DYRK1A and 21q22.13 deletion syndrome
**What is DYRK1A syndrome?**

*DYRK1A* is a gene that is involved in brain growth. It was identified several years ago but only recognised to be associated with a neurodevelopmental condition in 2008. The *DYRK1A* gene is on chromosome 21q22.13 and is one of the genes that is missing in the 21q22.13 deletion syndrome. When we compare children with the 21q22.13 microdeletion syndrome and those with changes in the *DYRK1A* gene, many of their features are similar. We now think that the key features of 21q22.13 microdeletion syndrome are caused by absence of *DYRK1A*.

**Most common features**

All children with the DYRK1A syndrome who have been identified to date have at least a moderate degree of learning disability and developmental delay. Some of these features are also found in many other genetic conditions so children may not be easily recognised without genetic investigations.

Other typical features include:
- Microcephaly (small head)
- Epilepsy
- Speech delay
- Short stature
- Ritualised behaviour and/or autism
- Common facial appearance.

**How many people have this condition?**

DYRK1A syndrome is a rare condition, first described in the medical literature in 2008. To date, around 30 children have been reported with this condition. However, with the increasing use of the latest ‘gene sequencing’ technology, it is expected that many more people will be diagnosed over the next few years (including adults). One large research study in the United Kingdom (Deciphering Developmental Disorders), which is seeking to identify the genetic causes of developmental delay in children, has so far identified *DYRK1A* as being one of the 10 most frequent genes involved.

**Was the diagnosis helpful?**

- Definitely. It was almost like a jigsaw puzzle being completed.
- Even though we started therapies before a formal diagnosis, it has been very helpful in terms of connecting with other families and knowing what to expect, what aspects of his life can we improve on and what aspects we should accept.
- The initial information given to us by the hospital’s pediatrician was not supportive at all and gave a very negative outlook to our daughter’s condition, life expectancy and quality of life.
What is 21q22.13 deletion syndrome and how is it related to DYRK1A syndrome?

Sometimes deletions can occur, removing a large segment of DNA from a chromosome. Such deletions may remove many adjacent genes. One chromosomal deletion, which removes a single copy of the *DYRK1A* gene along with neighbouring genes, is the 21q22.13 deletion. For this reason, the 21q22.13 deletion syndrome has features that overlap with DYRK1A syndrome. To date, around 30 children have been described with 21q22.13 deletions. All have very similar clinical features, but none has an identical chromosomal deletion. Broadly speaking, children with a 21q22.13 deletion have the same types of problems as are found in DYRK1A syndrome. So far, there is no evidence that children with a 21q22.13 deletion are more severely affected than children with a *DYRK1A* gene mutation. However, it is possible that wider deletions involving other neighbouring genes could contribute to a more severe phenotype.

Why did this happen?

When children are conceived their parents’ genetic material is copied in the egg and sperm that makes a new child. The biological copying method is not perfect and occasionally random, rare changes may occur in the genetic code of children for the first time. Such changes, therefore, cannot be found in a child’s parents. DYRK1A disorder occurs when one of these random, rare changes affects the DYRK1A gene on chromosome 21. In all families that we know about so far, the DNA change in DYRK1A occurred ‘out of the blue’ in this way [this is what you may hear a geneticist referring to as a de novo change, or a 'new mutation'].

Can it happen again?

The possibility of having another child affected by a rare gene disorder depends on the genetic code of the parents. For the DYRK1A disorder where parents do not carry the same DYRK1A change as their child, the chances of having another child are almost certainly no higher than anyone else in the population. Empirically, this risk is less than 1%. The reason why there is some residual risk of recurrence is due to a rare phenomenon called ‘germline mosaicism’. This is when a parent carries a genetic change, but it is limited to a small cluster of egg or sperm cells. The genetic change would not, therefore, be detected in the parents’ blood test. For specific advice about the chance of a DYRK1A change happening again, it would be sensible to speak to a clinical geneticist or a genetic counsellor so that they can give you specific advice for your family.

“Every milestone is a wonderful achievement to be celebrated and never to be forgotten or taken for granted. When I was pregnant I once said: I don’t think a second child can ever be as exciting as a firstborn, because you know every milestone will be surpassed by an even greater one. So we were given a child where every single milestone is simply awe inspiring and momentous.”
Development

Growth
Some babies are small for dates. Children with DYRK1A syndrome tend to grow along the 2nd to 9th centile, but some grow well and are of average height. The head circumference can be normal or small at birth, but most children present with progressive microcephaly [small head circumference] when they get older.

Feeding
Parents are likely to need support as feeding difficulties can be an issue at first. Some babies will suck weakly and some need high energy milks to encourage weight gain. Many babies readily bring feeds back (gastro oesophageal reflux) and need careful positioning for feeding and while sleeping. Some babies are helped by medicines for reflux. Some children can present with constipation.

Sitting, moving, walking
Babies are usually quite late to become mobile. All children have delayed motor development and some may need physiotherapy but most will achieve walking. Some children may have an unusual gait when walking because of stiffness, or balance issues (also called ataxia).

Speech
Children typically experience delay in communicating and learning to use words. The eventual range of achievement is very broad, but most children will not develop meaningful speech. Those who do develop speech may achieve single words, short phrases or basic sentences and others will use signing, gesture and vocal noises to express their needs. Some parents report good receptive language skills (understanding of spoken language).

Learning
All children that we know of have at least moderate learning disability and require specialist support with learning.

“Some ‘professionals’ gave their opinions on Channing’s future capabilities and have been completely wrong. She is a determined young girl and will not be stopped. We were told that she will never sit or walk, she now does both completely independently.” - 2½ years

“He is very vocal but non-verbal at this stage and does not respond to signing either. His non-verbal communication is very good and he does show many signs of understanding us.” - 21 months
Medical concerns
These disorders have been found in children with either a 21q22.13 deletion including \textit{DYRK1A} or a change [mutation] in \textit{DYRK1A}. They are not found in all children and your child may not be affected.

Low muscle tone  Low muscle tone  Low muscle tone  Low muscle tone
Low muscle tone (hypotonia) is usually obvious in the newborn period and may persist throughout childhood. This is likely to contribute to feeding difficulties and delay in reaching motor milestones. Although walking is nearly always achieved, some children may experience loss of previously achieved motor milestones as they grow older, although there is no evidence that DYRK1A syndrome is a progressive condition.

Feeding difficulties  Feeding difficulties  Feeding difficulties  Feeding difficulties
Feeding difficulties are fairly common in newborn babies. Some babies may require temporarily feeding by nasogastric tube. In some children, feeding difficulties may persist.

\begin{quote}
\textit{Louis has severe sensory issues. Due to his oral aversion and subsequent feeding difficulties, we had a MicKey placed at 15 months. He lost his oral intake 2 weeks afterwards and has taken nothing by mouth ever since. We struggled with severe and unexplained vomiting from 16-21 months, but after a blended diet was introduced, the vomiting gradually eased up.} " - 21 months
\textit{Severe reflux treated with a special diet and two forms of medication.}" - 2½ years
\end{quote}

Seizures  Seizures  Seizures  Seizures
Quite a few children will have seizures, although these may be rare or occasional. These episodes may warrant further investigation at some point (EEG, brain MRI).

Eyes and eyesight  Eyes and eyesight  Eyes and eyesight  Eyes and eyesight
A wide range of eyesight problems has been reported, including short or long-sightedness (myopia and hypermetropia) and strabismus (squint), but also more rarely small palpebral fissures (eye openings), ptosis (droopy eyelids), small optic nerves, cataracts and coloboma (a problem in the development of the eye).

Management recommendations
\textit{At diagnosis}
- EEG (measurement of brain’s electrical activity), if seizures are suspected
- Brain imaging with MRI
- Ophthalmology (vision) assessment
- Feeding management if necessary
- Consider heart and kidney ultrasound scans to rule out structural anomalies.

\textit{After diagnosis}
- Long term follow up by a developmental paediatrician
- Speech and language support as needed
- Physiotherapy and occupational therapy support as needed
- Regular eyesight checks may be recommended
**Other features**

Some families and doctors have noticed additional features. It is not known yet whether or not they are related to the *DYRK1A* spectrum.

- Endocrine defects (growth hormone deficiency, hypothyroidism, precocious puberty)
- Hallux valgus [the big toe is angled inwards]
- Cleft palate
- Scoliosis [curve in the spine] and contractures [joints cannot be flexed because muscles are shortened]
- Pulmonary stenosis [structural anomaly of the heart]
- Kidney missing or with a structural anomaly
- Recurrent infections.
- Most children share similar subtle facial features including deep-set eyes, a small chin (micrognathia) and a thin upper lip.

"Our daughter was born with pulmonary stenosis. She has undergone an operation to stretch the artery and now has normal flow through the heart chambers. She now sees the specialists once a year for a checkup." - 2½ years

**Behaviour**

We are not aware of a specific abnormal behaviour associated with *DYRK1A* disorder, and children typically tend to have behaviour in keeping with their overall degree of developmental delay. Some children have been reported as having autistic tendencies, anxiety, hyperactivity and hand stereotypies (flapping), but most have a happy disposition.

"Most of what Channing does to/with us is fantastic. Since she was able to, she would smile in such a manner that it was infectious. She will hardly ever complain for the sake of it. She is a relatively quiet girl but also loves her cuddles and will squeeze into our arms when she feels it’s time for some attention.”

- 2½ years

"Elise has a very dry sense of humour, and makes us laugh a lot. She doesn’t talk a lot, but when she does, she sparkles and lights up a room. She loves being outdoors and getting messy.”

- 10 years

"Our daughter was born with pulmonary stenosis. She has undergone an operation to stretch the artery and now has normal flow through the heart chambers. She now sees the specialists once a year for a checkup." - 2½ years
“Parenting a child with complex health needs, autism and a genetic disorder is the most challenging, rewarding, tiring and wonderful journey anyone can take. I am constantly amazed by Elise’s resilience, her ability to take all the challenges she faces in her stride. Elise is a wonderful, loving, joyful child who only wants people’s patience and understanding, love and care to make her feel happy and secure. Our lives have changed beyond recognition, but my perspective on life has changed completely. Elise has taught me patience, compassion, all consuming love - and it’s been one hell of a roller coaster ride! ” - 11 years

“We never did anything for charities before but now often take part for the charities or organisations that have helped us and our daughter. Channing has introduced us to a whole new world of people who we would never have met previously. She has managed to improve our quality of life in a way we would never have thought possible.” - 2½ years

“People always remark on his serious facial expression, probably due to his mild dysmorphic features. Because we know him, we know this not to be true at all. He is an extremely friendly, gentle little soul and we love getting to know him better every day. Besides his problems, which are obviously numerous, he is in many ways such an easy child. He can entertain himself for hours and is happy to sit and play with his favourite toys. He has a wonderful sense of humour and loves ‘talking’ to us. He is extremely strong willed, which we love!” - 21 months
Support and Information

Rare Chromosome Disorder Support Group,
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Join Unique for family links, information and support.
Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org Please help us to help you!

Website: http://dyrk1a.org
Facebook  DYRK1A gene changes
www.facebook.com/groups/dyrk1a

Unique lists external websites and webpages in order to be helpful to families looking for information and support. This does not imply that we endorse their content or have any responsibility for it.
This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. The text was written by Dr Muriel Holder, Consultant in Clinical Genetics, Guy’s Hospital, London, UK, and the guide was compiled by Unique.
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