How common is TBR1–related disorder?

TBR1-related disorder is extremely rare, about 40 people have been identified worldwide (2020), although many people currently remain undiagnosed. The absence of specific signs makes diagnosis difficult, diagnoses are made using DNA sequencing technologies.

Why did this happen?

When a child is conceived their parents' genetic material is copied in the egg and sperm that makes them. The biological copying method is not perfect and occasionally random, rare changes occur in the genetic code of a child that are not seen in the DNA of their parents. *TBR1*-related disorder occurs when one of these random changes affects the *TBR1* gene. These types of change happen naturally in all of us and are not due to lifestyle or anything anyone did prior to or during pregnancy.

Can it happen again?

The possibility of having another child affected by a rare gene disorder depends on the genetic code of the parents. In most families, this genetic change has happened for the first time in the child with *TBR1*-related disorder. This is called '*de novo*'. When the parents are unaffected, the risks of having another child with the same condition are very low (<1%). Very rarely, a parent may be identified as having germline mosaicism, which means the gene variant can be present in the egg or sperm but is not detected in a standard blood test. If somebody with *TBR1* related disorder were to have a child of their own, the risk of passing on the affected gene would be 50%. Nobody with *TBR1* related syndrome is known to be a parent. Each family situation is different and a clinical geneticist or genetic counsellor can offer family specific advice.

Can it be cured?

TBR1-related disorder cannot be cured however, knowing the diagnosis means that appropriate monitoring and treatment can be put in place. Some clinical trials may emerge in the future.

Facebook groups and other links:

There are 3 *TBR1* gene variant groups on Facebook :
https://www.facebook.com/groups/508232163293215
https://www.facebook.com/groups/TBR1gene
https://www.facebook.com/%C3%81lvaro-GEN-TBR1-974245972744292
There is also a french forum on a rare disease website:
https://forums.maladiesraresinfo.org/tbr1-t2980.html

Management recommendations

- An assessment of special educational needs should be carried out so that extra help can be put in place at school
- Early input from speech and language, physio– and occupational therapists is important as is continued therapy as needed
- Input from a neurology/neurodevelopment team may be required
- An ASD assessment and a neuropsychological assessment may be required
- Feeding management if necessary (for example NG tube feeding as a baby)
- EEG (measurement of the brain's electrical activity) if seizures are suspected
- Eye check may be required
- Brain imaging with MRI
- Follow up by a developmental paediatrician
- Clinical genetics referral (to help interpret genetic test results, advice about future pregnancy etc.)
- Orthopedic check if necessary

Inform Network Support

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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/donate Please help us to help you!

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Understanding Chromosome & Gene Disorders

TBR1–related disorder

rarechromo.org

What is *TBR1*–related disorder?

TBR1-related disorder is caused by changes (also known as variants or mutations) in, or a deletion of, the *TBR1* gene.

Children with *TBR1*-related disorder have neuro-developmental difficulties. They present mild to severe developmental delay (DD) and intellectual disability (ID). About 75% of the affected individuals have autistic traits. Aside from DD/ID and autistic traits, most of the other *TBR1* -associated features are either nonspecific or infrequent.

TBR1–related disorder features

Most children have:

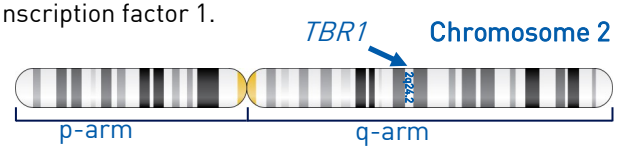
- Developmental delay
- Mild to severe ID
- Autistic traits
- Behavior disorders (mainly attention deficit and aggressive behavior)
- Hypotonia (low muscle tone/floppiness) and fine motor delay

Other possible features include:

- Facial particularities
- Skeletal features
- Intra-uterine growth retardation
- Abnormal movements
- Seizures / abnormal EEG (electroencephalogram) without seizure
- Abnormal brain MRI (Magnetic resonance imaging) findings
- Constipation
- Feeding difficulties
- Small head circumference (microcephaly)

TBR1 and chromosome 2q24.2

The *TBR1* gene is located at the middle of the long 'q' arm of chromosome 2 in a region called 2q24.2. Its name is an abbreviation of the protein it codes for, T-box brain transcription factor 1.



We have two copies of chromosome 2 and therefore two copies of the *TBR1* gene. *TBR1*-related disorder is caused by one copy of the *TBR1* gene not functioning properly.

This may be due to a change (a variant) within the gene, which disrupts its function, or to the loss (deletion) of the gene or part of it. The other copy of the *TBR1* gene is unaffected and so can carry out its usual function. This type of genetic change is called autosomal dominant, since the change occurred on an autosome (chromosome 1-22) and symptoms are apparent with only one altered copy (dominant).

The *TBR1* gene has multiple roles in the genetic control of our development and functioning. The TBR1 protein is a brain-specific factor, particularly expressed in the cerebral cortex. TBR1 regulates the expression of several genes associated with ID and autism spectrum disorders.

Development

Physical Development

Children with *TBR1*-related disorder learn to walk alone, but this may be slightly to severely delayed. Hypotonia and/or joint laxity may play a role in delays.

Learning

Children with *TBR1*-related disorder typically have learning difficulties and are often given a diagnosis of intellectual disability (ID). They typically need extra help in school. Although most go to a mainstream primary school, the extra demands of mainstream secondary school may prove too challenging, and children may transfer to special schooling or remain in mainstream schools with Educational Health Care Plans (EHCP).

Behaviour

Children with rare chromosome and gene disorders often have behavioural, social and/or communication difficulties and vulnerability in these areas means that children should be monitored and families offered early support. Behavior disorders are frequent in *TBR1*-related disorders notably autistic traits, attention deficit, anxiety and aggressive behavior. Children are also described by their parents as being happy and loving.

Speech and language

All children with *TBR1*-related disorder identified so far, have moderate to severe speech delay. Some children are non-verbal. Hearing and visual impairments must be detected and corrected as early as possible to limit delays.

Growth

Growth is generally normal. Some children have been reported with a short stature but a few children are known to be tall.

Medical concerns

Neurological features

Low muscle tone (hypotonia) and fine motor delays are frequent in early childhood and contribute to developmental delay. Gait disorders (not walking as expected) and abnormal movements such as uncontrolled muscle spasms (dystonia), involuntary rapid and jerky body movements (chorea), or involuntary, rhythmic muscle contractions (tremors) have been observed in some children.

Changes to brain structure that have been observed by MRI are an abnormal cortex, abnormal hippocampi and a thin/absent anterior commissure. These are the consequences of the dysfunction of the TBR1 protein and explain the cognitive difficulties.

Seizures

A few children with *TBR1*-related disorder have experienced seizures, including absence (sudden lapse in consciousness) tonic-clonic (when muscles stiffen (tonic) and arms/legs jerk (clonic), and generalized seizures (impaired consciousness with movement of arms and legs). Children respond to typical drug treatment for epilepsy. Some children have an abnormal EEG without clinical seizures.

Facial particularities

Just over half of children with *TBR1*–related disorder identified so far have minor and non-specific facial particularities such as a high or large forehead, wide nasal bridge, long groove between the nose and upper lip (philtrum), protruding jaw (prognathism), and wide mouth.

Skeletal features

Skeletal features concern about half of affected children. They are minor and variable, including 'loose' joints (joint laxity, flat feet (pes planus), curvature of the spine (scoliosis) and/or joint deformation.

Other less common medical conditions

- **Constipation** can be mild to severe and concerns about 25% of affected children.
- **Feeding** difficulties have been identified in about 15% of children described in the medical literature, potentially leading to severe complications or surgeries such as Nissen fundoplication [a surgical procedure to treat gastroesophageal reflux disease (GERD)]
- **Strabismus** (misaligned eye) is the only visual disorder reported so far and affects a few children.