COSTELLO SYNDROME

A BOOKLET BY PARENTS FOR PARENTS

Welcome!

We hope to provide you with support and understanding, and share what we know as we learn more about this very rare syndrome. If you are interested in looking at more photos of our children, they are available at the website described on the last page.

Costello syndrome is a rare multiple congenital anomaly disorder in which individuals have characteristic craniofacial features, failure to thrive, ectodermal and musculoskeletal anomalies, cardiac abnormalities, endocrinopathy, developmental delay and a predisposition to neoplasia,* both benign and malignant. [Estep et al, 2006]

[* malignant tumors]

GENETICS

TESTING If you have not yet had your child tested for the HRAS mutations, we strongly recommend that you do! One reason is because for some, it's hard to tell if the child has Costello syndrome or one of the other "RASopathies", and while they share some issues, there are issues that are unique to each syndrome. For instance, children with Costello syndrome have the highest risk of cancer among the RASopathies. Testing will also help researchers looking for clues about how the different mutations on the HRAS gene work.

In the United States, insurance companies usually approve a doctor's request for the test, and in most states, Medicaid will pay for it too. A list of clinical laboratories that do the test can be found at www.genetests.org/.

In the UK and Europe please discuss genetic testing with your doctor who will make arrangements for the testing to be carried out.

Because our children's syndrome is so extremely rare, it would be unusual for people to consider Costello syndrome prenatally if it was the first child, but there are labs that will test prenatally.

If you have not had genetic counselling, we urge you to ask your child's doctor for this service. Your having a child with a rare genetic condition makes you eligible for this service. Next are basic questions about Costello syndrome that would be fleshed out in a genetics counselling appointment:

Q: What are my chances of having another child with Costello syndrome?

A: Your chances of having another child are low. No one on our listserv of about 125 members have had another child with Costello syndrome. Researchers know that Costello syndrome is autosomal dominant, meaning that it affects the HRAS gene mutation on one copy of chromosome 11. This can happen a few ways:

1. The child inherits a mutation from one parent – who also has the syndrome. In our case, this means that if your child with Costello syndrome has children, your grandchild has a 50% chance of having Costello syndrome. There are no known children who have inherited Costello syndrome this way.

2. The child inherits a mutation from one parent – who doesn't have the syndrome but has a mutation in the reproductive system (sperm or egg) that developed when the child was in the womb. This is called mosaicism, and is very rare, even for Costello syndrome! The most effective way to consider this kind of mutation transmission is if there are siblings with Costello syndrome in the family – learning from the siblings, rather than being able to test for it. There are only two known sets of siblings with Costello syndrome, in old publications, but they have not been tested for the Hras mutation, so we're still not sure.

3. The child developed the mutation while in the womb – spontaneously (spontaneous mutation). This is the most likely way that your child developed Costello syndrome. Spontaneous mutations in general are not uncommon. Most do not survive past the first few weeks of conception – most pregnancies do not survive past the first trimester, and often times, the mother doesn't even know she's pregnant.

Q: How does this affect my healthy children?

A: Your healthy children are not affected at all by Costello syndrome. Their children will not be affected by Costello syndrome either. The only way your healthy children or their children could have a child with Costello syndrome is if situation (2) or (3) listed in the previous question was to happen. – The same chance as anyone else.With what we guess to be about 250 cases identified WORLDWIDE, our children are the information from which the scientists and doctors are making theories! If we use the numbers known in the United Kingdom to generalize, the prevalence is 1:500,000.

The Importance of Parent-to-Parent Communication

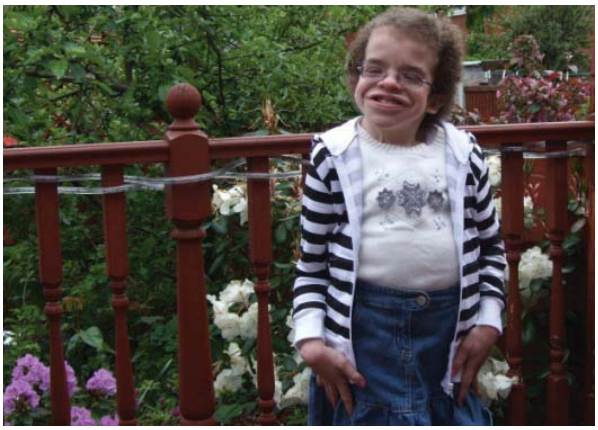
In addition to doctors and researchers observing our children for patterns, we parents have been important participants in developing a more detailed picture of what
Costello syndrome is. Our direct communication with each other speeds up the identification of a pattern, and starts an immediate database for a doctor interested in following the research.

Here are some shared observations many parents notice but are still mysteries:

- Our children are "hot-blooded." Whether it's the metabolism or the heart issue (both can cause a person to be hot all the time) or something else, or all of the above, many of our children sweat a lot - even to be a bit "ripe-smelling."
- Some children experience unexplainable fevers.
- Many parents notice their child is very sensitive to sunlight and touch, particularly the hands and feet.
- Most parents talk about difficulty sleeping through the night. Some grow out of it, but many don't.

THE GASTROINTESTINAL SYSTEM

We are still looking for a gastroenterology researcher!



This system is just about always involved, and some kind of intervention is needed. This is the most chronically difficult issue for our families. Families of older children outside the USA and Canada tell of spending time in the hospital every couple of months or so, with NG (nasogastric) tube feedings and i.v.'s for dehydration, or feeding their children via NG tube at home.

In the US particularly, most children have g-tubes (gastrostomy tubes), which go directly through the stomach wall for feeding either by "bolus" (pouring in the formula or meal in one sitting) or timed drip-feeding (requiring a pump, often scheduled for feeding overnight). Some children have a surgical procedure, a Nissen's fundoplication (fundo), performed, where a surgeon puts an extra fold in the esophagus just above the stomach to help reduce reflux. But for some children, the "fundo" is not appropriate.

The rate of feeding has been a serious issue for many families. Some need to start slower than 60cc/hr. These children also have a hard time ramping up after "NPO" (nothing by mouth) for surgery. Keep an eye on this and document it because you may need to provide evidence to your child's doctor.

Good news, the feeding issues usually resolve themselves somewhere between the ages of 2 - 8 years old. There are a few cases where the child will clearly need the g-tube for life. There are also a few children had mild feeding issues that resolved around when they were a year old!

Many children have difficulty with constipation. All do better with more fluids, but it's hard to get a child –any child- to drink enough! If your child is having trouble with constipation even with what the doctor can prescribe, you may find some useful suggestions on our website's Frequently Asked Questions (FAQ) section on our website at http://faq.costellokids.com/

Low muscle tone (hypotonia) affects smooth muscles particularly, and the gut is one long straight muscle from lips to butt.

ORTHOPEDICS

Our children's ribs, hands, arms, ankles, hips and spine and spinal cord are involved.

The ribs are unusually shaped, which may explain why many of the children don't go through a crawling phase, even with therapeutic intervention.

Most children' hands (and feet) have lots of loose skin (cutis laxa), are *very* flexible, and tend to turn away from the midline ("ulnar deviation" – towards the ulna bone in the forearm). The hyper-flexibility makes it hard for fine-motor strength in their hands.

The appearance of our children's hands look to be the one clear factor that separates Costello syndrome from Noonan or Cardio-Facio-Cuteo (CFC) syndromes.

Rolling, sitting and walking will be delayed. Several children have wheelchairs to help them get around school, which over time have been replaced with walkers. (They have little protection reflex if they fall.) While his protection reflex isn't the greatest, one boy loves to play basketball and ski -- unassisted!

Many children wear ankle-foot orthotics (AFO's or DAFO's), and have their Achilles tendons "released." Several children have also gotten hip tenotomies (tendon-releasing surgery), with generally good success. A few have had hip reconstruction surgery.

Most children have trouble straightening out their elbows. Australians call them "kangaroo arms."

Several children develop scoliosis (the spine curves sideways) and have braces for their backs. Some have had surgery. There are a few children whose bones are so soft that they cause complications. One child's doctors had trouble putting in rods to correct the scoliosis because the bones were so soft. Kyphosis (the spine curves outward) is not unusual either, but the thought among orthopedists these days is to leave it alone, as the cure is worse than the problem.

Also, a few children have tethered spinal cords, and a few *develop* syringomyelia and Chiari 1 malformations (this is unusual!). Some need to be surgically repaired. Dr. Karen Gripp's publication, *High Incidence of Progressive Postnatal Cerebellar Enlargement in Costello Syndrome,* can help your child's orthopaedist determine how to monitor this.

THERAPIES

Our children do very well to Occupational and Physical Therapy (OT and PT); and early intervention (in the US, provided by the public school system and state programs).

Our children's receptive language skills appear to be much better than their expressive skills. Speech is delayed and limited. It's probably connected to the poor oral-motor coordination overall, small mouths and slightly larger-than-typical tongues (macroglossia) and low muscle tone.

Speech therapy (ST) is strongly recommended, as the children appear to respond well. Many children learn sign language and may have communication boards to help them until (or if) their speech develops well enough.

VISION

A higher-than-average number of children are myopic (near-sighted), often with lateral-beating nystagmus (the eyes jiggle – horizontally), and some have strasbismus (cross-eyes). Except for some children having delayed vision (several parents talked about being fooled by their child's effective use of hearing to mask their visual delay!), most visual issues appear to be correctible with glasses.

Many children have a hard time walking down stairs or stepping across different-patterned floors, because they have difficulty interpreting the lower "quadrants" of their field of vision. Parents of children who receive vision therapy report that their child responded well to it.

THE HEART

Just about all our children have heart issues, but this can be anything from mild arrhythmia to such severe HCM (hypertrophic cardiomyopathy) that the child dies from it (not common). Because of this, it is recommended that your child get an echocardiogram done to rule out any problems. An article by Dr. Angela Lin and associates, *Further delineation of cardiac abnormalities in Costello syndrome,* published in the American Journal of Medical Genetics in 2002, will give your doctor medical justification for this test.

CANCER

Though there have been around 18 published cases of cancer, several children have since been tested molecularly for Costello syndrome. The revised risk is about 15%. Dr. Karen Gripp and associates' 2002 article, *Five additional Costello syndrome patients with rhabdomyosarcoma: proposal for a tumor screening protocol*, in the American Journal of Medical Genetics is a good resource, but an important lesson was learned after its publication. The neuroblastoma screening (using a urine sample), actually has more false positives, so they could make us worry needlessly. Dr. Gripp wrote in a follow-up article, *Elevated catecholamine metabolites in patients with Costello syndrome* in 2004, recommends not using this screening method because of the false-positives.

The most common cancer is rhabdomyosarcoma (RMS), which has no screening test. Lisa Schoyer (a mom) is very interested in collecting information about this, so if your child does develop RMS, please contact her. She would appreciate all the data that can be gathered, in order to be as accurate as possible. (See back panel.)

We urge you NOT to worry too much about cancer before thorough testing, because the odds are still smaller than one in five (1:5). Also, with the recommended screenings that have been done after 2004, cancers that have been found have been in earlier stages of malignancy, have given children a better chance of surviving the cancer.

THE SKIN

Your child's doctor may talk about papillomata – wartlike skin growths, because they are described in the literature. These may start to show on your child starting at age 2, or they may never show up. Doctors do recommend that any skin eruption be tested to distinguish between papillomata, which can be benign tumors, and wart-like 'lesions.'

Some children develop Acanthosis Nigricans, the darkening of the skin. Dermatologists' treatments for this appear to work fine, for the most part. Itchy skin, from mild to extreme (very frustrating!), is also a common problem.

SEIZURES?

There appear to be increasing numbers of newly diagnosed children with seizures -- but we don't have enough data

to link it to Costello syndrome. This may be something that's showing up in addition to the Costello syndrome effect. One child had seizures that went away when surgery was done on her Chiari malformation (a deformity in the brain where the brain and the spinal cord connect) -- which, before the surgery, wasn't clearly the source of the seizure. If more parents report on this, we will have better information from which to prove or disprove a link!

HANG IN THERE!

Our children are "globally developmentally delayed," but they generally eventually reach all the childhood milestones. Thank goodness for their "warm, social personalities" often described in publications -- when it kicks in (usually after the gastrointestinal issues start getting resolved). It seems that wherever they go, they endear people to them. And their sense of humour – mature beyond their developmental age – helps us help them through the tough times. Have you noticed?

A typical child with Costello syndrome may see many doctors, including (but not limited to):

- a geneticist
- a gastroenterologist
- a cardiologist
- an orthopaedist
- an endocrinologist
- a neuro-ophthalmologist
- a pulmonologist
- an ENT (ear, nose and throat) specialist
- a pediatric dentist specializing in craniofacial deformities
- a neurologist
- a developmental pediatrician
- in addition to the primary pediatrician

Our children are amazingly tough survivors.

A FEW OTHER THINGS

Many parents also talk about trouble with stuffy and/or runny noses, which even something as minor as a cold can fill a tummy with mucus, causing increased vomiting. Combinations of over-the-counter medications mostly help. Those who have had tonsillectomy and/or adenoidectomy surgery do better. Several children who didn't sleep well did, better after this surgery – but not all.

Some children also have tracheal and/or laryngeal malacia (floppiness with each breath), for which a small number of children needed a tracheostomy. The good news is that they appear to grow out of it. One child who had a trach (tracheotomy) grew out of the need for it in a couple of years.

Our children need more calories too.

We've noticed that a good number of our children metabolize pain medications very quickly. Be sure that you tell your child's doctors so that pain management can be more effective.

If your child needs surgery, be sure to enlist the anaesthesiologist's help. One parent was alerted by a very observant anaesthesiologist, who not only gave a copy of his report to her, proving how her child had needed more anaesthesia, but he also instructed her to be vigilant with each future anaesthesiologist her child

sees.

YOU ARE THE EXPERT ON YOUR CHILD

Be prepared to be the one who knows the most about your child, and the key person for your child's medical and educational needs. If you're up to it, ask for copies of all your child's medical reports so that when you visit the next doctor, you have all the information at hand. It makes a big difference! *Even if you don't understand them*, being able to provide reports to each specialist helps that specialist immensely! Because of the complexity of multiple issues, your child needs to be seen by the best in each field – if possible.

Some parents have found that a specialist who is able to say "I don't know" is someone confident enough to recognize his or her limitations – that doctor is being honest with you. The odds of their having treated another child with CS are really low. You are building and maintaining a team to support you. You need to be able to trust them with what they know – and don't.

Please remember that YOU are with your child for life, and the specialists are not. Trust your instincts, and do what you can to educate yourself so that you are taken seriously when you meet with the specialists your child will need to visit. If you have access to the internet, join our listserv!

Next Steps: With this new way of thinking about Costello syndrome and the other syndromes on the Ras Pathway, a number of possibilities for treatment can be considered! This pathway is known by cancer and other researchers. It could be that an existing medication could help cure our children of the worst effects! Incredible work is being done internationally on our children' syndrome. Members of our Professional Advisory Committee are actively researching and recruiting researchers. Your participation would be greatly appreciated!

In the meantime, treat each of your child's problems based on the specialty of the problem. Remember that your child shares your genes - and has needs and responses like any other child. Not everything can be "blamed" on the syndrome.

While they have incredibly challenging issues, our children are wonderful sons and daughters.

Please Contact Us!

ICSSG (International Costello Syndrome Support Group)
UK Registered Charity Number 1085605
Colin Stone, Webmaster and Founder, father of Helaina
http://costellokids.com
90, Parkfield Rd North
New Moston M/C40 3RQ
United Kingdom

CSFN (Costello Syndrome Family Network)
a 501c(3) Non-Profit organization
Sandra Taylor, President, mother of Jill
info@costellosyndromeusa.org
PO Box 516
Woodinville, WA 98072-0516
(848) 228-CSFN (2736)
www.costellosyndromeusa.org

RASopathies Network USA
a 501c(3) Non-profit organization
Lisa Schoyer, Chair, mother of Quin Johnson
rasopathies@earthlink.net
244 East Taos Road
Altadena CA 91001-3953
USA

Photo credits,

Rick Guidotti, http://www.positiveexposure.org/home.html
And the parents of, Helaina Stone, Kelsi Moore's hand and foot, Jayne Keizer, and Quin Johnson (in memoriam).