for the ones that are tube-fed or have sensory issues this may not be an option, but for others I would say to go with what feels right to you as a parent because each of our children is different and you never know what your child's accomplishments might be."

The newborn stage is the time when you will have assessments done to rule out some of the common issues children with ES have. Download our infographic of the common areas that require evaluation and hand it out to people involved with your child. Keep a copy with you when you visit specialists. You can find it on our website.

This is also the time when you get to learn how to care for your child:

• You may be adjusting to new ways of feeding your baby such as learning to use a cleft bottle, or gavage feeding;

- Some of our children have left the hospital with medical issues that require equipment, such as apnea or heart monitors, which you may need time to adjust to using;
- You will want to learn what you can about your child's diagnosis so that you can help others learn about your child, too.
- You will also have a lot to process.

Connecting with our families may help you through this early stage. Learning all you can will help empower you to be prepared for things to come. Believe it or not, you are going to become a very strong advocate for your child.

We are glad you found us, and we are all here for you.

WHAT TO EXPECT THE FIRST YEAR AND EARLY INFANCY

"Oh my gosh, it's SO hard! Appointments, so many appointments. Diagnosis after diagnosis. If you have a support system lean on them. Take time for yourself to heal from all of the emotional stuff that you go through - seeing your baby so sick. Get involved in any therapy that you can as soon as possible. There will be so many struggles but celebrate every single win. For me, it was so hard seeing all of our friends with typically developing kids hitting all their milestones, and just feeling like we never hit one. Feeding is still our biggest challenge. Learn to advocate hard for your baby. No one will be able to understand your child more than you. Take notes of everything, take videos of anything that worries you. Try not to worry so much about the 'what could happen' and take things day by day."

In this first year, one of the more common things our babies face is issues with feeding. They may not be eating well, be able to breastfeed or may require a special bottle if they are cleft affected, or require to be tube fed. As your baby grows, there may be more concerns about specially preparing foods if your baby has challenges with feeding and digestion (which could include issues with swallowing, smaller airways, risk of choking, reflux and constipation, which are all very common in our children.)

Children with ES typically develop slower than babies who do not have ES (especially if they have hypotonia, or weak muscle tone), but you may expect:

- During this year, most babies with ES learn to hold their head up (average by 8 months) and smile (as early as 2-4 months).
- Your child may learn to sit during these years. Most kids with ES sit independently between 13-36 months.
- Children with ES may learn to stand between the ages of 2 and 4.
- Only a small number of children with ES will be able to start learning to walk with support during these years, but most of our kids do learn to walk, at least with some support, but a bit later on (Carter et al., 2009).

This will be a time when you begin to start learning alternative communication methods. You will find that you have a lot of appointments, and become very busy attending therapies or medical appointments.





You may still be exploring medical concerns and seeing the doctor regularly to watch for growth, issues with feeding and digestion, and further tests to rule out any significant issues. See our infographic page which you can take to the doctor.

You will undergo hearing and vision screens, and get vaccinations.

You will start addressing developmental concerns. You will probably start getting referred to various therapists to ensure you do all you can to maximize your child's development (physiotherapy, speech, occupational therapy, music therapy and others). You will likely become involved with an early intervention specialist who can help you learn how to stimulate your baby physically and mentally. You will also likely begin work with a physiotherapist, especially if your baby has hypotonia (weak muscle tone).

"When they are babies and they are born not how you envisioned that is devastating. It's ok to feel those feelings. I also personally felt a lot of guilt that it was my fault I made a "messed up" baby because my genes are messed up. The appointments and unknown are very overwhelming. However, those snuggles quiet times with just you and baby probably in the middle of the night are totally worth it all. My daughter is 13 and I feel like even 13 years later there is so much more information and connection than there was before. Lean on a support group like ours or whomever you can relate to."

As parents, it is going to be a gradual acceptance of the new normal and becoming in tune with your child and what they need. The one thing that you will become is the expert on your child, be able to sense when things are off, and learn to use your instincts. Always listen to them. Your gut instincts are what will be developing and turning you into a strong advocate for your child.

"Our daughter was a year old when we received the diagnosis of ES. It took us a while to go through the various stages of grief and loss. As parents, ensure you reach out for your own support so that you do not get lost in the overwhelming amount of medical appointments for your child and the day-to-day challenges. Attending counselling and being temporarily on an anti-anxiety medication was so important for my own well-being. I remember my therapist saying, "You need to take care of yourself first and then take care of your child." At first, I thought this therapist was completely wrong; how on earth could I put myself first over my child with such extraordinary needs, but once I realized that if I were healthy mentally/physically, I could conquer what each day threw our way. There is no shame in assessing supports for mental health."

Your family and friends will be learning about your child, too. It may be an emotional first few months. You will be continuing to learn about ES and may choose to make connections with other parents.

For some of our children and their families, these early years may start out still feeling overwhelming, but gradually, you begin to feel more stable, and you start to really see your child's personality.

"The first two years were a lot to take in for us. Learning about a diagnosis that most doctors have never heard of and coming to an acceptance of how things will be different was hard. He had so many appointments close together in the first couple of years. It made it hard. They're all spread out more now so it's easier. You start to get into a new routine - your new normal."



It will be important to try to take time for yourself once in a while so that you can be strong and not get too overwhelmed.

Some of our parents wanted to share:

"I feel like I have so much to say on this. Not just for children with Emanuel syndrome, but for babies not born typically developing. There is just no support or insight into what to expect or 'now what?' when the baby arrives. It's terrifying. They are so vulnerable. You want to wrap them in a big bubble and keep everyone out. Well, my daughter was born during COVID-19 lockdown, in the height of the pandemic. There are so many health professionals to keep track of and expect you to match their pace and be an expert on your kid from day one. Get a diary. I use a day a week one, just to record conversations, write down

weight or times of unusual behaviour. Keep your medical reports together. Keep calm. TRUST YOUR GUT. Also, trust this group. Your kid is not a medical diagnosis. S/he is a baby, that needs love and cuddles and stories and play and walks with the dog and baking and cheering on their siblings and putting on fun costumes and making a mess and wearing the cute outfit... Just like every other baby. When we aren't



doing those hard stints in the hospital or in therapy, we're doing the regular family stuff. I think that's the bit I needed to hear at the start. The baby part still happens! It's tough seeing other toddlers toddle by. Say words. 'participate' more. But our kids teach us to listen harder, observe more closely. Celebrate the small stuff."

"How was I feeling? Scared. Mad. Frustrated. So many doctors, so many specialists and it seemed like every one of them just saw her as a number or an anomaly, and only cared about what milestones or growth chart she was failing at. But when she was 9 months old I finally had a specialist say to me "she's going to be exactly who she's supposed to be" and finally I believed it."

"We were completely out of our element at this age and because we did not have a diagnosis we still felt he would "grow out of it". Regardless, I did everything...home therapy, water therapy, feeding therapy....there's no shame in therapies!! Do them all, find what works. Also, start working with low tech or high tech AAC options - PECS are great!"

"Overwhelmed is what I think of. So much to absorb and figure out medically, mentally and financially. Every state is different so look on your Dept of Disabilities website or special needs groups, hospital social workers or our ES family. Achievements will be slow but celebrated no matter how big or small. You will learn from them what their needs are by every sound, facial expression, cry and movement. They will teach you something you never knew was possible or inside of you. You will be their biggest advocate."

"Exhausted and tired of being in the hospital. My daughter was in the hospital for most of her first 3 years. I would tell new parents to hang in there. Stay strong. Be your child's voice. And most importantly, it will get better."

"I love it when my child learns a new skill. Her milestones take much longer to achieve but I believe your hard work does pay off. Make sure your therapist believes in your child and continues to work with them. If you don't feel your child is getting the very best care, don't feel bad about being their advocate." While all children with ES will have delayed development, it is important to remember that even two children with the same diagnosis can develop at different rates. You may find it hard not to compare your child to others who do not have ES as you begin to notice that they do not always meet the milestones set out in all the baby guides. Don't forget to just ignore all that and enjoy your child.

Your child will benefit from going to playgroups and being as engaged as they can be in the world around them, exposing them to different sights, sounds, textures, people, animals, and places. The first three years are very important developmental years!



We know the first year can sometimes feel overwhelming. Please reach out to us during this time - we have all been there!



THE SCHOOL YEARS

The school years can be exciting but a bit daunting for parents of children with ES. There are so many considerations as our children go from ages 3-18.

School - will you homeschool or send them? Drive them or send them on the bus? Do they have medical concerns that require them to need extra care at school? Your child is going to need an Individualized Education Program or IEP.

Therapies - Speech and language, physio and occupational

and music therapies. These will be continuing and likely happen within the school setting.

Increasing support needs - As our children grow, not all of them will be on target developmentally for mobility, and we often need to provide more physical support. We may need to start thinking about mobility supports such as wheelchairs and walkers if you haven't already, or home modifications like ramps or home lifts.

Our children will also start to grow out of the diaper sizes they sell in the baby section, and we need to start looking at where we can access **briefs** that will fit.

Now that your child is also in the school system, you are going to likely become or learn strong **advocacy skills**.



As our children get older, you will start to really notice the differences in typical development from their peers. This may be hard on our hearts, and if your child has mobility issues, our bodies as well. We may also begin to start to feel the need to seek out respite care.

These years will be the time you may start to see your child make attempts at walking, especially as they begin or progress with therapies. Our children typically:

- Walk with support between 37-48 months of age
- Walk unsupported 97-150 months

(Carter et. al., 2009)

Here are some words shared by group members:

"From ages 4-present....things have been a roller coaster ride....but for my daughter mostly good.....she loves school, her friends,



teachers, and aides.....we are really lucky to have such an awesome school to send her to.....she really loves to show us all that she knows.....there are a lot of difficult things and one of the biggest headaches for us is lack of after school care.....we are fortunate we have found somebody that works within our schedule who will watch her after school....but if our sitter has something come up (sick, family emergency, or anything else) I need to take a half sick day (which are very few now because of Omicron)....on Long Island there are literally ZERO after-school programs for children with special needs and with both of us working full time (my wife a teacher, me 9-5) and our options are having her go to a place that does not have qualified/appropriate level of care she needs or we are on our own to find somebody."

"School age years are also tough when you see all the "normal kids" hitting all those milestones that yours may never hit. But watching them achieve their own goals is extremely rewarding. We were lucky we had a very small elementary school so almost all the kids embraced my daughter. They did an entire school assembly on 11/22 (Emanuel Syndrome Awareness) Day to explain her syndrome and just how rare she is. So getting school or therapy involved at making sure she was still involved was important to us. Don't ever be afraid to advocate for your kid; in school, therapy, doctor offices - you know them way better than any of those people. Listen to your gut or mom spidey senses. It's ok to have people think you are loud or pushy. They need you to be that so they can succeed because they will have to work so much harder. Never be afraid to ask for help."

"Big events like prom and graduation can be scary and sad. Luckily our school was fairly small so the girls (twins with ES) were invited to everything, but when you look around at the typical kids it makes it bittersweet. Thinking about what your kids should be doing but won't."

"My son is 6 years old and sometimes it's like the hurt is deeper at times when there younger there baby like and when you really start to see the differences and the kids joining sports and just there typical day at school and how your kids day looks totally different. Just had a IEP meeting and they talked about for 1 st grade what's going to fit [my son] more, as it will be more academic then being in Kindergarten and what won't fit. It's exciting hearing and seeing all his strengths and milestones but still sad at times not all the time. Definitely have your moments sometimes lonesome feeling. Our small school try's to do pretty good so far they have been."

My son is 11 and he is definitely more interactive with people than he was before. He knows when I'm telling a story about him, and giggles. I do notice how behind he is developmentally. I try to just remember that he is at his own stage. The difficult thing for us is finding people to watch him. My sitters

from before have a hard time lifting him. Needing a break is so important and very depressing if not able to get."

"My son attended public school from age 3 to 21. He had multiple different teachers until the last 7 years. He had the same teacher for those years, my best friend and his second mother. Our experience is not the norm. He participated in the graduation ceremony wearing the gown (refused the cap). His teacher walked with him."

"We are in the early stages of this and so far, it is the start of a marathon- an ultra marathon! The 0-3 years in our area were incredible! So much support, in-home therapies and a great preschool with more great teachers and therapists. My son is 6 now and in kindergarten. Turns out the school districts in our area are very anti-inclusion. They have a strategy of pushing special needs kids whose needs are more than mild into "county" schools. Away from our community and less socialization with typical peers. The gap of course is widening between james and his peers, but they are all still young enough to see james as james. It's been beautiful to see their interactions. But, it will be a fight to keep him in his neighborhood school. It's very stressful to have to fight for your child's basic rights. Pick your battles, but never give up!"

"My daughter's teachers, aides and therapists were all good. She usually had the same teacher for primary, middle and high school. She was in a contained class but always included in art, music, gym and lunch. Typical kids were always in the class helping. Take advantage of all the OT/PT/Speech etc that you could get and include it all in the IEP. Once they graduate it's harder to get. Get on a waiver so when graduation comes you can transition to adult programs. We didn't have many issues because she was so small and cute and received lots of attention. We had an incident where she was made fun of by a student and that student had to spend a week in her class on their lunch to get to know her. It was a great learning lesson for that student. We used a communication book so I knew how her day was, if she had any issues etc. The hardest thing is her not being able to communicate her day or hoping she learns a new skill or realizing it may never happen but excited when you see a new learned skill or improvement. My daughter graduated at 21 with her class also. It was very emotional for all of us."

Our group members will be here to help support you and share what has worked for them, and also share in some of the joys and accomplishments that your child will experience during this formative stage.

TRANSITION TO ADULTHOOD

Moving into adulthood, when your child is not able to be independent, can seem overwhelming. Many of the supports that are in place for children, such as school, therapies, recreational activities, respite services and case management, and especially, access to pediatricians and children's hospitals, end abruptly as our children age out of services. Our children are legally adults, but their needs have not changed. What will our children do once they are no longer in school?

A good plan is not to wait until your child is an adult. Start planning well in advance for the services they may need. Are there day programs available in your area? What types of supports will you need? Will you be able to stay home from work to care for your child? Will you consider residential care? Start talking to people involved with your child in their early teens. Make yourself aware of wait lists you may need to be on, services in your area, or changes to your life you may need to make to support your child at home.

Here are a few things that you will need to be prepared for:

- The move from children's specialists to adult health care, medical treatments, therapists. The focus is much different and less family-centered in adult care. Ensure referrals are done, paperwork is clear, and information shared with adult service providers.
- Loss of child programs, supports and activities. Are there programs or funding sources to help hire people to support your child in the community to continue to do meaningful daytime activities once school ends?
- Applying for Disability Benefits. Be aware of what you need to apply for, and the earliest you can apply. These will vary by country and state/ province.
- Applying for Guardianship (your child will not have the capacity to consent to you being their guardian, and you will need to go to court to apply for this when they become an adult.) Consult a lawyer for support in this area.
- Considering residential supports or group homes. While many of our families continue to care for their children at home well into adulthood, many parents have found excellent supports for their children in supported living settings. While this sounds scary, our children can find meaningful lives with peers and in settings that cater to their physical and recreational needs.



Valentina - age 41

 Estate planning. Talk to a lawyer who can ensure that wills and trusts (Things like a Henson Trust) are set up so that your child will not be

penalized should they inherit funds, and also, consider a power of attorney should you ever not be able to act on your child's behalf, should you become incapacitated.





Here are a couple of our newly transitioned adults!



"Tyler (L) was placed in a group home in 2021. He lives in a house with 3 other men with 24-hour care. He goes to a day center during the week where they socialize with many others and lots of activities. As hard as it was placing him there, I do see he is thriving. He is ready to go back after only one day visiting at home."

"Liam (R) moved into his own accommodation in 2022. He is sharing a supported flat with another male but within the block there are 3 other flats, so a right community for him. His first weekend and he had been invited out by the other male residents for a pub lunch. Liam started with shared care at 16, which was 3 weekends out of 4 with the wonderful Jenny. At

18, Liam moved there full time and was also supported by a team of 3 carers and home to us every 2nd weekend and holidays. He's settled in so well and the staff are really responding to him. His cheeky smile would get him anywhere!"



Adulthood doesn't have to be too intimidating if you plan ahead and prepare. Our parents will be happy to help and share their experiences.

TREATMENT

Your child will likely be followed by many different specialists throughout their life. Medical treatment will be specific for each child, depending on their medical needs. For example, children with cleft palates will need to be followed and undergo surgery by a plastic surgeon, those with heart defects may need to be followed by a cardiologist, and so on.

They will likely be seen by a geneticist for follow-up. This is partly to ensure that your child is monitored, and for you to obtain information on risks of being a t(11;22) carrier, but your child can teach the geneticist as well. Even genetics specialists, who tend to see the most rare conditions, may not have other patients with ES.

All of the children will require assessments by speech, physical and occupational therapists that can help them reach their full potential.





There is no cure for Emanuel syndrome, but there are

many things we can do to help our children be the best that they can be.

Some parents have asked if there is gene therapy to help our children, and unfortunately, there is not. Our children have many extra genes in every cell that affects how they develop and learn. Gene therapy is an experimental treatment for conditions that affect only one gene, such as Duchenne Muscular Dystrophy or cystic fibrosis, and it is usually aimed at replacing a missing or dysfunctional gene. In ES, there are "too many" genes, and there is no way to remove them. Even if we could remove them, the problems associated with ES are from abnormal development of organs, a process that occurs mostly before birth.



CONSIDERATIONS FOR UNDERGOING MEDICAL PROCEDURES

"My daughter's airway is so narrow (She has Pierre Robin sequence), that intubation is extremely difficult. We need to have any procedures done far from home, at a hospital that is capable of dealing with her airway concerns."

Like any person with a developmental disability, people with ES may require special attention when undergoing surgery. The most important person to talk to before surgery is the anesthesiologist. This doctor administers medication to induce sleep, and manages his or her airway and fluid balance during and after the surgery. You should be able to tell the doctor if your child has had difficulty with prior surgery, and make sure they know about any airway anomalies, heart and kidney problems, and allergies.

As a general rule, any test that requires sedation should be something that you talk to your doctor about. Make sure you and the doctor are aware of any airway concerns or potential negative reactions to sedative medications. Ask the doctor if the results of the test will change the treatment plan.

Many children with ES have had very difficult experiences with sedation and intubation for certain medical procedures. This is often due to the airway difficulties associated with clefts or high arched palates, small jaw, small airways, neurological and cardiovascular system issues, hemodynamic responses to anesthetic agents, and developmental delays.

Our children are "at high anaesthesia risk due to coexisting disorders and anatomical anomalies" (Kilic et. al., 2020).

It is important to discuss with your doctors that great care should be taken in this regard.

Care should be provided by an experienced pediatric anesthesiologist. Even many of our children who are adults, due to the nature of growth in some, require pediatric size equipment.

Many people with ES have been diagnosed with narrow airways, palate abnormalities (often in combination with Pierre Robin sequence) and laryngomalacia. Some have had difficulty following extubation with swelling and they have had serious breathing issues. This is a very important concern.

Some of the recommendations made by other doctors in recent literature include:

- Detailed preoperative evaluation including review of airway, craniofacial, cardiovascular, kidney, neurological (spinal cord) and other systems;
- Having an emergency tracheotomy set on hand during intubation;
- Consideration of the type of anesthetic agent used to avoid risk of agitation or seizures
- Consideration of the type of devices used for intubation.

OCCUPATIONAL THERAPY

Occupational Therapists (OT) work with people to support access to the activities of daily living. This ranges from tasks such as self-care to access to leisure activities education and work.

People with Emanuel syndrome may access an OT for a range of different reasons which







EMANUELSYNDROME.ORG



may include:

- Assessment and recommendations about appropriate equipment to support day-to-day care such as bathing and toileting equipment or specialist cutlery.
- Assessment and recommendations regarding specialist seating to promote head control and arm function.
- Exploring options for assistive technologies for example using switches or eye-gaze technologies for environmental control or communication.
- Assessment and support for fine motor skills development, particularly in the arm and hand e.g. writing, typing.
- Working with families, other therapists and professionals (e.g. Speech and Language Therapists, Physiotherapists, Teachers and Social Workers) to develop education and care plans.
- Assessment and support for sensory needs, sensory integration and sensory modulation.
- Support for carers using moving and handling techniques and equipment.



Aimee working on her pincer grasp.

OTs work across a range of services. You may meet through early intervention services, for equipment provision or in school. OTs also provided services that could be privately indeed or covered by insurance. How and where OT services are available will vary from country and country or region to region.



Nora doing homework, math and learning to write her name!



PAGE 61 OF 95

PHYSICAL THERAPY

Just like Speech and Occupational Therapy people with ES will need physiotherapy (Physical Therapy/ PT) support at different times and for different reasons during their life.

Some of the ways physiotherapists support people with ES are:

- Assessment of physical abilities and needs.
- Activities to develop physical skills, especially in the early and school years.
- Assessing and providing supportive equipment to aid mobility such as walking frames/ gait trainers, standing frames, orthotics and specialist footwear.
- Monitoring physical health for example hip and spinal alignment.
- Assessing equipment to support posture and physical well-being such as specialist seating/ sleep systems (also called 24-hour postural care).
- Working with other teams such as therapists and surgeons.
- Supporting respiratory wellbeing (chest/ respiratory physio

Evyn, Colin and Harper, all working hard!

SPEECH AND LANGUAGE THERAPY/PATHOLOGY

Speech and Language Therapists (SLT) go by lots of names across the world, Speech Language Pathologists, Logopaedie, Phoniatricians. They all have in common that they support people with Speech, Language, Communication, Eating and/ or Drinking Difficulties.

People with Emanuel syndrome may need support from an SLT throughout their life for a number of different reasons and in a number of different ways:

Assessment of communication.









- Assessment of eating and drinking skills.
- Providing programmes to support and develop communication.
- Providing programmes to support and develop eating and drinking skills.
- Making recommendations for safe eating, drinking and nutrition.
- Supporting the use of Alternative and Augmentative Communication (AAC) in people with no verbal communication or whose speech is hard to understand.
- Working with families, other therapists and professionals (e.g. Occupational Therapists, Physiotherapists, Teachers and Social Workers) to develop education and care plans.
- Training and coaching families and other professionals in how to support communication and eating and drinking.

Speech and Language Therapists work across a lot of different settings. You might first meet an SLT working with babies on feeding skills or in the cleft palate clinic, then in early years provision and later employed by schools or the school district. There are also SLTs who work privately either through direct payment or health insurance. Information about how to find and get in touch with an SLT is below and where and how it's provided and who pays will vary from country to country and region to region.

ASSISTIVE DEVICES

"Try to find out early the type of equipment your child will need to make his or her life better and start the process of applying for it or getting on waiting lists six months prior to needing it. It takes an extremely long time to get it approved."

What are assistive devices and what types of assistive devices do children with Emanuel syndrome need?

Children with Emanuel syndrome have a variety of needs and there will likely come a time when you may need to obtain something special to support your child.

Some of the more commonly seen assistive devices our children use are:

- **Mobility and positioning aids:** Many of our children use wheelchairs in different forms, walkers, standers, special car seats and adaptive vehicles to help with transportation, vehicle lifts and orthotics, standing frames, special seating and desks, special bath seats and lifts.
- **Hearing devices:** We have children with hearing aids and even a few who have cochlear implants.
- **Technology:** We have some children who are able to use special switches to work computer programs games, or for communication such as using a touch screen to choose words or pictures to help people understand what they need.
- assist with lifting to and from a bed or a bathtub.

- Home modifications: If your child requires a wheelchair, your home may need a ramp, or a special lift to

There are so many devices available now to help those with disabilities that there are almost too many to name here, and these are just a few common examples.







Who will help me assess what is right for my child?

Your child's own doctor will be a good start for this. They can make referrals to the people you need. You will likely have a physical therapist help support you with mobility aids, an occupational therapist support you with educational needs, and a speech therapist support you with communication devices. What you need will of course depend on the nature of your own child's needs.

How will we pay for the equipment that we need?

This will depend on where you live in the world. In Ontario, for example, there is a program called the Assistive Devices Program that helps fund special equipment. There are also various charity organizations that may offer grants to help pay for things. As the scope of our group is international, it's impossible to list all the places here, but your child's therapists can assist you in identifying how to pay for any assistive devices they may need.

What other kinds of things will my child need as he gets older?

Most of our children do not develop independent toileting habits and require briefs and incontinence supplies. There may also financial supports for these depending on where you live. In Ontario, Canada, for example, Easter Seals provides an Incontinence grant. You will need to inquire with your child's treatment providers about the available financial support where you live.

MUSIC THERAPY



Who doesn't love music? Music is something our children enjoy so much. We can sing together, play music and instruments during play time, or engage them in a more therapeutic way, through music therapy.

"Music and love are the doors to his heart and reason. We started with the Baby Einstein DVDs when he was a baby and he recognizes many Beethoven, Bach, and Mozart music. Whenever he is out of control, music happens to be a great help. Music always helps to stop a bad mood or a frustration episode."



Music therapy is an evidence-based therapy. There are so many benefits!

- Improved communication and sensoimotor skills
- Enhanced learning
- Improved attention and expression
- Increased motivation to participate in social interactions

- Fostering relationships
- Improved brain development
- Improved behaviour and positive impacts on mood
- Joy!

Many of our children benefit from music therapy in school settings, but there may be additional music therapy services in your area. Or, take them to a concert!



Kids with ES are, after all, just kids! They love to do what we are doing - get them involved in as many things as you can and see what they love! This is our favourite page - we are showing how much fun our kids have and how much fun we have with them!

HIPPOTHERAPY AND THERAPEUTIC RIDING

Hippotherapy is more an actual therapy that integrates aspects of physical, occupational and speech therapy. Therapeutic Riding is more horse riding adapted for those with special needs and also has fantastic benefits. Our kids love it!





Madison LOVES concerts.



SWIMMING



HANGING OUT AT THE PLAYGROUND





COOKING







ENJOYING THE BEACH

















GARDENING / FARM





BIKING



PETS /ANIMALS



BOWLING





TRAVELING



MINI PUTT



MOVIES!

FUN IN THE SNOW!





HOCKEY!

BOATING!





CLIMBING SAND DUNES AND BEING A MERMAID FOR THE DAY!





RESPITE CARE

If you are caring for a child or adult with exceptional medical or developmental needs, you may need additional support or a break from time to time. Respite care is a way for parents and caregivers to receive this support by having others help support your family member temporarily.

Utilizing respite care can help a parent or caregiver attend to activities outside the home, spend time with other children, recharge, avoid caregiver burnout, and potentially, a crisis. It is not lazy parenting, or shirking your responsibilities. It can be a necessary support for many families and a choice to be proactive to keep you well, so you can keep doing the remarkable job you are doing to care for your family member.



Respite care can be provided within the family home, or outside the home. Depending on available services where you live, there may be agencies that have apartments or people who will provide respite care in their own homes, day programs or programs that offer extended respite services so you can take a vacation. Due to the international nature of our group, it is not possible to list all places here. There may be government funding, local service agencies or insurance that will help you access this type of care.

For example, in Ontario, Canada, there are government programs that help families pay for such care, and these will be different for children and adults. One such service is Developmental Services Ontario, which supports adults with disabilities.

Families and friends can also help provide informal respite support. Do you have people in our support circle you can turn to for support?

Many of us will be providing high levels of support for many years. While we love our family members, sometimes the break respite offers can help us recharge, help us find balance in our own lives, and give us the needed break to keep providing care to our family members for the long-term. We may not want to recognize that our mental or physical health can be suffering as we support our loved one. Sometimes we have to provide more physical care than a typical parent. We may be developing anxiety or depression. Caregiver burnout is very real and respite care can help you to avoid this.

As our children get older, we often worry about how to provide a high level of care long-term. Some of our families have successfully transitioned their adult children into supportive living homes.

PALLIATIVE, HOSPICE AND END OF LIFE CARE

Children and adults living with Emanuel syndrome may experience serious illness.

There are children born with serious medical issues such as complex heart conditions, congenital diaphragmatic hernias, and medical issues such as poorly functioning kidneys, among other medical problems, that may be life-threatening or life-limiting. Sometimes, even with the best medical intervention, a child with ES may be given a poor prognosis or require intensive medical care.

PALLIATIVE CARE VERSUS HOSPICE CARE

Palliative care is specialized medical care that can improve the quality of life for a person living with a serious or life-threatening illness by addressing both symptoms and the stress resulting from the illness. It is individualized, family-centred and mistakenly, often thought of as only end-of-life care. In fact, palliative care can be provided when there are treatments intended to cure an illness. It is care provided by a team of providers, typically within the family home, that helps address not only the person with the illness but the distress the illness may have on the individual and their family.

Hospice care is provided when there are no longer treatments available for the person living with the illness, and the focus moves to the reduction of pain and suffering of the individual. It is also provided by a team of specialists who help a family support an individual through to the end of life.

Having to consider palliative or hospice care is an unimaginable discussion for a parent, but one that is okay to discuss with your medical team.

There are members of our group who have had to make these difficult decisions. You can connect with some of our families by joining our discussion group on Facebook.

LOSING A CHILD

One of the hardest things to face as a parent is the loss of a child. Children with Emanuel syndrome can experience life-threatening illness or birth defects.

There are members in our group who have lost children at all ages. Some as a newborn, others as adults. Sometimes it is after a lengthy illness and it is expected, and sometimes it happens suddenly and we cannot prepare. The one thing that our parents have in common is the meaning made from the life of their child, however long it may be. Even after your child is no longer with you, the support from our group continues. We are a small group and much like family, every loss is deeply felt by our community.

How can we make sense of such losses? Parenting is central to our existence. It provides us identity. Our children are supposed to carry a part of us into the future. We are supposed to protect our children, and sometimes we cannot save them. But we can honour them and remember them:

• For a newborn, hold and name your baby. Have a memorial service.



- Take photos. Make hand and footprints.
- Keep reminders of your child—a lock of hair, some clothing.
- Find a way to memorialize your child—a memento to keep with you, plant a tree, release butterflies or balloons, tell others about your child—write about them, get a tattoo. There are so many ways to keep their memory alive .

Talking to others who have gone through this experience can help. Your child was loved and valued. They mattered.

AWARENESS

Emanuel Syndrome Awareness Day is November 22.

We chose the 11th month and 22nd day for our Awareness Day, to represent chromosomes 11 & 22 which are involved in Emanuel Syndrome (ES). We have been holding our annual awareness day since 2010 and use this opportunity to share photos, stories, facts and hold events to share about our amazing children and make people aware of this rare chromosome 22 disorder.

While carriers of the balanced 11q22q translocation are quite common (it is the most common recurrent balanced reciprocal translocation known in humans), Emanuel syndrome, the unbalanced version of the translocation, is considered a rare chromosome disorder.

While disorders like Down syndrome occur in 1 in 800 births, Emanuel syndrome is far more rare. There have been more than 275 cases reported in the scientific literature since it began to emerge as a disorder dating back to the early 70s (and some cases from the late 60s which cannot be definitively confirmed). It is estimated to occur in 1 in 110,000 live births (Ohye et al, 2014).



Emanuel SYNDROME

Each year on November 22 (and in the weeks leading up to the day) we take the time to post about Emanuel Syndrome on Facebook and Instagram, tweet, share statistics, information, articles, photos, videos, stories, make the local paper, host online meetings in different time zones, hold fundraisers, have family meet-ups and marvel at the worldwide flood of "purple and blue on 11/22".

Once upon a time, our disorder was unnamed and it was difficult for families to connect with each other. Now, we have members all over the world and we celebrate as one big family. We embrace and continue to extend and grow the community that we have built for our family members with ES and educate others about the 11/22 translocation and Emanuel syndrome.

We invite you to join us!

How can you participate? Share your photos and child's bio with us and we will add you into our yearly photo blitz in the template we use that year. Here are examples of of our past campaign bios:



From Canada to Japan and everywhere else in between, we continue to raise awareness about this rare chromosome disorder year after year.



Want to learn more? Participate? Contact us at c22central@gmail.com and we will get you set up!


RESEARCH



Many of our members have been very interested in supporting researchers to advance our understanding of Emanuel syndrome and the 11;22 translocation. For example, members have previously participated in research by sending blood samples as t(11;22) carriers;

Long AT-rich palindromes and the constitutional t(11;22) breakpoint Hiroki Kurahashi, Beverly S. Emanuel *Human Molecular Genetics*, Volume 10, Issue 23, 1 November 2001

Alu-mediated PCR artifacts and the constitutional t(11;22) breakpoint Hiroki Kurahashi, Tamim H. Shaikh, Beverly S. Emanuel *Human Molecular Genetics*, Volume 9, Issue 18, 1 November 2000

Regions of genomic instability on 22q11 and 11q23 as the etiology for the recurrent constitutional t(11;22)

Hiroki Kurahashi, Tamim H. Shaikh, Ping Hu, Bruce A. Roe, Beverly S. Emanuel, Marcia L. Budarf. *Human Molecular Genetics*, Volume 9, Issue 11, 1 July 2000

Tightly Clustered 11q23 and 22q11 Breakpoints Permit PCR-Based Detection of the Recurrent Constitutional t(11;22) Hiroki Kurahashi, Tamim H. Shaikh, Elaine H. Zackai, Livija Celle, Deborah A. Driscoll, Marcia L. Budarf and Beverly S. Emanuel.

American Journal Human Genetics. 2000 Sep; 67(3)

People have helped by answering surveys to contribute to the shared understanding of medical and developmental considerations of Emanuel syndrome or being a carrier of t(11;22);



Phenotypic Delineation of Emanuel Syndrome (Supernumerary Derivative 22 syndrome): Clinical features of 63 individuals. Melissa T Carter, Stephanie A St. Pierre, Elaine H Zackai, Beverly S Emanuel, and Kym M Boycott. *American Journal of Medical Genetics*. 2009

Risk of Breast Cancer Not Increased in translocation 11;22 carriers: Analysis of 80 pedigrees. Melissa T Carter, Nicholas J Barrowman, Stephanie A St. Pierre, Beverly S Emanuel, and Kym M Boycott. *American Journal of Medical Genetics.* 2010.

Or by submitting photographs to help with developing technology:

Next generation phenotyping in Emanuel and Pallister-Killian syndrome using computer-aided facial dysmorphology analysis of 2D photos

T. Liehr, N. Acquarola, K. Pyle, S. St-Pierre, M. Rinholm, O. Bar, K. Wilhelm, I. Schreyer. Clinical Genetics

From time to time, we will share information about study requests from researchers through our social media groups and encourage families to join in the efforts to expand our knowledge. There is never any obligation to participate in any of these studies.

There have been many articles written both on Emanuel syndrome (previously cited in literature as partial trisomy 11;22, supernumerary der (22) syndrome etc., as well as the 11/22 translocation.) We have compiled a fairly comprehensive list of these articles with links to either the abstract or full articles, if available. These articles go back several decades and show an evolving understanding of the 11q;22q translocation and the rare chromosome disorder we have come to know today as Emanuel Syndrome. You can find the resources on our website, emanuelsyndrome.org.



RAISING THE GODDESS OF SPRING



In 2021, Stephanie Rese, founder of C22C, along with Dr. Melissa Carter and current C22C President Murney Rinholm, published *Raising the Goddess of Spring: A guide for parents raising children with rare chromosome disorders.* Many of the parents who contributed to the book have children with Emanuel syndrome and are also carriers of the t(11;22).

In addition to serving as a guide for parents, it is also a fundraiser for our group, with all proceeds donated directly to Chromosome 22 Central. The book is available internationally on Amazon both in print and ebook.

While this guidebook on Emanuel syndrome does cover a lot, Raising

the Goddess of Spring goes more in depth on many information topics such as learning the basics of chromosomes and disorders, parent advocacy, learning to adjust and tips to cope day to day, how to manage your mental health, communication with others about your child's disorders, planning for the future and more, and was written with you in mind by a parent of a child with ES.

ABOUT THE BOOK:

More children than ever before are being diagnosed with rare chromosome disorders and surviving not only to birth, but well into adulthood. The most common chromosome disorder is Down syndrome, which occurs in 1 out of 700 babies, however, there are hundreds of others that are individually rare, but collectively common. This book serves as a guide for parents new to the world of rare chromosome disorders.

Raising the Goddess of Spring shares the story of Stephanie and her daughter Maia, who was diagnosed with a rare chromosome disorder in 1995. Stephanie is the founder of Chromosome 22 Central, an international parent support group, as well as being a Registered Social Worker. Contributors Dr. Melissa Carter and Murney Rinholm, are well-established experts in their fields.



Melissa Carter, MD, is a Clinical Geneticist specializing in Developmental Disabilities, working out of the Children's Hospital of Eastern Ontario in Ottawa, Ontario. She is currently an Associate Professor at the University of Ottawa, Department of Pediatrics.

Murney Rinholm has been president of Chromosome 22 Central since 2002. She is a mother to a son with Emanuel syndrome. She has experience as a special education teacher and paralegal specializing in estates and guardianships. She has also served as a past parent & family advocate for the State of North Carolina's Office of Emergency Medical Services.



Together, the authors combine a wealth of experience in parenting, advocacy, mental health, special education, estates and benefits, clinical genetics, and child development.

Dr. Beverly Searle, former CEO of the international support group, Unique - the Rare Chromosome Disorder & Gene Disorder Support Group, based in the UK, has written the foreword for the book.

Stephanie's journey, along with stories from other parents, is woven around explanations of chromosomes, advice on common medical and developmental concerns, as well as covering reproductive issues for carriers of chromosome differences. Raising the Goddess of Spring also discusses relationships, planning for the future, and child loss. You will learn how to manage your mental health and find humour and joy in raising your child. You will also learn how to find your strengths, become a fierce advocate, and build resilience along the way.

This book will be of interest to parents of children who have rare chromosome disorders, as well as physicians, nurses, genetic counsellors, developmental therapists, special education teachers, or anyone who is involved in the care and support of children with rare chromosome disorders.

"In this remarkable book, Stephanie has compiled a wealth of valuable and insightful information for parents affected by the diagnosis of a rare chromosome disorder in their child. She tackles many topics from the perspective of her own experience as the parent of her lovely "goddess of spring," Maia. Touching on the long-term emotional impact of Maia's diagnosis, she has helped point the way for others towards understanding and to the identification of often needed support resources for immediate and long-term issues. This is a book that acts as a guide to assist parents and families today and for their future. I am honored to partner in research with Stephanie and this extraordinary group of children and adults."

> -Dr. Beverly Emanuel, Professor of Pediatrics University of Pennsylvania School of Medicine The Children's Hospital of Philadelphia, Division of Human Genetics

From the Foreword:

"Stephanie has not shirked from tackling some of the most sensitive and intimate subjects and thoughts that families often encounter. From the moment of diagnosis through the different stages and events of their changed forever lives and beyond."

-Dr. Beverly Searle, CEO (former)

UNIQUE, The Rare Chromosome and Gene Disorder Support Group, UK

Check out the reviews on Amazon - leave one once you are done! Thanks for your support!

BECOMING YOUR CHILD'S ADVOCATE



When you have a child who has extra needs, you might not always have everything you need to help them be the best that they can be. Our children will need additional resources, and sometimes you have to work hard to make sure they get them. People may not automatically know what your child needs, and you are going to be stepping up to express concerns and offer suggestions to others involved in supporting your child in the community, the school, or with their medical care team.

Advocacy will happen in many different ways. It will involve

learning about and teaching others about your child's disorder and what they need; it will be ensuring that your child gets all the services and benefits they are entitled to; it may be ensuring they get proper medical care and getting second and or third opinions; it may mean ensuring that your child gets what they need for their school success - advocacy can look like a lot of things.

You will learn to know when your child is not getting what they need and you will find ways to become an effective communicator, how to be proactive, organized, well-prepared, collaborative and strong. You will become the voice of your child.

Not everyone comes with a natural skill set to become a strong advocate for their child, and so we are offering a few recommendations that may help. The resources may be specific to different diagnoses like autism but they will be universally relevant. There are many websites you can search for in addition to these which are great places to start. Visit our website for the links.

If you need support, encouragement or motivation, connect with other parents on our social media sites. Likely someone has already walked the same path and can offer some advice when you need it.

"Advocate for what you need, utilize all the resources - they won't just give you everything. I learned slowly but surely I have to fight and appeal for all his needs."

CONNECT

Now that you are part of the family, there are a few ways you can connect with us.

- Join our Facebook group Emanuel Syndrome and the 11/22 Translocation
- Join our Facebook group just for carriers (t11;22 and others) C22C Carriers
- Join our main Facebook group C22C International Supporting all chromosome 22 disorders
- Like our C22C Facebook Page
- Follow C22C on Instagram @chromosome22central
- Follow us on Twitter @C22Central
- Find us on YouTube Chromosome 22 Central
- Follow us on LinkedIn Chromosome 22 Central
- Subscribe to our Blog, and share your story c22central.blogspot.com/

Or email us at c22central@gmail.com. We can set up a time to talk to you by phone or video if you have questions or need support.

We can't wait to meet you!



CONTACT

CHROMOSOME 22 CENTRAL



Murney Rinholm, President

1129 Carolina Gardens Ave., Fuquay-Varina, North Carolina, 27526 USA

EMAIL: c22central@gmail.com tel: 919-762-7979

Contact Murney if you have questions about donations or C22C operations.



Stephanie Rese, Founder

338 Spruce Street North Timmins, Ontario, Canada P4N 6N5

Email: c22central@gmail.com

Contact Stephanie if you want to submit information to share about research studies, events, or have general inquiries.

Murney & Stephanie are parents of adult children with Emanuel syndrome.

GLOSSARY OF TERMS

Amniocentesis – a medical test involving the insertion of a needle into the uterus through the abdomen in order to remove a small amount of amniotic fluid, which is then tested for genetic abnormalities. It is typically performed between 15-18 weeks gestation.

Anal Atresia – also known as imperforate anus. It is an abnormal or incomplete development of the anorectal region.

Aspiration (pulmonary) – when food or secretions enter the lungs. Aspiration can be direct or due to reflux. Tube feeding may be needed to prevent aspiration. Aspiration can cause pneumonia, and over time recurrent aspiration can lead to significant lung damage.

Atrial septal defect (ASD) – a hole in the wall between the two upper chambers of the heart.

Balanced translocation – when two chromosomes have pieces break off and switch places with each other. No genetic material is missing or extra.

Bifid uvula – the uvula is the fleshy part of the soft palate that hangs at the back of the throat. Sometimes it can appear to be split in two.

Cat Eye Syndrome - a syndrome in which the entire short arm and a small area of the long arm of chromosome 22 to the breakpoint 22q11.2, is present either three or four times, rather than just twice. It can result in colobomas of the eyes, defects in the heart, kidneys and anal region, and possible cognitive impairment.

Cerebellum – the area of the brain that regulates balance and coordination.

Cerebral Atrophy – a loss of neurons and connections in the brain.

Corpus Callosum – the part of the brain that connects the right and left hemispheres.

Chromosome – a structure made of DNA and proteins which contains genes and is found in cells.

Cleft palate – when the roof of the mouth (palate) fails to form completely during fetal development, and leaves an opening.

Chiari Malformation – a structural defect of the cerebellum.

Chorionic villus sampling (CVS) – a form of prenatal testing in which a small piece of placental tissue is obtained and tested for genetic abnormalities. It is usually done between 10-12 weeks gestation.

Coarctation of the Aorta – a narrowing of the aorta at some point. The aorta is the largest artery of the body, and carries blood away from the heart.

Cochlear Implant – an electronic device that is surgically implanted within the cochlea, which is part of the inner ear. A receiver is worn behind the ear. which can provide the perception of sound for people with profound deafness.

Conductive (hearing loss) – hearing loss caused when sound waves cannot travel from the outer ear to the inner ear. The most common cause of this is fluid accumulation behind the eardrums.

Cryptorchidism – also known as undescended testicles – it is a condition where the testicles fail to move from the pelvis into the scrotum near the end of gestation.

Dandy Walker Malformation – a brain malformation involving the cerebellum and area surrounding it. It can include enlargement of the fourth ventricle of the brain, partial or complete absence of the cerebellar vermis, as well as the presence of a cyst at the base of the skull.

De novo occurrence – the arising of a genetic abnormality that was not inherited from either parent.

Diaphragmatic Hernia – an abnormal opening in the diaphragm that allows organs from the abdominal region to enter the area near the lungs and heart.



Duane Syndrome – an eye condition in which there is a problem with the eye muscles, and a person has limited ability to move the eye outwards (towards the ear) and sometimes inwards (towards the nose)

Dysmorphic – a medical term used to describe a body structure that is indicative of a difference in embryonic development. IE – sometimes our children are described as having "dysmorphic features" such as low-set ears.

FISH – Fluorescence *in situ* hybridization - a technique in which fluorescent probes are used to discover specific areas that may be missing or extra on a chromosome.

Glaucoma – increased inner eye fluid pressure that can lead to blindness if left untreated.

Glossoptosis – a downward displacement of the tongue towards the back of the throat, which in severe cases can cause airway obstruction.

Hydrocephalus – excess fluid in the brain which can cause brain damage due to increased intracranial pressure.

Hypothyroidism – a decrease in production of the thyroid hormone.

Hypotonia – low muscle tone.

Immunoglobulins – proteins in the blood that are used by the immune system to fight viruses and bacteria.

Intrauterine growth restriction – poor growth of the baby during pregnancy.

Intestinal Malrotation – a developmental defect of the bowel in which the intestines are improperly rotated within the abdominal cavity, which can lead to bowel twisting and obstruction.

In vitro fertilization – a medical procedure in which egg cells are fertilized by sperm outside of the body, and then implanted into the womb (uterus).

Imperforate Anus – also known as anal atresia. The anus is malformed and the opening is missing or blocked.

Joint Contractures – stiffness of the joints that prevents them from fully extending or flexing.

Karyotype – an individual's chromosomes usually presented in an image and number form, which will explain any genetic abnormalities. A normal karytoype will read 46,XX for a female, or 46,XY for a male.

Kyphosis – a forward curvature of the upper spine.

Microcephaly – a smaller than usual head size.

Micrognathia - a smaller, underdeveloped jaw.

Microtia – a deformity of the outer ear, in which it is small and may be undeveloped or absent.

Nuchal Skin – skin behind the neck. In children with ES, excess neck skin is sometimes seen at birth.

Nystagmus – involuntary movements of the eyes.

Oligohydraminos – during pregnancy, less amniotic fluid is present than should be.

Optic Atrophy – loss of some of the optic nerves, affecting vision.

Otitis Media – middle ear infection.

Patent Ductus Arteriosis (PDA) – typically seen right after birth, it is a defect causing abnormal blood flow between the two major arteries connected to the heart.

Pierre Robin Sequence – a combination of a U-shaped cleft palate, a small under-developed jaw, and downward displacement of the tongue towards the back of the throat.

Philtrum – the area of skin between the nose and the upper lip.

Preimplantation genetic diagnosis – during the IVF process, screening of embryos for genetic problems, before implantation into the womb.



Pulmonic Stenosis – An obstruction of the outflow of blood from the right ventricle of the heart. It can reduce the flow of blood to the lungs.

p arm – The short arm of a chromosome.

q arm – The long arm of a chromosome.

Reciprocal translocation – an equal exchange of genetic material between two chromosomes.

Sacral dimple – a small indentation found in the skin at the base of the spine. It can sometimes mean a problem with the spinal cord and should be investigated.

Scoliosis – a lateral curvature of the spine.

Sensorineural hearing loss – when damage to the inner ear (cochlea) or nerves that take sound to the brain are damaged or malformed. It causes permanent hearing loss.

Skin tags – small pieces of extra skin. In people with ES, they are often seen at birth on the face or ears.

Strabismus – an eye condition wherein the eyes turn in or out involuntarily.

Submucous cleft palate – a cleft palate that is covered by a mucous membrane on the roof of the mouth, making the cleft difficult to see.

Supernumerary der(22) syndrome – Another term for Emanuel Syndrome.

Tetralogy of Fallot – a heart condition which includes the following four defects:

A Ventricular septal defect, pulmonic stenosis, right ventricular hypertrophy and an overriding aorta.

Thrush – a yeast infection on the mouth and tongue.

Torticollis – a twisting of the neck where the head is tilted to one side.

Total Anomalous Pulmonary Venous Return (TAPVR) – a heart malformation where the four pulmonary veins do not connect properly to the left atrium of the heart, and drain abnormally to the right atrium.

Ventricular Septal Defect (VSD) – a heart defect where there is a hole in the wall between the two bottom chambers of the heart.

Ventriculomegaly – enlargement of the lateral ventricles of the brain.

Vesicoureteral reflux – an abnormal flow of urine from the bladder, back to the ureters. It can lead to kidney damage if untreated.

REFERENCES

Abeliovich, D., & Carmi, R. (1990). The translocation 11q;22q: a novel unbalanced karyotype. *American Journal of Medical Genetics*, 37(2), 288. https://doi.org/10.1002/ajmg.1320370227

Adams, L. E., Chapman, A., Cormack, C. L., Campbell, K., Ebanks, A. H., Annibale, D. J., & Hollinger, L. E. (2021). Emanuel syndrome and congenital diaphragmatic hernia: A systematic review. *Journal of Pediatric Surgery*, S0022-3468(21)00777-6. Advance online publication. https://doi.org/10.1016/j.jpedsurg.2021.11.005

Afroze, B., Ngu, L. H., Roziana, A., Aminah, M., & Noor Shahizan, A. (2008). Supernumerary derivative (22) syndrome resulting from a maternal balanced translocation. *Singapore Medical Journal*, *49*(12), e372–e374. http://smj.sma.org.sg/4912/4912cr11.pdf

Alfi OS, Sanger RG, Donnell GM. 1975. Trisomy 22: A clinically identifiable syndrome. *Birth Defects* Orig Artic Ser. 11:241-245.

Allanson J. E. (1993). Unusual segregation for 11q;22q parental translocation. *Prenatal Diagnosis*, 13(9), 889–891. https://doi.org/10.1002/pd.1970130915

Allotey, J., Lacaille, F., Lees, M. M., Strautnieks, S., Thompson, R. J., & Davenport, M. (2008). Congenital bile duct anomalies (biliary atresia) and chromosome 22 aneuploidy. *Journal of Pediatric Surgery*, *43*(9), 1736–1740. https://doi.org/10.1016/j.jpedsurg.2008.05.012

Annerén, G., & Gustavson, K. H. (1981). Trisomy 22 syndrome in a 26-year-old female--A follow-up examination. *Hereditas*, 94(1), 67–71. https://doi.org/10.1111/j.1601-5223.1981.tb01733.x

Anton, E., Vidal, F., Egozcue, J., & Blanco, J. (2004). Preferential alternate segregation in the common t(11;22)(q23;q11) reciprocal translocation: sperm FISH analysis in two brothers. *Reproductive Biomedicine Online*, *9*(6), 637–644. https://doi.org/10.1016/s1472-6483(10)61774-9

Antonenko V.G., Svetlychnaya D.V., Djurcova N.V., Haritonova N.A., Shilova N.V. A case of Emanuel syndrome on a newborn girl with congenital heart defect. *Medical Genetics*. 2019;18(9):34-39. (In Russ.) https://doi.org/10.25557/2073-7998.2019.09.34-39

Armstrong, S. J., Goldman, A. S., Speed, R. M., & Hultén, M. A. (2000). Meiotic studies of a human male carrier of the common translocation, t(11;22), suggests postzygotic selection rather than preferential 3:1 MI segregation as the cause of liveborn offspring with an unbalanced translocation. *American Journal of Human Genetics*, *67*(3), 601–609. https://doi.org/10.1086/303052

Ashley, T., Gaeth, A. P., Inagaki, H., Seftel, A., Cohen, M. M., Anderson, L. K., Kurahashi, H., & Emanuel, B. S. (2006). Meiotic recombination and spatial proximity in the etiology of the recurrent t(11;22). *American Journal of Human Genetics*, *79*(3), 524–538. https://doi.org/10.1086/507652

Aurias, A., & Laurent, C. (1975). Trisomie 11q. Individualisation d'un nouveau syndrome [Trisomy 11q. Individualization of a new syndrome]. *Annales de Genetique*, *18*(3), 189–191.

Aurias, A., Turc, C., Michiels, Y., Sinet, P. M., Graveleau, D., & Lejeune, J. (1975). Deux cas de trisomie 11q(q231 leads to qter) par translocation t(11;11) (q231;q111) dans deux familles différentes [2 cases of trisomy 11q(q231--qter) by translocation t(11;22) (q231;q111) in 2 different families]. *Annales de Genetique*, *18*(3), 185–188.

Ayraud, N., Galiana, A., Llyod, M., & Deswarte, M. (1976). Trisome 11q (q23.1 leads to qter) par translocation maternelle t (11.1). Une nouvelle observation [Trisomy 11 q (q23.1 - qter) through maternal translocation t(11;22) (q23.1;q11.1). A new case]. *Annales de Genetique*, *19*(1), 65–68.



Babu, K. A., Verma, R. S., Nigam, R. B., & Alsheikh, S. N. (1986). Precise location of breakpoints in a frequent reciprocal translocation between chromosomes 11 and 22. *The Journal of Heredity*, 77(1), 63–64. https://doi.org/10.1093/oxfordjournals.jhered.a110175

Balci, S., Engiz, O., Yilmaz, Z., & Baltaci, V. (2006). Partial trisomy (11;22) syndrome with manifestations of Goldenhar sequence due to maternal balanced t(11;22). *Genetic Counseling (Geneva, Switzerland)*, *17*(3), 281–289.

Bartsch, O., Loitzsch, A., Kozlowski, P., Mazauric, M. L., & Hickmann, G. (2005). Forty-two supernumerary marker chromosomes (SMCs) in 43,273 prenatal samples: chromosomal distribution, clinical findings, and UPD studies. *European Journal of Human Genetics: EJHG*, *13*(11), 1192–1204. https://doi.org/10.1038/sj.ejhg.5201473

Beedgen, B., Nützenadel, W., Querfeld, U., & Weiss-Wichert, P. (1986). "Partial trisomy 22 and 11" due to a paternal 11;22 translocation associated with Hirschsprung disease. *European Journal of Pediatrics*, 145(3), 229–232. https://doi.org/10.1007/BF00446075

Benítez J, Ayuso C, Garcia Aparicio J, Saez E, Perez Sotelo A, Bello MJ. 1981. Trisomía parcial 11q;22;. Aportación de dos nuevos casos en dos familias portadoras de translocatión. *An Esp Pediatr* 15:293-300.

Biederman, B. M., Lin, C. C., Lowry, R. B., & Somerville, R. (1980). Tertiary trisomy (22q11q),47,+der(22),t(11;22). *Human Genetics*, *53*(2), 173–177. https://doi.org/10.1007/BF00273491

Bofinger, M. K., & Soukup, S. W. (1977). Cat eye syndrome. Partial trisomy 22 due to translocation in the mother. *American Journal of Diseases of Children (1960)*, *131*(8), 893–897. https://doi.org/10.1001/archpedi.1977.02120210071015

Boué, A., & Gallano, P. (1984). A collaborative study of the segregation of inherited chromosome structural rearrangements in 1356 prenatal diagnoses. *Prenatal Diagnosis, 4 Spec No*, 45–67. https://doi.org/10.1002/pd.1970040705

Blancato, J. K., Eglinton, G., George, J., Benkendorf, J., Pinckert, T., & Meck, J. (1995). Prenatal diagnosis of partial trisomy through in situ hybridization on amniocytes with whole chromosome and centromere-specific DNA probes. A case report. *The Journal of Reproductive Medicine*, *40*(7), 537–539.

Borooova, I., Bernasovsky, I., Bernasovska, J., & Puschauerova, M. (2017) Constitutional Translocation t(11,22) in Slovak Romanies from the Prešov Region (Slovakia). Pages 1-4 | Published online: 17 Oct 2017 https://doi.org/10.1080/09720073.2008.11891021

Carter, M. T., Barrowman, N. J., St Pierre, S. A., Emanuel, B. S., & Boycott, K. M. (2010). Risk of breast cancer not increased in translocation 11;22 carriers: analysis of 80 pedigrees. *American Journal of Medical Genetics. Part A*, *152A*(1), 212–214. https://doi.org/10.1002/ajmg.a.33166

Carter, M. T., St Pierre, S. A., Zackai, E. H., Emanuel, B. S., & Boycott, K. M. (2009). Phenotypic delineation of Emanuel syndrome (supernumerary derivative 22 syndrome): Clinical features of 63 individuals. *American Journal of Medical Genetics. Part A*, 149A(8), 1712–1721. https://doi.org/10.1002/ajmg.a.32957

Chandley A. C. (1992). Involvement of 3:1 disjunction in the common reciprocal translocation t(11;22) (q23.3;q11.2). *Human Genetics*, *90*(1-2), 191–192. https://doi.org/10.1007/BF00210779

Chauveau, P., Gruchy, D., Herouin, C., & Levesque, L. (1980). A propos d'une nouvelle observation de trisomie 11q secondaire a une translocation maternelle t(11;22)(q23.1;q11.1) [A new observation of trisomy 11q due to t(11,22)(q23.1; q11.1) mat (author's transl)]. *Annales de Genetique*, *23*(4), 213–215.

Chen, C. P., Liu, F. F., Jan, S. W., Yang, Y. C., & Lan, C. C. (1996). Prenatal diagnosis of supernumerary der(22)t(11;22) associated with the Dandy-Walker malformation in a fetus. *Prenatal Diagnosis*, *16*(12), 1137–1140. https://doi.org/10.1002/(SICI)1097-0223(199612)16:12<1137::AID-PD979>3.0.CO;2-K



Chen, C. P., Wang, T. H., Chang, T. Y., Lee, C. C., Chen, W. L., Chen, L. F., & Wang, W. (2006). Prenatal diagnosis of the supernumerary der(22)t(11;22) syndrome associated with abnormal sonographic findings. *Genetic Counseling (Geneva, Switzerland)*, 17(4), 469–472.

Chetcuti-Ganado, C., & Grech, V. (2003). Complex congenital cardiac disease in a patient with partial trisomy for the long arms of chromosomes 11 and 22. *Cardiology in the Young*, *13*(5), 481–483.

Choudhary, M. G., Babaji, P., Sharma, N., Dhamankar, D., Naregal, G., & Reddy, V. S. (2013). Derivative 11;22 (Emanuel) syndrome: a case report and a review. *Case Reports in Pediatrics*, 2013, 237935. https://doi.org/10.1155/2013/237935

Clark R. D. (1991). A cytogenetic abnormality in tuberous sclerosis. Report of an affected infant with 47,XX, + der22,t(11;22)(q23.3;q11.2)mat. *Annals of the New York Academy of Sciences*, 615, 243–251. https://doi.org/10.1111/j.1749-6632.1991.tb37765.x

Correll-Tash, S., Conlin, L., Mininger, B. A., Lilley, B., Mennuti, M. T., & Emanuel, B. S. (2018). The Recurrent t(11;22)(q23;q11.2) Can Occur as a Post-Zygotic Event. *Cytogenetic and Genome Research*, 156(4), 185–190. https://doi.org/10.1159/000494648

Dawson, A. J., Mears, A. J., Chudley, A. E., Bech-Hansen, T., & McDermid, H. (1996). Der(22)t(11;22) resulting from a paternal de novo translocation, adjacent 1 segregation, and maternal heterodisomy of chromosome 22. *Journal of Medical Genetics*, *33*(11), 952–956. https://doi.org/10.1136/jmg.33.11.952

Dean, J. C., Couzin, D. A., Gray, E. S., Lloyd, D. J., & Stephen, G. S. (1991). Apparent Fryns' syndrome and aneuploidy: evidence for a disturbance of the midline developmental field. *Clinical Genetics*, *40*(5), 349–352. https://doi.org/10.1111/j.1399-0004.1991.tb03108.x

de Beaufort, C., Schneider, F., Chafai, R., Colette, J. M., Delneste, D., & Pierquin, G. (2000). Diaphragmatic hernia and Fryns syndrome phenotype in partial trisomy 22. *Genetic Counseling (Geneva, Switzerland)*, *11*(2), 181–182.

Deepika, M.L., Sunitha, T., Srinadh, B., Prasoona, K.R., Sujatha, M., Ramaiah, A., Jyothy, A., & Nallari, P. (2016). Prenatal assessment of Three Rare Syndromes from Telangana region by 3D/4D Sonography. *Journal of Genetic Syndromes & Gene Therapy*, 7, 1-5.

de Lonlay-Debeney, P., de Blois, M. C., Bonnet, D., Amiel, J., Abadie, V., Picq, M., Lyonnet, S., Sidi, D., Munnich, A., Vekemans, M., & Cormier-Daire, V. (1998). Ebstein anomaly associated with rearrangements of chromosomal region 11q. *American Journal of Medical Genetics*, *80*(2), 157–159. https://doi.org/10.1002/ (sici)1096-8628(19981102)80:2<157::aid-ajmg12>3.0.co;2-u

Doyen, J., Carpentier, X., Haudebourg, J., Hoch, B., Karmous-Benailly, H., Ambrosetti, D., Fabas, T., Amiel, J., Lambert, J. C., & Pedeutour, F. (2012). Renal cell carcinoma and a constitutional t(11;22)(q23;q11.2): case report and review of the potential link between the constitutional t(11;22) and cancer. *Cancer Genetics*, *205*(11), 603–607. https://doi.org/10.1016/j.cancergen.2012.09.006

Drum, E. T., Herlich, A., Levine, B., & Mayhew, J. F. (2005). Anesthesia in a patient with chromosome 11;22 translocation: a case report and literature review. *Paediatric Anaesthesia*, *15*(11), 985–987. https://doi.org/10.1111/j.1460-9592.2005.01561.x

Dudarewicz, L., Jakubowski, J., Hawula, W., Kozlowska, M., Laskowska, U. Ramsauer, B., Herbst, H & Rickert, C. (2014). Emanuel syndrome. https://thefetus.net/content/emanuel-syndrome/

Dufke, A., Leipoldt, M., & Enders, H. (2003). Chromosomal mosaicism in familial reciprocal translocation carriers: necessity of karyotyping different tissues. *American Journal of Medical Genetics. Part A*, 121A(3), 292. https://doi.org/10.1002/ajmg.a.20288

Emanuel, B. S., Zackai, E. H., Aronson, M. M., Mellman, W. J., & Moorhead, P. S. (1976). Abnormal chromosome 22 and recurrence of trisomy-22 syndrome. *Journal of Medical Genetics*, *13*(6), 501–506. https://doi.org/10.1136/jmg.13.6.501



Emanuel B. S. (2008). Molecular mechanisms and diagnosis of chromosome 22q11.2 rearrangements. *Developmental Disabilities Research Reviews*, *14*(1), 11–18. https://doi.org/10.1002/ddrr.3

Edelmann, L., Spiteri, E., Koren, K., Pulijaal, V., Bialer, M. G., Shanske, A., Goldberg, R., & Morrow, B. E. (2001). AT-rich palindromes mediate the constitutional t(11;22) translocation. *American Journal of Human Genetics*, *68*(1), 1–13. https://doi.org/10.1086/316952

Edelmann, L., Spiteri, E., McCain, N., Goldberg, R., Pandita, R. K., Duong, S., Fox, J., Blumenthal, D., Lalani, S. R., Shaffer, L. G., & Morrow, B. E. (1999). A common breakpoint on 11q23 in carriers of the constitutional t(11;22) translocation. *American Journal of Human Genetics*, *65*(6), 1608–1616. https://doi.org/10.1086/302689

Edoardo, Taddei, Elena, Sartori, Luigi, Raio Bulgheroni and Andrea, Papadia. "Early detection of Emanuel syndrome: a case report" Case Reports in Perinatal Medicine, vol. 10, no. 1, 2021, pp. 20200049. https://doi.org/10.1515/crpm-2020-0049

Estop, A. M., Cieply, K. M., Munne, S., & Feingold, E. (1999). Multicolor fluorescence in situ hybridization analysis of the spermatozoa of a male heterozygous for a reciprocal translocation t(11;22)(q23;q11). *Human Genetics*, *104*(5), 412–417. https://doi.org/10.1007/s004390050977

Fokstuen, S., Binkert, F., Munoz, A., Erb, N., Dürig, P., Altermatt, H. J., Blouin, J. L., & Kotzot, D. (2013). Contamination of amniotic fluid with maternal balanced t(11;22) translocation cells. *American Journal of Medical Genetics. Part A*, *161A*(5), 1101–1104. https://doi.org/10.1002/ajmg.a.35774

Fraccaro, M., Lindsten, J., Ford, C. E., & Iselius, L. (1980). The 11q;22q translocation: a European collaborative analysis of 43 cases. *Human Genetics*, *56*(1), 21–51. https://doi.org/10.1007/BF00281567

Feldman, G. M., & Sparkes, R. S. (1978). The problem of partial trisomy 22 reconsidered. *Human Genetics*, 45(1), 97–101. https://doi.org/10.1007/BF00277580

Fu, W., Borgaonkar, D. S., Ladewig, P. P., Weaver, J., & Pomerance, H. H. (1976). Structural aberrations of the long arm of chromosome no. 22. Report fo a family with translocation t(11;22) (q25;q11). *Clinical Genetics*, *10*(6), 329–336. https://doi.org/10.1111/j.1399-0004.1976.tb00057.x

Fung, J., Munné, S., Garcia, J., Kim, U. J., & Weier, H. U. (1999). Molecular cloning of translocation breakpoints in a case of constitutional translocation t(11;22)(q23;q11) and preparation of probes for preimplantation genetic diagnosis. *Reproduction, Fertility, and Development, 11*(1), 17–23. https://doi.org/10.1071/rd98110

Fuster, C., Miguez, L., Miró, R., Rigola, M. A., Perez, A., & Egozcue, J. (1997). Familial complex chromosome rearrangement ascertained by in situ hybridisation. *Journal of Medical Genetics*, *34*(2), 164–166. https://doi.org/10.1136/jmg.34.2.164

Garcia-Vielma, C., de la Rosa-Alvarado, R. M., Nieto-Martinez, K., Cortes-Gutierrez, E. I., & de la Fuente-Cortez, B. (2010). Emanuel syndrome (supernumerary derivative 22), the result of a maternal translocation. A case report. *Journal of the Association of Genetic Technologists*, *36*(4), 189–193. https://www.researchgate.net/publication/

49675804_Emanuel_syndrome_supernumerary_derivative_22_the_result_of_a_maternal_translocation_A_cas e_report

Giraud, F., Mattei, J. F., Mattei, M. G., & Bernard, R. (1975). Trisomie partielle 11q et translocation familiale 11--22 [Partial trisomy 11q and familial translocation 11--22 (author's transl)]. *Humangenetik*, *28*(4), 343–347.

Glaser, T. S., Rauen, K. A., Jeng, L. J., & de Alba Campomanes, A. G. (2013). Lipodermoid in a patient with Emanuel syndrome. *Journal of AAPOS : the official publication of the American Association for Pediatric Ophthalmology and Strabismus*, *17*(2), 211–213. https://doi.org/10.1016/j.jaapos.2012.11.011

Goodman, R. M., Katznelson, M. B., Spero, M., Shaki, R., Padeh, B., & Sadan, N. (1971). The question of trisomy 22 syndrome. *The Journal of Pediatrics*, *79*(1), 174–175. https://doi.org/10.1016/ s0022-3476(71)80096-3

Gordillo González G, Rojas A, Zarante I, Gómez A, Moreno OM, Osorio G. Emanuel syndrome or supernumerary derived chromosome 22 syndrome. latreia [Internet]. 2010 Nov 28 [cited 2022 Jan 26];23(4-S):S-78. Available at: https://revistas.udea.edu.co/index.php/iatreia/article/view/8227

Gotter, A. L., Shaikh, T. H., Budarf, M. L., Rhodes, C. H., & Emanuel, B. S. (2004). A palindrome-mediated mechanism distinguishes translocations involving LCR-B of chromosome 22q11.2. *Human Molecular Genetics*, *13*(1), 103–115. https://doi.org/10.1093/hmg/ddh004

Gremeau, A. S., Coste, K., Blanc, P., Goumy, C., Francannet, C., Dechelotte, P. J., Vago, P., Laurichesse-Delmas, H., Labbe, A., Lemery, D., Sapin, V., & Gallot, D. (2009). Congenital diaphragmatic hernia and genital anomalies: Emanuel syndrome. *Prenatal Diagnosis*, *29*(8), 816–818. https://doi.org/10.1002/pd.2289

Gustavson, K.H., Hagberg, B., Finley, S.C., & Finley, W.H., (1962). An apparently identical extra autosome in two severely retarded sisters with multiple malformations. *Cytogenetics*, 1, 32–41. https://doi.org/10.1159/000129711

Guven MA, Ceylaner G, Ceylaner S, Coskun A. 2006. Prenatal diagnosis of a case with Emanuel Syndrome (supernumerary der(22) syndrome. Poster Abstract. Ultrasound Ob Gyn 28:522. https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/uog.3429

Hall B. 1963. Mongolism and other abnormalities in a family with trisomy 21-22 tendency. *Acta Pediatrica. Supplementum*, 77–91. https://doi.org/10.1111/j.1651-2227.1963.tb05520.x

Harewood, L., Schütz, F., Boyle, S., Perry, P., Delorenzi, M., Bickmore, W. A., & Reymond, A. (2010). The effect of translocation-induced nuclear reorganization on gene expression. *Genome Research*, *20*(5), 554–564. https://doi.org/10.1101/gr.103622.109

Hao, X., Wu, J., Fu, W., Zhang, R., Zhong, S., Deng, Y., Zhu, Y., Ye, Y., & Fang, Q. (2022). Prenatal Diagnosis of Fetuses with Emanuel Syndrome: Results of Ultrasound Examination and Invasive Genetic Testing. *Prenatal Diagnosis*, 10.1002/pd.6098. Advance online publication. https://doi.org/10.1002/pd.6098

Hill, A. S., Foot, N. J., Chaplin, T. L., & Young, B. D. (2000). The most frequent constitutional translocation in humans, the t(11;22)(q23;q11) is due to a highly specific alu-mediated recombination. *Human Molecular Genetics*, *9*(10), 1525–1532. https://doi.org/10.1093/hmg/9.10.1525

Hou J. W. (2003). Supernumerary chromosome marker Der(22)t(11;22) resulting from a maternal balanced translocation. *Chang Gung Medical Journal*, *26*(1), 48–52. http://cgmj.cgu.edu.tw/2601/260107.pdf

İkbal Atli, E., Gürkan, H., Vatansever, Ü., Ulusal, S., & Tozkir, H. (2016). A case with Emanuel syndrome: extra derivative 22 chromosome inherited from the mother. *Balkan Journal of Medical Genetics: BJMG*, *18*(2), 77–82. https://doi.org/10.1515/bjmg-2015-0089

Imataka, G., Takaya, Y., Hagisawa, S., Yamanouchi, H., & Eguchi, M. (2004). Trisomy 11/22 diagnosed by spectral karyotyping (SKY). *Genetic Counseling (Geneva, Switzerland*), 15(3), 391–394.

Iselius, L., & Faxelius, G. (1978). Trisomy 22 in a newborn girl with multiple malformations. *Hereditas*, 89(2), 269–271. https://doi.org/10.1111/j.1601-5223.1978.tb01286.x

Iselius, L., Lindsten, J., Aurias, A., Fraccaro, M., Bastard, C., Bottelli, A. M., Bui, T. H., Caufin, D., Dalprà, L., & Delendi, N. (1983). The 11q;22q translocation: a collaborative study of 20 new cases and analysis of 110 families. *Human Genetics*, 64(4), 343–355. https://doi.org/10.1007/BF00292366

Ivanovic V, Grkovic S. 2003. Unbalanced 11;22 translocation – case report. ABSTRACT-4th European Cytogenetics Conference, Italy.

Jancevska, S., Kitanovski, M., Laban, N., Danilovski, D., Tasic, V., & Gucev, Z. S. (2015). Emanuel Syndrome (ES): new case-report and review of the literature. *Prilozi (Makedonska akademija na naukite i umetnostite. Oddelenie za medicinski nauki)*, 36(1), 205–208.

Jobanputra, V., Chung, W. K., Hacker, A. M., Emanuel, B. S., & Warburton, D. (2005). A unique case of der(11)t(11;22),-22 arising from 3:1 segregation of a maternal t(11;22) in a family with co-segregation of the translocation and breast cancer. *Prenatal Diagnosis*, *25*(8), 683–686. https://doi.org/10.1002/pd.1196

Jun, Y.S., So, C.H., Yu, S.T., Park, D.S., Cho, E.H., & Oh, Y.K. (2010). A case of supernumerary derivative (22) syndrome resulting from a paternal balanced translocation. *Journal of the Korean Society of Neonatology*;17(1):127-131. https://neo-med.org/upload/pdf/J%20Korean%20Soc%20Neonatol._17_1_127_131.pdf

Kadir, R. A., Hastings, R., & Economides, D. L. (1997). Prenatal diagnosis of supernumerary chromosome derivative (22) due to maternal balanced translocation in association with diaphragmatic hernia: a case report. *Prenatal Diagnosis*, *17*(8), 761–764.

Kamath, V., Srivastava, V.M., Yuvarani, S., Chacko, M.P., Bhattacharya, S.K., Oomen, S.P., Danda, S & Korula, G. (2019). The constitutional balanced translocation t(11;22)(q23.3q11.2)-An Indian account. *Journal of Clinical and Diagnostic Research*. DOI: 10.7860/JCDR/2019/36950.12438 https://www.jcdr.net/articles/PDF/ 12438/36950_CE[Ra1]_F(SL)_PF1(AGAK)_PFA(AK)_PB(AG_SHU)_PN(SL).pdf

Kankante, D. S., Misal, D. G., & Mhaske, D. S. N. (2018). Emanuel Syndrome: A Case Report. *VIMS Health Science Journal*, *5*(3), 131-132. Retrieved from https://vimshsj.edu.in/index.php/main/article/view/104

Kapoor S. (2015). Emanuel syndrome: A rare disorder that is often confused with Kabuki syndrome. *Journal of Pediatric Neurosciences*, *10*(2), 194–195. https://doi.org/10.4103/1817-1745.159183

Karempelis, P., Hagen, M., Morrell, N., & Roby, B. B. (2020). Associated syndromes in patients with Pierre Robin Sequence. *International Journal of Pediatric Otorhinolaryngology*, 131, 109842. https://doi.org/10.1016/j.ijporl.2019.109842

Karimi-Nejad, R., Ghofrani, M., Najafi, A., & Karimi-Nejad, M.H. (1989). Reconsideration of the cat eye syndrome: Reciprocal translocation t(11,22) leading t partial trisomy of 11q and 22. *Medical Journal of The Islamic Republic of Iran* (MJIRI)Volume 3, Issue 1 And 2 (8-1989) https://mjiri.iums.ac.ir/browse.php? a_id=1607&sid=1&slc_lang=fa

Kariminejad, M.H., Moshtagh, A., & Kariminejad, R. (2013). Translocation Between Chromosomes 11 and 22 [t(11,22)]: The Most Common Non Robertsonian Translocation Evaluation of 38 Cases of t(11,22) and a Review of the Literature. *Genetics in the Third Millennium*, 11, 3180-3189.

Kashiwagi, Y., Morishima, Y., Agata, K., Go, S., Nishimata, S., Numabe, H. and Kawashima, H. (2017) Efficacy of Intravenous Immunoglobulin in a Case of Emanuel Syndrome. *Open Journal of Pediatrics*, **7**, 32-36. doi: 10.4236/ojped.2017.71005.

Katafuchi, Y., Hashino, K., Maeno, Y., Komori, H., Yamashita, Y., Horikawa, M., Abe, K., Niikawa, N., & Kato, H. (1990). Partial trisomy 22 with Dandy-Walker malformation. *Acta Paediatrica Japonica : Overseas Edition*, *32*(5), 566–570. https://doi.org/10.1111/j.1442-200x.1990.tb00883.x

Kato, T., Inagaki, H., Kogo, H., Ohye, T., Yamada, K., Emanuel, B. S., & Kurahashi, H. (2008). Two different forms of palindrome resolution in the human genome: deletion or translocation. *Human Molecular Genetics*, *17*(8), 1184–1191. https://doi.org/10.1093/hmg/ddn008

Kato, T., Inagaki, H., Yamada, K., Kogo, H., Ohye, T., Kowa, H., Nagaoka, K., Taniguchi, M., Emanuel, B. S., & Kurahashi, H. (2006). Genetic variation affects de novo translocation frequency. *Science (New York, N.Y.)*, *311*(5763), 971. https://doi.org/10.1126/science.1121452

Kato, T., Yamada, K., Inagaki, H., Kogo, H., Ohye, T., Emanuel, B. S., & Kurahashi, H. (2007). Age has no effect on de novo constitutional t(11;22) translocation frequency in sperm. *Fertility and Sterility*, *88*(5), 1446–1448. https://doi.org/10.1016/j.fertnstert.2007.01.019

Kazandi, M., Turan, V., Zeybek, B, & Argon, A. (2010). Emanuel Syndrome. *Ege Journal of Medicine*. 49(3):209-211. https://www.researchgate.net/publication/236659695_Emanuel_Syndrome

Kee, S. K., See, V. H., Chia, P., Tan, W. C., Tien, S. L., & Lim, S. T. (2013). Differential outcomes in an extended family with constitutional t(11;22)(q23.3;q11.2). *Journal of Pediatric Genetics*, *2*(1), 37–41. https://doi.org/10.3233/PGE-13046

Kessel, E., & Pfeiffer, R. A. (1977). 47,XY,+der(11;22)(q23;q12) following balanced translocation t(11;22) (q23;q12)mat. Remarks on the problem of trisomy 22. *Human Genetics*, *37*(1), 111–116. https://doi.org/10.1007/BF00293781

Kilic, Y., Vural., M., Gulec, M.S., Anaesthetic management for tethered cord syndrome in a child with Emanuel syndrome. *International Journal of Medical Reviews and Case Reports*; 4(12):46-47. do:10.5455/ IJMRCR.tethered-cord-syndrome-child

Kim JH, Kim Y, Lee BH, Kim J, Seo E, Yoo H. (2012). A Case with Emanuel Syndrome Resulting from a Maternal Balanced Translocation. *Journal of Genetic Medicine* 9:35-37. https://doi.org/10.5734/JGM.2012.9.1.35

Koduru, P. R., & Chaganti, R. S. (1989). Meiotic chromosome segregation in human t(11;22)(q23;q11) carriers: a theoretical consideration. *Genome*, *32*(1), 24–29. https://doi.org/10.1139/g89-405

Kogo, H., Inagaki, H., Ohye, T., Kato, T., Emanuel, B. S., & Kurahashi, H. (2007). Cruciform extrusion propensity of human translocation-mediating palindromic AT-rich repeats. *Nucleic Acids Research*, *35*(4), 1198–1208. https://doi.org/10.1093/nar/gkm036

Kulharya, A. S., Lovell, C. M., & Flannery, D. B. (2002). Unusual mosaic karyotype resulting from adjacent 1 segregation of t(11;22): importance of performing skin fibroblast karyotype in patients with unexplained multiple congenital anomalies. *American Journal of Medical Genetics*, *113*(4), 367–370. https://doi.org/ 10.1002/ajmg.b.10801

Kurahashi, H., & Emanuel, B. S. (2001). Long AT-rich palindromes and the constitutional t(11;22) breakpoint. *Human Molecular Genetics*, *10*(23), 2605–2617. https://doi.org/10.1093/hmg/10.23.2605

Kurahashi, H., & Emanuel, B. S. (2001). Unexpectedly high rate of de novo constitutional t(11;22) translocations in sperm from normal males. *Nature Genetics*, *29*(2), 139–140. https://doi.org/10.1038/ ng1001-139

Kurahashi, H., Inagaki, H., Ohye, T., Kogo, H., Kato, T., & Emanuel, B. S. (2006). Palindrome-mediated chromosomal translocations in humans. *DNA Repair*, *5*(9-10), 1136–1145. https://doi.org/10.1016/j.dnarep.2006.05.035

Kurahashi, H., Inagaki, H., Yamada, K., Ohye, T., Taniguchi, M., Emanuel, B. S., & Toda, T. (2004). Cruciform DNA structure underlies the etiology for palindrome-mediated human chromosomal translocations. *The Journal of Biological Chemistry*, *279*(34), 35377–35383. https://doi.org/10.1074/jbc.M400354200

Kurahashi, H., Inagaki, H., Ohye, T., Kogo, H., Tsutsumi, M., Kato, T., Tong, M., & Emanuel, B. S. (2010). The constitutional t(11;22): implications for a novel mechanism responsible for gross chromosomal rearrangements. *Clinical Genetics*, *78*(4), 299–309. https://doi.org/10.1111/j.1399-0004.2010.01445.x

Kurahashi, H., Shaikh, T. H., & Emanuel, B. S. (2000). Alu-mediated PCR artifacts and the constitutional t(11;22) breakpoint. *Human Molecular Genetics*, *9*(18), 2727–2732. https://doi.org/10.1093/hmg/9.18.2727

Kurahashi, H., Shaikh, T. H., Zackai, E. H., Celle, L., Driscoll, D. A., Budarf, M. L., & Emanuel, B. S. (2000). Tightly clustered 11q23 and 22q11 breakpoints permit PCR-based detection of the recurrent constitutional t(11;22). *American Journal of Human Genetics*, *67*(3), 763–768. https://doi.org/10.1086/303054

Kurahashi, H., Shaikh, T. H., Hu, P., Roe, B. A., Emanuel, B. S., & Budarf, M. L. (2000). Regions of genomic instability on 22q11 and 11q23 as the etiology for the recurrent constitutional t(11;22). *Human Molecular Genetics*, *9*(11), 1665–1670. https://doi.org/10.1093/hmg/9.11.1665

Laurent, C., Biemont, M. C., Bethenod, M., Cret, L., & David, M. (1975). Deux observations de trisomie liq(q23.1 leads to qter) avec la mème anomalie des organes genitaux externes [2 cases of trisomy 11q(q23.2-- qter) with the same abnormality of external genitalia]. *Annales de Genetique*, *18*(3), 179–184.

Li, F., Tang, J., Xie, X., Tang, S., Wu, A., Tang, Q., Tan, W., & Guo, X. (2019). Zhonghua yi xue yi chuan xue za zhi = Zhonghua yixue yichuanxue zazhi = Chinese Journal of Medical Genetics, 36(6), 632–635. https://doi.org/10.3760/cma.j.issn.1003-9406.2019.06.026

Liehr, T., Acquarola, N., Pyle, K., St-Pierre, S., Rinholm, M., Bar, O., Wilhelm, K., & Schreyer, I. (2018). Next generation phenotyping in Emanuel and Pallister-Killian syndrome using computer-aided facial dysmorphology analysis of 2D photos. *Clinical Genetics*, *93*(2), 378–381. https://doi.org/10.1111/cge.13087

Lin, A. E., Bernar, J., Chin, A. J., Sparkes, R. S., Emanuel, B. S., & Zackai, E. H. (1986). Congenital heart disease in supernumerary der(22),t(11;22) syndrome. *Clinical Genetics*, *29*(4), 269–275. https://doi.org/10.1111/j.1399-0004.1986.tb01254.x

Lindblom, A., Sandelin, K., Iselius, L., Dumanski, J., White, I., Nordenskjöld, M., & Larsson, C. (1994). Predisposition for breast cancer in carriers of constitutional translocation 11q;22q. *American Journal of Human Genetics*, *54*(5), 871–876. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1918254/

Lindenbaum R. H. (1990). Unusual segregation of constitutional 11q;22q translocation may be explained by crossover in interchange segment, followed by 3:1 segregation at meiosis I. *Human Genetics*, *85*(1), 143. https://doi.org/10.1007/BF00276346

Lockwood, D. H., Farrier, A., Hecht, F., & Allanson, J. (1989). Not all chromosome imbalance resulting from the 11q;22q translocation is due to 3:1 segregation in first meiosis. *Human Genetics*, *83*(3), 287–288. https://doi.org/10.1007/BF00285174

Luo, J. W., Yang, H., Tan, Z. P., Tu, M., Luo, H., Yang, Y. F., & Xie, L. (2017). A clinical and molecular analysis of a patient with Emanuel syndrome. *Molecular Medicine Reports*, *15*(3), 1348–1352. https://doi.org/ 10.3892/mmr.2017.6107

Luo, Y., Lin, J., Sun, Y., Qian, Y., Wang, L., Chen, M., Dong, M., & Jin, F. (2020). Non-invasive prenatal screening for Emanuel syndrome. *Molecular Cytogenetics*, 13, 9. https://doi.org/10.1186/s13039-020-0476-7

Lurie, I. W., & Podleschuk, L. V. (1992). 11q;22q translocation: Third case of imbalance not due to 3:1 nondisjunction in first meiosis. *American Journal of Medical Genetics*, *42*(2), 216. https://doi.org/10.1002/ajmg.1320420218

Lur'e, I. V., Rumiantseva, N. V., Podleshchuk, L. V., Kozlova, S. I., Kulak, V. D., Naumchik, I. V., Gorelik, L. B., Zolotukhina, T. V., & Kuznetsov, M. I. (1992). Translokatsii 11q; 22q: kliniko-tsitogeneticheskoe issledovanie [Translocation 11q;22q: a clinico-cytogenetic study]. *Genetika*, *28*(10), 129–135.

Mackie Ogilvie, C., & Scriven, P. N. (2002). Meiotic outcomes in reciprocal translocation carriers ascertained in 3-day human embryos. *European Journal of Human Genetics : EJHG*, *10*(12), 801–806. https://doi.org/ 10.1038/sj.ejhg.5200895

Macville, M. V., Loneus, W. H., Marcus-Soekarman, D., Huys, E. H., Schoenmakers, E. F., Schrank-Hacker, A., Emanuel, B. S., & Engelen, J. J. (2006). XX male with sex reversal and a de novo 11;22 translocation. *American Journal of Medical Genetics. Part A*, *140*(18), 1973–1977. https://doi.org/10.1002/ajmg.a.31397

Maluf SW, Felix TM, Schwartz IVD. 2000. Partial trisomy 22qpter-q11 and 11q23-qter: an extra chromosome originated from a constitutional t(11;22) translocation in a Brazilian family. *Brazilian Journal of Dysmorphology and Speech-Hearing Disorders*. 3:11-16. {ABSTRACT}



Martin R. H. (1984). Analysis of human sperm chromosome complements from a male heterozygous for a reciprocal translocation t(11;22)(q23;q11). *Clinical Genetics*, *25*(4), 357–361. https://doi.org/10.1111/j.1399-0004.1984.tb02004.x

Musa, J., Horjeti, E., Guy, A., Saliaj, K., Shtiza, S., Ceka, E., Musa, D., & Rakovica, L. Diagnosis and Management of Genetic Derivation 22 and 11 Chromosome-Emanuel Syndrome in 10-Year Old Boy. *Journal of Pediatrics, Perinatology and Child Health* 4 (2020): 052-057. https://www.fortunejournals.com/articles/ diagnosis-and-management-of-genetic-derivation-22-and-11-chromosomeemanuel-syndrome-in-10year-oldboy.html

Najafzadeh, T. M., & Dumars, K. W. (1981). Duplication of distal 11q and 22p occurrence in two unrelated families. *American Journal of Medical Genetics*, *8*(3), 341–347. https://doi.org/10.1002/ajmg.1320080313

Nakai, H., Yamamoto, Y., & Kuroki, Y. (1979). Partial trisomy of 11 and 22 due to familial translocation t(11;22) (q23;q11), inherited in three generations. *Human Genetics*, *51*(3), 349–355. https://doi.org/10.1007/BF00283408

Narahara, K., Kodama, Y., Kimura, S., Kamoi, M., Inoue, H., & Kimoto, H. (1979). A case of partial trisomy 22 resulting from maternal 11/22 translocation. *Jinrui idengaku zasshi. The Japanese Journal of Human Genetics*, *24*(4), 253–258. https://doi.org/10.1007/BF01907825

Nishinarita, R., Mihara, T., Nakamura, N., Miyamoto, Y., & Ka, K. (2015). Anesthetic management of pediatric patients with Emanuel syndrome. *Journal of Anesthesia*, *29*(3), 450–452. https://doi.org/10.1007/s00540-014-1955-y

Noel, B., Levy, M., & Rethoré, M. O. (1976). Trisomie partielle du bras long du chromosome 11 par malségrégation d'une translocation maternelle t(11;22)(q231; q 111) [Partial trisomy of the long arm of the chromosome 11 by malsegregation of a maternal translocation t(11;22)(q23 1;q1 11)]. *Annales de Genetique*, *19*(2), 137.

Noir, A., Leroux, M., Bresson, J. L., Menget, A., Burguet, A., & Raffi, A. (1987). La trisomie 11q: à propos de deux cas [11q trisomy: apropos of 2 cases]. *Pediatrie*, *42*(6), 441–444.

Oakley, J. R., Else, P., Asplin, P., & Taitz, L. S. (1976). Balanced translocation, impaired sperm motility, and offspring anomaly. *Archives of Disease in Childhood*, *51*(8), 638–640. https://doi.org/10.1136/adc.51.8.638

Ohye, T., Inagaki, H., Kato, T., Tsutsumi, M., & Kurahashi, H. (2014). Prevalence of Emanuel syndrome: theoretical frequency and surveillance result. *Pediatrics International: Official Journal of the Japan Pediatric Society*, *56*(4), 462–466. https://doi.org/10.1111/ped.12437

Pai, G. S., Thomas, G. H., Leonard, C. O., Ward, J. C., Valle, D. L., & Pyeritz, R. E. (1979). Syndromes due to chromosomal abnormalities: partial trisomy 22, interstitial deletion of the long arm of 13, and trisomy 8. *The Johns Hopkins Medical Journal*, 145(4), 162–169.

Pallotta, R., Fusilli, P., Ehresmann, T., Cinti, R., Verrotti, A., & Morgese, G. (1996). Cerebral defects confirm midline developmental field disturbances in supernumerary der(22), t(11;22) syndrome. *Clinical Genetics*, *50*(5), 411–416. https://doi.org/10.1111/j.1399-0004.1996.tb02398.x

Pangalos, C., Couturier, J., Bartsocas, C., & Theodorou, S. (1980). Trisomie partielle 11 q par malségrégation d'une translocation maternelle t (11;22) (q23;q11.1) [Partial 11q trisomy due to missegregation of maternal t(11;22) (q23;q11.1) translocation (author's transl)]. *La Nouvelle Presse Medicale*, *9*(41), 3065–3067.

Pattemore, P. K., Shaw, R. L., & Gunn, T. R. (1987). The neonatal recognition of partial 11q trisomy (previously 'trisomy 22'). *Australian Paediatric Journal*, *23*(3), 197–199. https://doi.org/10.1111/j.1440-1754.1987.tb00245.x

Penchaszadeh, V. B., & Coco, R. (1975). Trisomy 22. Two new cases and delineation of the phenotype. *Journal of Medical Genetics*, *12*(2), 193–199. https://doi.org/10.1136/jmg.12.2.193



Petković, I., de Capoa, A., Giancotti, P., & Barisić, I. (1996). Unusual segregation of t(11;22) resulting from crossing-over followed by 3:1 disjunction at meiosis I. *Clinical Genetics*, *50*(6), 515–519. https://doi.org/10.1111/j.1399-0004.1996.tb02725.x

Pohkn H, Thermn E, Uchida I. (1981). Partial 11q trisomy syndrome. Human Genetics 58: 129-134.

Prieto, J. C., Garcia, N. M., Elder, F. F., Zinn, A. R., & Baker, L. A. (2007). Phenotypic expansion of the supernumerary derivative (22) chromosome syndrome: VACTERL and Hirschsprung's disease. *Journal of Pediatric Surgery*, *42*(11), 1928–1932. https://doi.org/10.1016/j.jpedsurg.2007.07.030

Puranik, C. P., & Katechia, B. (2019). Oral and dental findings in Emanuel syndrome. *International Journal of Paediatric Dentistry*, *29*(5), 677–682. https://doi.org/10.1111/ipd.12502

Rassu S, Pilloni G, Boccone , Puddu R, Bernard L, Rossino R, Gasperini D. (2003). Der(11)t(11;22) resulting from a balanced reciprocal subtelomeric translocation in a Sardinian family. ABSTRACT. 4th European Cytogenetics Conference, Italy.

Rosa, Rafael Fabiano M. et al. Variabilidade fenotípica na síndrome do cromossomo supernumerário der(22)t(11;22) (síndrome de Emanuel). *Revista Paulista de Pediatria* [online]. 2010, v. 28, n. 3 [Acessado 26 Fevereiro 2022], pp. 367-371. Disponível em: Epub 22 Nov 2010. ISSN 1984-0462. https://doi.org/10.1590/S0103-05822010000300017.

Saffren, B. D., Capasso, J. E., Zanolli, M., & Levin, A. V. (2018). Ocular manifestations of Emanuel syndrome. *American Journal of Medical Genetics. Part A*, *176*(9), 1964–1967. https://doi.org/10.1002/ajmg.a.40361

Schinzel, A., Schmid, W., Auf der Maur, P., Moser, H., Degenhardt, K. H., Geisler, M., & Grubisic, A. (1981). Incomplete trisomy 22. I. Familial 11/22 translocation with 3:1 meiotic disjunction. Delineation of a common clinical picture and report of nine new cases from six families. *Human Genetics*, *56*(3), 249–262. https:// doi.org/10.1007/BF00274675

Shaikh, T. H., Budarf, M. L., Celle, L., Zackai, E. H., & Emanuel, B. S. (1999). Clustered 11q23 and 22q11 breakpoints and 3:1 meiotic malsegregation in multiple unrelated t(11;22) families. *American Journal of Human Genetics*, *65*(6), 1595–1607. https://doi.org/10.1086/302666

Shenoy, R. D., Shenoy, V., & Shetty, V. (2018). Chromosomal Abnormalities in Syndromic Orofacial Clefts: Report of Three Children. *Case Reports in Genetics*, *2018*, 1928918. https://doi.org/10.1155/2018/1928918

Shi Q, Martin RH. Aneuploidy in human spermatozoa: FISH analysis in men with constitutional chromosome abnormalities, and in infertile men. 2001. *Reproduction* 121:655-666.

Schoemaker, M. J., Jones, M. E., Higgins, C. D., Wright, A. F., UK Clinical Cytogenetics Group, & Swerdlow, A. J. (2019). Mortality and cancer incidence in carriers of constitutional t(11;22)(q23;q11) translocations: A prospective study. *International Journal of Cancer*, *145*(6), 1493–1498. https://doi.org/10.1002/ijc.32031

Shokeir M. H. (1978). Complete trisomy 22. *Clinical Genetics*, *14*(3), 139–146. https://doi.org/10.1111/j.1399-0004.1978.tb02119.x

Simi, P., Ceccarelli, M., Barachini, A., Floridia, G., & Zuffardi, O. (1992). The unbalanced offspring of the male carriers of the 11q;22q translocation: nondisjunction at meiosis II in a balanced spermatocyte. *Human Genetics*, *88*(4), 482–483. https://doi.org/10.1007/BF00215688

Slater, H. R., Voullaire, L. E., Vaux, C. E., Bankier, A., Pertile, M., & Choo, K. H. (1993). Confirmation of trisomy 22 in two cases using chromosome painting: comparison with t(11;22). *American Journal of Medical Genetics*, *46*(4), 434–437. https://doi.org/10.1002/ajmg.1320460417

Soler, A., Carrio, A., Perez-Vidal, M. T., Borrell, A., & Fortuny, A. (1993). Unusual segregation for 11q;22q parental translocation in a triplet pregnancy: prenatal diagnosis in chorionic villi and amniotic fluid. *Prenatal Diagnosis*, *13*(2), 137–141. https://doi.org/10.1002/pd.1970130209

Soto-Brambila, A. P., Marín-Medina, A., Michel-Ocampo, M., Figuera-Villanueva, L. E., & Rivero-Moragrega, P. (2018). Emanuel Syndrome: first case reported in Mexico. *Investigación Clínica*, *59*(1), 41- 46. Recuperado a partir de https://www.produccioncientificaluz.org/index.php/investigacion/article/view/29078

Sou, S., Takabayashi, T., Sasaki, H., Sasamoto, K., Shintaku, Y., Li, Z. J., Ozawa, N., & Yajima, A. (1987). Prenatal diagnosis of partial trisomy 22 derived from a maternal t(11; 22) (q23; q11). *The Tohoku Journal of Experimental Medicine*, *153*(4), 389–393. https://doi.org/10.1620/tjem.153.389

Spiteri, E., Babcock, M., Kashork, C. D., Wakui, K., Gogineni, S., Lewis, D. A., Williams, K. M., Minoshima, S., Sasaki, T., Shimizu, N., Potocki, L., Pulijaal, V., Shanske, A., Shaffer, L. G., & Morrow, B. E. (2003). Frequent translocations occur between low copy repeats on chromosome 22q11.2 (LCR22s) and telomeric bands of partner chromosomes. *Human Molecular Genetics*, *12*(15), 1823–1837. https://doi.org/10.1093/hmg/ddg203

Stankiewicz, P., Korniszewski, L., Bocian, E., & Stańczak, H. (1996). Marker chromosomowy jako produkt rodzinnej translockacji (11;22) rozpoznanej metodami cytogenetyki molekularnej [Marker chromosomes as a product of familial translocation (11;22) identified with molecular cytogenetic methods]. *Pediatria Polska*, *71*(3), 241–245.

Tachdjian, G., Muti, C., Gaudelus, J., Druart, L., Martin, B., Tamboise, E., & Nessmann, C. (1992). Unbalanced karyotype due to adjacent 1 segregation of t(11;22)(q23.3;q13.2). *Annales de Genetique*, *35*(4), 231–233.

Tapia-Páez, I., O'Brien, K. P., Kost-Alimova, M., Sahlén, S., Kedra, D., Bruder, C. E., Andersson, B., Roe, B. A., Hu, P., Imreh, S., Blennow, E., & Dumanski, J. P. (2000). Fine mapping of the constitutional translocation t(11;22)(q23;q11). *Human Genetics*, *106*(5), 506–516. https://doi.org/10.1007/s004390000287

Tovo, P. A., Davi, G., Fraceschini, P., & Delpiano, A. (1986). Thymic hormone dependent immunodeficiency in an infant with partial trisomy of chromosome 22. *Thymus*, *8*(5), 313–318.

Toyoshima, M., Yonee, C., Maegaki, Y., Yamamoto, T., Shimojima, K., Maruyama, S., & Kawano, Y. (2009). Vertebral fusion in a patient with supernumerary-der(22)t(11;22) syndrome. *American Journal of Medical Genetics. Part A*, 149A(8), 1722–1726. https://doi.org/10.1002/ajmg.a.32762

Tsukamoto, M., Hitosugi, T., Esaki, K., & Yokoyama, T. (2016). Anesthetic Management of a Patient With Emanuel Syndrome. *Anesthesia Progress*, 63(4), 201–203. https://doi.org/10.2344/16-00028.1

Vahidi Mehrjardi, M. Y., Dehghan Tezerjani, M., Nori-Shadkam, M., Kalantar, S. M., & Dehghani, M. (2016). Newborn with Supernumerary Marker Chromosome Derived from Chromosomes 11 And 22- A Case Report. *Iranian Journal of Public Health*, *45*(3), 376–380.

Van Assche, E., Staessen, C., Vegetti, W., Bonduelle, M., Vandervorst, M., Van Steirteghem, A., & Liebaers, I. (1999). Preimplantation genetic diagnosis and sperm analysis by fluorescence in-situ hybridization for the most common reciprocal translocation t(11;22). *Molecular Human Reproduction*, *5*(7), 682–690. https://doi.org/10.1093/molehr/5.7.682

Vigliano P, Duca S, Isocrono A, & Silengo M. (2003). Hippocampal malrotation in supernumerary der(22) syndrome and epilepsy: a case report. *Journal of Pediatric Neurology* 1(1):39-42. https://content.iospress.com/articles/journal-of-pediatric-neurology/jpn1-1-08

Welter, D. A., Scharff, L., 3rd, Teal, N. M., & Thevaos, T. G. (1978). Trisomy 22 in a 20-year-old female. *Human Genetics*, 43(3), 347–351. https://doi.org/10.1007/BF00278845

Werding, N., Holland, H., Hueckel, D., Froster, U. G., Häusler, H. J., & Kiess, W. (2003). Partial trisomy 22 resulting from rearrangements between chromosomes 11/22 and 16/22: a report of two cases. *Acta Paediatrica (Oslo, Norway : 1992)*, *92*(7), 865–868. https://doi.org/10.1111/j.1651-2227.2003.tb02550.x

Woo, H. Y., Cho, H. J., Kong, S. Y., Kim, H. J., Jeon, H. B., Kim, E. C., Park, H., Kim, Y. J., & Kim, S. H. (2003). Marker chromosomes in Korean patients: incidence, identification and diagnostic approach. *Journal of Korean Medical Science*, *18*(6), 773–778. https://doi.org/10.3346/jkms.2003.18.6.773

Wieland, I., Muschke, P., Volleth, M., Röpke, A., Pelz, A. F., Stumm, M., & Wieacker, P. (2006). High incidence of familial breast cancer segregates with constitutional t(11;22)(q23;q11). *Genes, Chromosomes & Cancer*, *45*(10), 945–949. https://doi.org/10.1002/gcc.20358

Xie, C. L., & Cardenas, A. M. (2019). Neuroimaging findings in Emanuel Syndrome. *Journal of Radiology Case Reports*, *13*(10), 1–5. https://doi.org/10.3941/jrcr.v13i10.3625

Yik, M.Y., Mydin, R.B., Moses, E.J., Zaini, S.H.M, Azhari, A.R., & Yusoff, N.M. (2020). a case study of distinctive phenotypes arising from emanuel syndrome in two karyotypically identical patients. *Malaysian Journal of Medicine and Health Science*. 16(SUPP2):78-80. https://medic.upm.edu.my/upload/dokumen/ 2020051111452012_MJMHS_0463_11_5_2020.pdf

Yosunkaya Fenerci, E., Guven, G. S., Kuru, D., Yilmaz, S., Tarkan-Argüden, Y., Cirakoglu, A., Deviren, A., Yüksel, A., & Hacihanefioğlu, S. (2007). Supernumerary chromosome der(22)t(11;22): Emanuel syndrome associates with novel features. *Genetic Counseling (Geneva, Switzerland)*, *18*(4), 401–408.

Youings, S., Ellis, K., Ennis, S., Barber, J., & Jacobs, P. (2004). A study of reciprocal translocations and inversions detected by light microscopy with special reference to origin, segregation, and recurrent abnormalities. *American Journal of Medical Genetics. Part A*, *126A*(1), 46–60. https://doi.org/10.1002/ajmg.a.20553

Zafar, A., Chaudari, M, & Crossland, D. (2014). Emanuel syndrome with unique cardiac defects: a case series. *Infant Journal* 10(3), 101-102. https://www.infantjournal.co.uk/pdf/inf_057_dia.pdf

Zackai, E. H., & Emanuel, B. S. (1980). Site-specific reciprocal translocation, t(11;22) (q23;q11), in several unrelated families with 3:1 meiotic disjunction. *American Journal of Medical Genetics*, 7(4), 507–521. https://doi.org/10.1002/ajmg.1320070412

Zenagui, R., Bernicot, I., Ranisavljevic, N., Haquet, E., Ferrieres-Hoa, A., Pellestor, F., & Anahory, T. (2019). Inheritance of imbalances in recurrent chromosomal translocation t(11;22): clarification by PGT-SR and sperm-FISH analysis. *Reproductive Biomedicine Online*, *39*(1), 40–48. https://doi.org/10.1016/ j.rbmo.2019.02.010

Zienkiewicz, E. (2019). Emanuel syndrome: the case study. *European Academy of Childhood Disability*. https://edu.eacd.org/node/620

Zhao, Y., Pang, H., Gao, M., Feng, X., Guan, Y., Zhao, H., Tong, D., Hua, J., Cao, X., He, S., & Li-Ling, J. (2017). Genetic diagnosis and follow up of a fetus with Emanuel syndrome *Zhonghua yi xue yi chuan xue za zhi = Zhonghua yixue yichuanxue zazhi = Chinese Journal of Medical Genetics*, *34*(5), 709–713. https://doi.org/10.3760/cma.j.issn.1003-9406.2017.05.020

Zou, P. S., Li, H. F., Chen, L. S., Ma, M., Chen, X. H., Xue, D., & Cao, D. H. (2016). A rare case of trisomy 11q23.3-11q25 and trisomy 22q11.1-22q11.21. *Genetics and Molecular Research: GMR*, 15(2), https://doi.org/10.4238/gmr.15028140



A flower does not think of competing with the

flower next to it. It just blooms." – Zen Shin



EMANUELSYNDROME.ORG © CHROMOSOME 22 CENTRAL, INC. 2022 WWW.C22C.ORG