



Understanding Chromosome & Gene Disorders

# **IQSEC2- related disorder**



rarechromo.org

This guide is designed to help families and healthcare professionals looking after people affected by IQSEC2-related disorder. It contains information about the cause, the ways in which it can affect people and suggestions about the help and management that can benefit people with this disorder. It also contains details about support groups and further information that families can access.

## What is IQSEC2 related disorder?

IQSEC2-related disorder is a rare genetic condition that results from a change in function of a gene called *IQSEC2*. IQSEC2 is an abbreviation of 'IQ motif and Sec7 domain 2', which is a technical description of what the gene codes for. This gene has previously been named *BRAG1*, *MRX1*, *MRX78*, *MRX18* and *IQ-ArfGEF*.

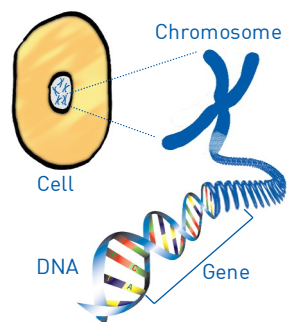
## What are genes, DNA and chromosomes?

Genes are the 'instructions' that our bodies use for many functions including the control of growth and development. The majority of important genes, like IQSEC2, code for proteins. Genes can be described as carrying instructions for our cells and proteins carry out specific tasks.

Genes are made from a complex structure called DNA. DNA, and therefore genes, can be described as a sequence of letters but unlike an alphabet, the sequence (or code) only uses 4 letters (G, A, T, C). DNA sequences are incredibly long and include all the information for the thousands of genes included in our 'genome' (our complete set of DNA). However, they need to fit inside the microscopic cells that our bodies are made from. DNA is therefore tightly compacted into organized structures called chromosomes.

Most of our cells normally contain 46 chromosomes, organised as 23 pairs. We usually inherit one chromosome of each pair from our mother and the other from our father. Chromosome pairs are numbered 1 to 22 and the 23<sup>rd</sup> pair comprises the sex chromosomes, which determine biological sex (whether we are male or female). Females usually have two X chromosomes (XX) and males usually have an X and a Y chromosome (XY).

Since chromosomes come in pairs, so do the genes contained within them. We therefore have two copies of each gene in chromosomes 1 to 22, and females (XX), have two copies of each gene on chromosome X. Males have one copy of chromosome X and although chromosome Y does contain some genes that exist on chromosome X, the majority are not present, so males have a large number of genes on the X chromosome that are only present as a single copy. This is the main reason why we often see a difference in the outcome between boys and girls if a gene on the X chromosome is affected. IQSEC2 is located on chromosome X.



Chromosomes pairs 1-22, X and Y (male)

## What genetic changes cause IQSEC2-related disorder?

There are many different changes that can occur in the coding sequence of the *IQSEC2* gene, they are commonly called 'variants' or 'mutations'. Some variants will result in the production of no or very small amounts of a shorter (truncated) protein, these are named 'loss of function (LOF) truncating mutations'. Some sequence variants may result in the production of a protein that has gained an altered function. Some may result in no protein being produced from the altered gene sequence. The effect on the protein depends on the exact sequence variation. These gene alterations can be described as:

'**missense**' - like a 'spelling mistake in the genetic code.

'**nonsense**' - like a full stop has been introduced into the genetic code.

'**frameshift**' - the genetic code is not read properly since the code has shifted.

Some changes to the *IQSEC2* gene result in no, or a mild, outcome for some people whereas others are more seriously affected. The exact reasons for this are not currently fully understood but the unique genetic background of each individual may be involved. There are also genetic changes that have been identified in the *IQSEC2* gene that are thought to be 'benign', meaning nobody is expected to be affected by them.

**Girls and women (XX):** Since most mutations are found in one copy of the *IQSEC2* gene, and most females also have a second copy of *IQSEC2*, it is possible for girls and women to have mild to moderate symptoms, or no obvious outcome. X-linked gene variants are often complicated due to a phenomenon known as X-inactivation. Although females have two X chromosomes, one is usually switched off (and most, but not all of its genes are inactivated). X-inactivation is even more complicated by the fact that not all cells in all organs switch off the same X chromosome and some genes escape X-inactivation. *IQSEC2* is thought to escape X-inactivation, which means both copies of the gene are expected to be active.

**Boys and men (XY):** The situation is different for boys and men since they only have one copy of the *IQSEC2* gene. If this copy carries a variant of clinical significance, also known as a 'pathogenic' variant (meaning a variant that can cause symptoms) a child will be affected since there is no second copy of the gene with normal function. Boys and men are thought to be more severely affected than girls and women.

The information in this guide is drawn from clinical data, publications in the medical literature and information from *Unique* members. Publications used for this guide include: Radley 2019, Mignot 2018, Shoubridge 2018, Zerem 2015 and Tran Mau-Them 2014. Original articles and/or abstracts can be found on the internet in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>). If you wish, you can obtain most articles from *Unique*.

## What does IQSEC2 do?

The *IQSEC2* gene codes for the IQSEC2 protein which is known to interact with other proteins, which are involved in transmission of chemical messages by neurons (nerve cells) in the brain. When the *IQSEC2* gene is not working properly, the IQSEC2 protein is abnormal or absent and this interferes with the sending of chemical messages in the brain. IQSEC2 is also thought to play a role in the normal growth of structures called dendritic spines, which are projections that grow out of neurons, which help transmit electrical signals to the cell body (the central part) of the neuron. Not all the functions of IQSEC2 are currently known but knowledge of IQSEC2 and its functions will improve over the years with further research.

The *IQSEC2* gene instructs different cells in different organs at different stages of development, changes to this gene could therefore affect different parts of the body in different ways. The most important role of IQSEC2 is thought to be in the brain during early development. It is possible that if a mutation occurs later in development, and is not present in all cells (i.e. is mosaic), the time at which the mutation arose may influence a person's symptoms.

## Why did this happen and can it happen again?

The majority of individuals with an alteration in one copy of the *IQSEC2* gene reported so far have not inherited it, it has occurred as a new event in them (this is called a *de novo* (*dn*) gene alteration). *De novo* gene alterations are random events so cannot be predicted. *IQSEC2* gene alteration have also been reported to have been inherited from mothers who have mild developmental or learning problems or no detectable symptoms.

When a child is identified as having an *IQSEC2* mutation, both parents are usually offered a genetic test to establish possible inheritance. Where neither parent is found to have an *IQSEC2* mutation, following a DNA test from a blood sample, it is unlikely that they will have another child with the same mutation or any other chromosome disorder. However, very rarely (less than 1% of the time), both parents can be found to have unaffected chromosomes, but a few of their eggs or sperm can carry an *IQSEC2* mutation. This is called **germline mosaicism** and it means that parents whose chromosomes appear normal when their blood is tested can have more than one child with the mutation. Although this is incredibly rare, there are at least two reports in the medical literature of siblings with an *IQSEC2* gene alteration, which was not present in their parents' blood samples. It is not currently possible to test eggs or sperm for gene alterations.

It is for these reasons, parental testing and genetic counselling are recommended for families wanting to have further children. It is important to emphasize that this is nobody's fault. There is nothing either parent did before, during or after pregnancy that could have caused this genetic change. If you have any concerns about having further children, or would like more information, please read our 'Planning your next child' guide.

## How common is IQSEC2-related disorder?

A change in the *IQSEC2* gene was first described in a single child in 2013 and since then, about 100 children/people have been described in the medical literature as having a gene alteration in *IQSEC2* (2019).

Genetic testing was once a complicated, costly and time consuming process. Recently, there have been major advances in technology and cost efficiency, that have enabled a more prolific use of genetic testing, so it is likely that increasingly more people will be diagnosed with gene alterations in *IQSEC2*.

## What features and symptoms do people with IQSEC2-related disorder have?

As with many genetic conditions, children with IQSEC2-related disorder can have a range of symptoms. As more children are diagnosed, and information is shared, the range of difficulties and the likelihood of a child having these features will become more clear. Since the *IQSEC2* gene is located on the X chromosome, the effect will vary between boys and girls. The outcome will also vary according to the exact genetic change and its effect on the IQSEC2 protein.

### Common features:

- Developmental delay
- Intellectual disability
- Speech and language difficulties or absent speech
- Seizures and epilepsy
- Autism spectrum disorder or autistic like behaviour
- Hypotonia (low muscle tone/floppiness)
- Developmental regression

### Other possible features:

- Ataxia (unsteadiness when walking and/or running)
- Drooling
- Unexplained laughter
- Vision problems and/or squint
- Unusual head shape
- Structural brain anomalies on brain scan
- Feeding difficulties
- Gastro-oesophageal reflux
- Constipation
- Sleep disturbance
- Scoliosis (curvature of the spine)

## ■ Pregnancy and Birth

The majority of pregnancies of children with IQSEC2-related disorder reported so far have progressed to term (38-42 weeks) and have been mostly unremarkable. Some children were delivered by emergency caesarean section, but this is also true of children without a genetic disorder.

## ■ Feeding and Growth

Some children with IQSEC2-related disorder have feeding difficulties. A few babies have been reported as having gastro-oesophageal reflux or vomiting. For some, the use of medications to help control reflux can be beneficial, for others, nasogastric tube feeding (where a tube is placed through the nose into the stomach) may be required. As children get older, feeding issues can improve, but for some children, difficulties feeding or retaining food causes a gradual but consistent weight loss and a gastric feeding tube (known as a G-tube or PEG (percutaneous endoscopic gastrostomy)) may be recommended (a tube is inserted into the stomach via the body wall through which regular feeds can be administered). Some children also have constipation which may need to be medically managed. However, children with IQSEC2-related disorder are expected to have normal growth.

If a child with IQSEC2-related disorder has a developmental disorder such as ASD (autism spectrum disorder) or SPD (sensory processing disorder), this may have an impact on their eating behaviour. Some children may have an aversion to certain foods, be a 'picky eater', reluctant to try new foods, be very sensitive to different textures (which may result in vomiting) or will not eat food of a certain colour.

**“ He has a mashed diet as he cannot chew food. He has a gastrostomy for fluids & medication & if he won't eat he has feeds. ”** Age 24 years

**“ She is a great eater but she often eats too quickly. ”** Age 13 years

## ■ Development

Most children identified so far (2019) with IQSEC2-related disorder have been described as having developmental delay. This means that they are delayed in reaching milestones like sitting and walking and have learning difficulties. All children with IQSEC2-related disorder develop differently and the severity of developmental delay varies. Some children are able to sit and stand shortly after the standard milestone range but most take longer.

The majority of children identified so far have hypotonia, which is low muscle tone causing a child to appear 'floppy' and this can have a significant effect on reaching certain milestones. Children will benefit from physiotherapy (also known as physical therapy) and occupational therapy to help them achieve their full potential. Once your child has shown their individual pattern of development it will become easier to predict their longer term possibilities.

## ■ Motor skills and self care

The majority of children for whom we have information, have poor gross motor skills but this varies greatly, especially between girls. Most girls learn to walk and run albeit often with some unsteadiness or clumsiness while boys may not develop the ability to walk and are described as 'non-ambulatory'. Hypotonia can affect mobility. Physio-therapists can supply children with equipment like walking frames and wheelchairs and can suggest and perform specific exercises and stretches to aid movement and prevent the development of muscular problems and spinal curvature. Boys are more likely to require the use of a wheelchair; it is currently (2019) thought that males with 'nonsense' or 'frameshift' gene alterations (see page 3) will not learn to walk or sit up unaided.

“ She walked at 16 months, but was a little slow in meeting early physical milestones. She was/is somewhat floppy but she can run, jump, walk stairs, etc. Her physical strength is not much of a concern. ” Age 12 years

“ He has ataxia in all 4 limbs. He is unable to walk or weight-bare. He has no strength in his legs. ” Age 24 years

“ She began walking at 18 months. Used SMOs for several years. She has hypotonia and is unable to run consistently or ride a bike. She is able to walk and climb stairs without issue. ” Age 13 years

Developmental regression (losing skills once learnt) is a feature of this condition. It is not yet known whether lost skills can be re-learnt.

“ She has regressed from early age. When she was about 2 years old, she had a few words but those have all gone. She seemed to be more responsive to verbal commands earlier now she has a longer processing time. She has had therapy her whole life and has had made minimal progress. ” Age 13 years

The majority of children for whom we have information also require assistance for all areas of daily living.

“ She is not fully potty trained. We have been working full-time for over 4 years. She does relatively well at school and when asked. She sometimes will go to the restroom on her own or will ask to go. ” Age 12 years

“ He requires full assistance with all personal care. He is doubly incontinent. He resists getting dressed/undressed. He clamps his mouth shut when trying to clean his teeth. He wears incontinence pads. ” Age 24 years

“ She is toilet-trained but only because we take her once per hour and she still has accidents. She is unable to do any self-care activities independently and requires full support for 100% of daily living. ” Age 13 years

## ■ Intellectual Abilities and Schooling

Intellectual disability (ID) or intellectual development disorder (IDD) are terms used to describe significant limitations in intellectual functioning (measured by IQ scores) and adaptive behaviour (types of behaviour used to adjust to other

behaviours or situations). So far, most children reported in the medical literature with IQSEC2-related disorder have also been given a diagnosis of intellectual disability, ranging from mild to severe for girls and severe to profound for boys. Further diagnoses will establish if this is due to the fact that only children who are more severely affected have been offered a genetic test or if all children with IQSEC2-related disorder will develop moderate to severe ID.

As infants become older, schooling can be a concern for some parents. The vast majority of children with IQSEC2-related disorder will require special needs schooling. Some have very limited intellectual ability. Nonsense and frameshift gene alterations are thought to lead to more significant intellectual disability. In general, intellectual disability is more marked in males.

“ She currently attends a regular elementary school. She spends most of her time in the ID room. She has speech and OT at school. She attends special events with her 5th grade class. She also eats lunch with them, gym, and goes to recess with them. They have been great at including her. ” Age 12 years

“ He attended a PMLD school which was weekly boarding. The school was excellent & supported us all. ” Age 24 years

“ She attends a specialized school for kids with severe developmental delays. She has a 1:1 teacher with her all day and her curriculum is completely specialized to work on life skills. ” Age 13 years

### ■ **Speech, language and communication**

Speech and language skills can be very variable between children with IQSEC2-related disorder, however marked speech problems are expected. Children are often very delayed in their ability to speak with language being very limited or they do not learn any spoken language but learn other ways to communicate their feelings and needs. It is thought that boys with nonsense or frameshift gene alterations may never learn to talk.

Speech and language therapists can help by assessing communication skills. They can help with speech development and introduce communication devices. They can also help to ensure that whatever your child's ability, they are supported in achieving their full communication potential.

“ She generally can meet her needs with verbal communication. She uses a communication aid at school so she can anticipate what will come. She has a much longer processing time than most. She likes to ask someone repeated question, usually the same question. ” Age 12 years

“ He cannot communicate at all. He can be extremely noisy. ” Age 24 years

“ She is working to use an iPad but has very limited communication abilities. Only able to use a few signs and limited iPad use. Otherwise, completely non-verbal. ” Age 13 years



## ■ Behaviour

Although behavioural difficulties have not been fully described for all children reported in the medical literature, behavioural, social and communication difficulties are common in children with IQSEC2-related disorder. Vulnerability in these areas means that children should be monitored and families offered early support.

Autism has been diagnosed in many children with IQSEC2-related disorder. Girls may be more likely to be diagnosed with autism because the more severe intellectual disability in boys may preclude a diagnosis of autism (about half of girls reported to date have been diagnosed with autism). However, severely affected boys may still have some autistic-like behaviour, for example not liking to be touched or a dislike of loud noises. Some children may also have other stereotypic movements (non purposeful movements) such as rocking or hand flapping. Some behaviours may be more prominent when a child is feeling anxious and has difficulties with comprehension and communication.

From birth to at least 3 years of age, most children are routinely screened for developmental milestones. If there are any concerns about a child's development or behaviour they should be referred for developmental evaluation, which may include an autism specific screening.

There is not a 'medical test' that can diagnose autism, children undergo an autism-specific behavioural evaluation usually carried out by a specially trained physician and psychologist. Evaluations will vary according to the age of the child and may be multidisciplinary. A child may be assessed by a speech and language therapist as well as an occupational therapist. Depending on the outcome, further evaluation by a specialist such as a developmental paediatrician, neurologist, psychiatrist or psychologist may be offered or recommended.

Depending on a child's abilities, joining a social skills group may help with social difficulties, to learn and practise important skills. A parenting course for autism may also help parents to learn behaviour management tools and help to encourage communication and cooperative behaviour in their child to strengthen their emotional wellbeing. Some parents have tried medication to help control their child's behaviour when it becomes of great concern (such as self harming or aggression). An occupational therapist may also be able to help with some behaviours by giving your child tools to deal with their sensitivities.

**“ ASD diagnosis around age 5. She has some sensory issues, but not extreme. She is like a light switch with moods. In a flash she can go mad or become happy. Her triggers are not always known. On good days she will participate, follow directions, and be generally agreeable. On bad days she will hit, throw herself on the floor and say swear words. I would guess 90% of the time she is sweet and 10% of the time she is having a rough time. Again, the mood swings are difficult to detect and correct. Medication has helped some what. ”**

Age 12 years

“ He is in his own world most of the time. On a good day he is happy, eats well & is noisy. On a bad day he is withdrawn, refuses food & drink & is noisy & manic or quiet & withdrawn. ” Age 24 years

“ She has many stereotypic movements including hand flapping and unexplained laughter. She will often grab spontaneously - either other people or objects. ” Age 13 years

## ■ Seizures and the brain

The majority of children with IQSEC2-related disorder have experienced some form of seizure (sudden and unexpected electrical activity in the brain). These can be of different types, from absences seizures (when the child appears vacant and unresponsive for a short period of time) to ‘generalised tonic clonic seizures’ which means that the whole body is involved and, when seizing, alternate stiffening and shaking of the body is seen (dropping to the ground and jerking). More than one type of seizure may be present in the same individual. Epilepsy (recurrent seizures) has been diagnosed between the ages of 1 and 3 years. There is marked variation in the persistence of seizures with treatment, some children can have their seizures well controlled with one or two medications, whilst others (mainly boys) have very poorly controlled epilepsy, and can suffer several seizures a day, despite tenacious treatment efforts.

Seizures can cause a lot of worry for families and can be frightening to observe but in the majority of cases they self-resolve, or resolve with minor medical treatment and do not cause permanent problems. If your child has a seizure for the first time it’s important to remove nearby danger so they can’t hurt themselves and call for an ambulance.

Children who experience seizures may have investigations to check the activity of their brain and to rule out any revisable causes. This may include an ‘EEG’ (electroencephalogram) that looks at the electrical activity in the brain. This is done by attaching stickers to the scalp, that are connected by wires, to the machine used for analysis.

Some children have been offered an MRI (magnetic resonance imaging) scan of their brain, to look for structural changes. Different types of structural anomalies have been found including a smaller than usual brain.

“ His seizures have become worse as he’s got older. Cold food has set off seizures in the past. Strobe lights can trigger seizures. ” Age 24 years

## ■ Sleep

Children affected by genetic disorders often have higher instances of sleep difficulties than typically developing children. Some families have reported their child with IQSEC2-related disorder finds it difficult to fall asleep at night, early waking and insomnia have also been reported. The reasons for these sleeping difficulties are not yet well understood.

It can be challenging having a child who won't settle to sleep or who does not have sufficient uninterrupted sleep, and it can be very difficult for parents to function well during the day if they have a continuous lack of sleep. There are many interventions that can be put in place to help improve a child's sleep difficulties. From having a good routine, being aware of strong sensory responses and blocking out natural light in their bedroom to synchronising their natural 'body clock' (circadian rhythm) using 'light therapy' (when a child sits near a special light box for a certain amount of time each day to regulate the brain's natural sleepiness/wakefulness hormone release) or the use of the hormone melatonin (this is not helpful for all children but may be tried if children have severe sleeping difficulties).

Daytime exercise as well as food and drink consumption may also have an effect on your child's ability to sleep at night dependant on their age and muscle tone. It has also been suggested that certain food supplements may help with sleeping issues, you may be able to discuss suitability with your doctor. Some families recommend aromatherapy, homeopathy and massage.

It is also worth considering that pain, discomfort, allergies and intolerances can all impact on sleep. Medical conditions such as reflux or constipation can also have an effect. In older children, difficulties falling asleep at the end of the day may be associated with anxiety. Sleep onset association disorder, when the child associates sleep with a person or something in the environment, may also be something that may need to be considered. Unique also publishes a freely available sleep guide as part of our practical guide series, it can be found at the following link: <https://www.rarechromo.org/practical-guides-for-families>

**“ We have conducted a sleep study-no concerns. She is a good sleeper and will sleep 10+ hours a night. ”** Age 12 years

**“ He has never slept well. He often wakes & is noisy in the night. He has tried melatonin which didn't work. He is on a sedative which helps a bit. Some nights he hardly sleeps at all. ”** Age 24 years

**“ She sleeps from 7pm to 6:30am. She often wakes up once per night. ”**  
Age 13 years

## ■ **Skeletal features**

There is thought to be an increased chance of scoliosis (curvature of the spine) in children with IQSEC2 - related disorder. This is likely due to hypotonia and the muscles not being strong enough to hold the spine straight. Scoliosis can range from very mild and diagnosed incidentally on X-ray to more severe and needing treatment with a back brace or surgery.

## ■ **Appearance**

Children with IQSEC2-related disorder all look different but you may have been told your child has a few mild facial features. In some cases such features are not obvious to a parent or anyone else but may be identified by a paediatrician or

clinical geneticist. This is because professionals looking after children with genetic changes are trained to notice physical features that may suggest a child's difficulties are of a genetic origin. Making a note of these may help establish common features observed in children with the same genetic change and therefore aid diagnosis.

Facial features that have been identified in children with IQSEC2-related disorder vary, not all children with IQSEC2-related disorder will have all or any of these features but the majority have some. Perhaps the most noticeable feature is a squint (strabismus). Other features include deep set eyes, full lips and a frontal upsweep of hair.

### ■ Eyes and vision

Some children with IQSEC2-related disorders have a squint (strabismus) which can be managed by an ophthalmologist (eye doctor). This is observed in newborn babies but should resolve by 6 months. It is important to identify a strabismus since it is correctable and can cause damaged vision if not corrected. There may be an increased chance of long sightedness. A few children have been diagnosed with cortical blindness or cortical vision impairment. This means that the eyes themselves can function as expected but the part of the brain that interprets messages from the eyes is not developed properly, so that the child is unable to see.

### ■ Ears and Hearing

There have not been any reports of hearing problems in children with IQSEC2-related disorder. It is often difficult to successfully conduct hearing tests in children with severe intellectual disability, however parents do not report any concerns about their child's hearing.

### Puberty

Most children with IQSEC2-related disorder are expected to enter puberty at the expected time. There is at least one report of a girl who had early-onset puberty but it is not yet known whether or not this was related to her IQSEC2-related disorder since it also occurs naturally in the general population.

**“ Mood swings have dramatically increased with puberty. We have started on cammilla to stop menses. ” Age 13 years**

### Adults

We do not currently have much information regarding adults with IQSEC2-related disorder. The eldest people reported in the medical literature are in their 50's. Unique's eldest member is 24 years old and the IQSEC2-related disorder support groups eldest member is in their 40's.

### Other observations

Some children with IQSEC2-related disorder tend to dribble (drool) a lot. There are medications available to help with this (although medication may not work for everybody).

## Medical/Educational Guidance Summary

- Children should be under the care of a general or community paediatrician to monitor their health and development.
- Input from the neurology/neurodevelopment teams may also be required.
- Seizure activity may need monitoring.
- Health visitors and community nurses play an important role in caring for individuals with IQSEC2-related disorder.
- Monitoring weight gain in infancy is important. Feeding difficulties and reflux may need significant medical support.
- An assessment of special educational needs should be carried out so that extra help can be put in place at school.
- Early input from a speech and language therapist is important.
- Early input from a physiotherapist and occupational therapist is important.
- Sleep disturbance may improve with melatonin.

## Families say ...

“She is very social, loves music, and loves being around other people. Especially other girls her own age. Motion makes her very happy. She can spend hours being pushed on a swing. But, her very favorite thing is live music. She absolutely loves listening to the rhythm and beats of live music. ”

“We have a closed Facebook Group. IQSEC2! I like knowing we are not alone in this journey, and many parents have become close friends. ”

“Keep fighting for everything you need. ”

## Favourite things....

“Anything done outside, Coloring, Stickers, Watching TV, Playing on iPad, Listening to music, Playing babies/dolls, Playing on swings, Playing with her cats, Snuggling. ” Age 12 years

“He enjoys hydrotherapy. He enjoys music. He enjoys going out for walks in his wheelchair. ” Age 24 years

“She loves live music, swings, and being outdoors. ” Age 13 years

## **IQSEC2 Support group:**

Our Facebook group for any families with children with IQSEC2 has gone from 2 members to 308 members in 3 years. There is a HUGE diversity in skills and capabilities in this community. Each one of our kids is an individual and it's hard to know what they can achieve.

# Chromosomes, genes and proteins

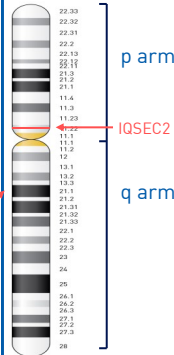
## Chromosomes

Most of our cells contain 22 chromosome pairs and two 'sex' chromosomes (that establish gender). The image below shows chromosome pairs 1 to 22 together with an X and a Y chromosome (male). A female usually has two X chromosomes and no Y. The *IQSEC2* gene is located on chromosome X (circled in red).



## Chromosome X and *IQSEC2*

When chromosomes are prepared in a specific way and visualised under a microscope, they can be seen as having a short (p) and long (q) arm and a distinguishing banding pattern that is numbered outwards from where the two arms meet (the centromere, coloured yellow in the image below).



Each chromosome X contains one copy of the *IQSEC2* gene. It is located on the short 'p' arm within band 11.22 so its location is referred to as Xp11.22.

Girls/women with *IQSEC2*-related disorder have a second copy of *IQSEC2* on their other X chromosome, boys/men only have one copy of *IQSEC2* since they have a single X chromosome.

## The *IQSEC2* gene

The *IQSEC2* gene contains 15 exons (coloured yellow below) which are the pieces of DNA sequenced during a whole exome sequencing (WES) test. Each exon is of a different size but all together, the exons code for a protein known as the *IQSEC2* protein. A shorter protein is also produced using fewer exons, a third protein is also produced from the same DNA sequence.



*IQSEC2*-related disorders causing variants have been found in all 15 exons of the longest form of the gene. Some people have been identified with non-pathogenic *IQSEC2* mutations and do not have *IQSEC2*-related disorder or any obvious symptoms.

## *IQSEC2* exons



It is thought that the position and type of mutation could contribute to the severity of symptoms experienced by people with *IQSEC2*-related disorder, as well as whether the person is male (XY) or female (XX).

## The *IQSEC2* protein

Most of the disorder causing *IQSEC2* gene sequence variations identified to date (2019) are called 'truncating mutations' which means, if a protein were to be made from the gene, it would be shorter than it should be (truncated).

Since proteins are 3D structures, a sequence variation can cause a change in protein shape, a possible loss of functional regions and a change in functional abilities such as a loss of function or gain of an altered function. It is also possible that some sequence variations lead to 'nonsense-mediated decay' which means a protein is not made from the gene.

## *IQSEC2* protein functional domains



## X-inactivation

Since boys/men have a single copy of the *IQSEC2* gene, pathogenic variations are expected to have an affect on the individual concerned. Girls/woman have two X chromosomes, so they can have a second fully functional copy of the *IQSEC2* gene. Although the natural process of X-inactivation contributes to the outcome in some X-linked disorders, this is not thought to be the case for *IQSEC2* since this gene is thought to escape X-inactivation.

**Notes:**

## Inform Network Support



### Rare Chromosome Disorder Support Group

The Stables, Station Road West, Oxted, Surrey RH8 9EE, UK

Tel: +44(0)1883 723356

info@rarechromo.org | www.rarechromo.org

Understanding Chromosome & Gene Disorders

### 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

<http://www.rarechromo.org/donate> Please help us to help you!

### Websites and Facebook groups

Human Disease Genes website series:

<http://iqsec2gene.com>

IQSEC2 Foundation

<https://www.iqsec2foundation.org/>

Facebook groups

<https://www.facebook.com/IQSEC2>

Closed Facebook Support Group that provides a community for people who know someone with an IQSEC2 mutation. <https://www.facebook.com/groups/iqsec2mutation/>

*Unique* mentions other organisations' message boards and websites to help families looking for information. 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. This booklet was written by Dr Jessica Radley, MSc, MRCP (UK), Speciality Registrar in Clinical Genetics, Birmingham Women's NHS Foundation Trust, UK and *Unique* (AP) and reviewed by Dr Meena Balasubramanian MBBS, DCH, FRCPCH, MD, Consultant Clinical Geneticist, Sheffield Clinical Genetics Service.

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