Understanding Chromosome & Gene Disorders

Bainbridge-Ropers syndrome (BRPS)

(ASXL3 'loss of function')

rarechromo.org

This guide is designed to help families and healthcare professionals looking after people affected by Bainbridge-Ropers Syndrome (BRPS). 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 syndrome. It also contains details about support groups and further information that families can access.

What is Bainbridge-Ropers syndrome?

Bainbridge-Ropers syndrome (BRPS) is a rare genetic condition that results from a change in function of a gene called ASXL3. The syndrome is named Bainbridge-Ropers after two researchers who first published the association of changes in the ASXL3 gene with specific characteristics and difficulties observed in some children (Bainbridge 2013). ASXL is an abbreviation of 'Additional Sex Combs Like' which is the name of a gene first identified in fruit flies (commonly used in genetic studies), hence the unusual name.

What are genes?

Genes are the 'instructions' that our bodies use for many functions including the control of growth and development. They are made from a complex structure called DNA. DNA, and hence 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'. However, they need to fit inside the microscopic cells from which our bodies are made. DNA is hence tightly compacted into organized structures called chromosomes. Most of our cells normally contain 46 chromosomes. We usually inherit 23 chromosomes from our mother and 23 from our father to make our very own unique 'instruction manual' containing two copies of most genes. The majority of important genes code for proteins. Genes can be described as carrying instructions for our cells and proteins carry out specific tasks.

What genetic changes cause Bainbridge-Ropers syndrome?

There are many different changes that can occur in the coding sequence of the ASXL3 gene, they are commonly called 'variants' or 'mutations'. Some 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'. LOF mutations are thought to be responsible for BRPS, a deletion of the entire ASXL3 gene may also cause a similar outcome. Mutations in ASXL3 have also been identified that cause a change in the functional protein but do not cause BRPS or any obvious outcome, as we understand it at present.

Most mutations are found in one copy of the ASXL3 gene, and most people will also have a second fully functional copy of ASXL3. It is expected then that half the amount of unaffected ASXL3 protein would be produced.

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: Bainbridge 2013, Dinwiddie 2013, Srivastava 2014, Hori 2016 and Kuechler 2017, Balasubramanian 2017, Koboldt 2018 and and Verhoeven 2018. 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 ASXL3 do?

The ASXL3 gene codes for the ASXL3 protein which is known to be involved in controlling the production of other proteins from other genes. Not all the functions of the ASXL3 gene/protein are currently known but knowledge of ASXL3 and its functions will improve over the years with further research.

The ASXL3 gene is known to instruct different cells in different organs at different stages of development, changes to this gene can therefore affect different parts of the body in different ways. Perhaps the most important role of ASXL3 is in the brain during early development. It is possible that if a mutation occurred later in development, the time at which the mutation arose may influence a child's outcome.

Why did this happen and can it happen again?

Bainbridge-Ropers syndrome is thought to be most often caused by a new (*de novo* (*dn*)) 'mutation' in the ASXL3 gene which randomly occurred in the formation of the egg or sperm from which a child is conceived.

Mutations in ASXL3 that cause BRPS are not often inherited from a parent, the risk of having another child with this syndrome is therefore thought to be very low. When a child is identified as having an ASXL3 mutation, both parents are usually offered a genetic test to establish possible inheritance. Although it is rare, it is possible for an adult with BRPS, to pass on their genetic variation to their child. This has been reported in a family where the parent has a much milder outcome to their child (Dr Balasubramanian personal communication).

Where neither parent is found to have an ASXL3 mutation, following a DNA test from a blood sample, it is unlikely that they will have another child with an ASXL3 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 egg or sperm cells can carry an ASXL3 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, one such incidence has been reported in the medical literature (Koboldt 2018) and Unique has a family member with two children with BRPS.

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 the pregnancy that could have caused this genetic change.

How common is BainbridgeRopers Syndrome?

Bainbridge-Ropers syndrome was first described in 2013 and since then about 30 children have been described in the medical literature as having a mutation in one of their two copies of the ASXL3 gene. However, many more children, are known to have Bainbridge-Ropers Syndrome, currently (2018) an estimated 200 are known worldwide and many more have yet to be diagnosed. The ASXL3 support group (BRSfamilies) currently has approximately 180 families registered with a child with an ASXL3 variant.

Genetic testing was once a complicated, costly and time consuming process and was normally only offered to children with severe difficulties for which an explanation could not be found. Relatively recently there have been major advances in technology and cost efficiency, that have enabled a more prolific use of genetic testing, and children with a 'spectrum' of difficulties are more frequently identified with similar genetic changes. Following on from initial research findings where the majority of children with BRPS have quite severe outcomes, children with ASXL3 LOF mutations and milder difficulties are now being identified (Dr Balasubramanian personal communication).

What features and symptoms do people with BRPS have?

As with many genetic conditions, children with Bainbridge-Ropers syndrome 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. At the moment (2018), most children who have been given a diagnosis of BRPS have been identified as having moderate to severe intellectual disability, limited or absent speech, autism or autistic traits and significant feeding difficulties when young. A number of children are also identified as having low muscle tone (hypotonia) or being 'floppy' as a baby or young child. Other less frequently reported features have been identified and will be described in this guide.

Common features:

- Intellectual disability
- Autism spectrum disorder or autistic like behaviour
- Feeding difficulties as a baby and in early childhood
- Developmental delay
- Postnatal growth problems
- Speech and language difficulties or absent speech
- Hypotonia (low muscle tone/floppiness)
- Sleep disturbance
- Specific facial features

Pregnancy and Birth

The majority of pregnancies of children with BRPS reported so far have progressed to term (38-42 weeks) and have been mostly unremarkable. There are a few reports of poor foetal growth in the womb which is commonly referred to as IUGR (intrauterine growth restriction).

A caesarean section was performed for about half of the births reported to date mainly due to the baby being in a breech position (when a baby is not positioned in a way that allows the head to move first through the birth canal). A third of babies reported in the medical literature were admitted to a neonatal unit following birth due to respiratory difficulties or apnoea (pauses in breathing or shallow breathing during sleep). Overall, children with BRPS have been reported to have birth weights within the normal range, but few Unique families have reported a low birth weight for their BRPS child.

Feeding and Growth

Poor growth after birth has commonly been reported and babies may be described as 'failure to thrive'. This may be due to feeding difficulties and possibly poor appetite, babies may also have a poor suck or swallow reflex related to hypotonia. Babies with BRPS are commonly reported as having gastro-oesophageal reflux or vomiting. For some, the use of medications to help control reflux has been beneficial, others have required nasogastric tube feeding (where a tube is placed through the nose into the stomach) and a few have required a surgical intervention called fundoplication (to strengthen a muscle so stomach content is less likely to travel back into the food pipe).

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.

If a child with BRPS 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.

“ Her diet has become more restricted over time. She will eat one or two foods every day for 3-6 months and then suddenly reject it. She does not have problems chewing, swallowing, or show aversion to different textured foods. We are concerned about her weight loss and it took a lot of soul searching to decide on a g-tube. But with more than half the kids with a g-tube who have an ASXL3 mutation, we know it will really help her to grow. ” Age 10 years

“ He is solely PEG fed, we have regular checks around this, he has recently stopped taking medication for reflux but needs daily medication for constipation. Large volume vomiting has recently stopped being an issue, prior to this it would be 3+ times a day. ” Age 20 months

Development

All children identified so far with BRPS 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 BRPS 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 affect on reaching certain milestones. Children will benefit from physiotherapy (also known a 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.

“ We have had fortnightly intervention since our boy was 5 months old. He started with physiotherapy and occupational therapy, working with a squiggle mat and tumbleform chair to improve his ability firstly to control his head in a prone position, then be upright sitting. A vision therapist was involved monthly working with us to improve our son’s ability to focus and eventually look at our faces, something that was very important to us. This intervention has definitely helped us get to where we are today, I have no doubt at all that we would be further behind in milestones had it not been for our fantastic therapists. ” Age 20 months

Motor skills and self care

The majority of children for whom we have information, have poor gross motor skills and restricted mobility. Some children have not developed the ability to walk and are described as 'non-ambulatory'. Hypotonia, hypermobility and collapsed foot arches can all 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.
The majority of children for whom we have information also require assistance for all areas of daily living.

"She started walking with walker at 3 years and started walking short distances independently at 5 years and 6 months. At 10 years and 4 months she can't walk longer than approximately the length of a city block and requires a wheel chair for longer distances. She can't run, skip, or jump. She has trouble going up and down stairs although she can do so independently." Age 10 years

"She started to walk when she was 4. She walks now but is a bit unstable, she needs someone to balance her." Age 11 years

"He has never walked." Age 20 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, all children reported in the medical literature with a BRPS diagnosis have also been given a diagnosis of intellectual disability, ranging from moderate to severe or profound. 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 BRPS will develop moderate to severe ID.

As infants become older, schooling can be a concern for some parents. Some children will attend a mainstream school and may need a dedicated support worker and others will attend a school specifically for children with special educational needs. Some families choose to home school.

“ Even though it takes her a long time to learn something new, she has never stopped developing or regressed. She does things at her own pace and is stubborn about it but there have been a few times when she seemed to gain new skills very rapidly and made leaps in development. ”
Age 10 years

“ He definitely learns in 'waves', we will have massive progression followed by consolidation. ”
Age 20 months

“ She is in a special education classroom at a public elementary school, I worried that she would be bullied but the children love her! I would encourage parents to be willing to at least let their child try to go to school and interact with other children. She has progressed much more than we ever thought she would. She is very motivated to learn new things when she sees other children doing them too. ” Age 10 years

Speech, language and communication

Children with BRPS 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. Roughly 2/3 of children reported in the medical literature were noted to have absent speech (ages ranging from 1 to 22 years) but research on a larger group of children shows a much lower frequency (Dr Balasubramanian personal communication). Parents have mentioned that their child's ability to understand is much better than their ability to speak. 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 has been in speech therapy continuously and has slowly learned how to communicate using her speech device. ” Age 10 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 BPRS. Vulnerability in these areas means that children should be monitored and families offered early support.

About half the children reported so far with BPRS are thought to have ASD (autistic spectrum disorder) or autistic like traits. In some children, autism has not been confirmed but is described as likely.

Other reported behaviours include ADD (attention deficit disorder), Tourette's syndrome (vocal and motor tics) and Pica (eating substances that have no nutritional value e.g. rubber wheels from toy cars). Some children have also been described as having other behaviours such as hand flapping, head rocking, clicking, hyperventilation, inappropriate or compulsive laughter, frequent tantrums, teeth grinding (bruxism), aggressiveness and self harming. Although there are few reports in the medical literature describing such behaviours, they have been described by parents of children with BRPS. 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.

"He has been diagnosed with autism. He has very repetitive behaviours such as head shaking and hand flapping. When he is frustrated he bites himself, his therapist gave him some protective cuffs for his arms when he bites." Age 20 months

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.

"We are in the process of enrolling in ABA therapy to help with difficult behaviours. We think that hunger is also contributing to her tantrums." Age 10 years

"She frequently holds her breath and rolls her eyes to one side (it's not a seizure) and she will do this several times an hour when she is doing something mentally, it can be frequent enough to interfere with her schooling and eating at home." Age 10 years

Seizures and the brain

Nine children with BPRS reported so far in the medical literature have experienced some form of seizure (sudden and unexpected electrical activity in the brain). These can be 'generalised tonic clonic seizures' which means that the whole body is involved and, when seizing, alternate stiffening and shaking of the body is seen. Some children have absence seizures, which is when they appear vacant and unresponsive for a short period of time. The causes are not fully understood but are under investigation (Myers 2018).

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.

"Our sons EEGs have confirmed that he has very rapid brainwaves but his tremors have been diagnosed as non epileptic in nature. He has had 2 occasions of actual seizures." Age 20 years

Almost half of the children with BRPS reported so far in the medical literature have microcephaly (when the brain does not develop as expected resulting in a small head). Some children are offered an MRI (magnetic resonance imaging) scan of their brain, to look for structural changes. White matter changes have been reported in a few children with BRPS.

"A CT scan at 4 months old presented cerebral atrophy above the left eye. There were also agenesis of the corpus callosum and white matter changes." Age 20 years

Sleep

Children effected by genetic disorders often have higher instances of sleep difficulties than typically developing children. The majority of families have reported their child with BRPS has some form of sleep disruption. This can include finding it difficult to fall asleep at night, night waking, and waking up far too early in the morning, night terrors and sleep apnoea. 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 undisrupted 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 brains 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).

Some children with BRPS have sleep apnoea. This is when there are prolonged pauses in breathing or very shallow breathing. After a period of not breathing, individuals often gasp or snore loudly. If you think your child has sleep apnoea, it is important to let your doctor know. Investigative sleep studies can be carried out and sleep devices can be used if your child is identified as having sleep apnoea.


6 years

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.

Immunity and Infections

Children with BRPS are not reported to have specific problems with immunity but frequent upper respiratory infections have been observed. Frequent ear infections have also been noted and some children have PE (Pressure Equalizer) tubes inserted. Some families also opt for adenoid and tonsil removal.

"She was hospitalized at 5 weeks for RSV and acute bronchiolitis. She had frequent ear infections and she had PE tubes placed and her adenoids removed at 10 months. She later had her tonsils removed at 3. These were all helpful in reducing the amount of times she was ill with upper respiratory infections. We were using a nebulizer several times a year from birth to about age 8 but she hasn't needed it in the past two years." Age 10 years

Skeletal features

Some children with BRPS have been reported to have marfanoid habitus, this means they are tall and slender and have long fingers and toes. Others have been

identified as having mild pectus excavatum (an unusual growth of the sternum and rib cage), joint hypermobility, flat foot (pes planus) and bent fingers and/or toes (clinodactyly). A high arched palate in the mouth has also been observed. One Unique member had scoliosis that required surgery, they also underwent complete hip reconstruction.

Appearance

Children with BRPS 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 hence aid diagnosis.

Facial features that have been identified in children with BRPS vary, not all children with BRPS will have all or any of these features but the majority have some. Perhaps the most noticeable feature is a squint (strabismus) noted in almost half of the children reported to date. This is observed in new-born babies but should resolve by 6 months. It is important to identify a strabismus since it is correctable and can cause damaged vision in one eye if not corrected.

Other possible facial features include eyes that appear to slant downwards slightly at the outer edges (downslanting palpebral fissures), eyes that are slightly wider apart than expected (hypertelorism) and arched and/or thin eyebrows. A high arched palate is commonly observed and a few children have a small jaw (micrognathia) and dental overcrowding of adult teeth. Some children have an overbite with prominent upper teeth, a short nose where the tip of the nose is higher than the base (anteverted nares), a high forehead and low set ears. One Unique member mentioned their child was identified as having an 'ear pit' (a small nodule or dimple close to the ear). Ear pits have been identified in the general population but may have an increased frequency in children with some genetic disorders.

A number of children with BRPS have also been identified as having deep palmer creases, the creases that run across the palm of a hand and allow skin to stretch and squeeze.

Eyes and vision

Apart from strabismus, as previously mentioned, problems with vision in children with BRPS are not commonly reported in the medical literature. Some children with an ASXL3 mutation are known to require glasses, further information from families will help us to understand if vision is specifically affected in any way. Three Unique members are known to be longsighted, three have a strabismus ad one has an astigmatism (where the lens or front surface of the eye (cornea) has an irregular curve). One child with BRPS described in the literature is considered blind (Dad 2017).

Ears and Hearing

There do not appear to be any specific hearing problems associated with BRPS.

Puberty

There is currently very limited information available on puberty in children with BPRS. Early onset puberty has been mentioned but the frequency may not be higher than that normally observed in children without BRPS.

"She started showing signs of puberty at 8 and we took her to a paediatric gynaecologist at age 9 to talk about starting her period. It was something not one ever really brings up when it comes to girls with ID. But our doctor was very knowledgeable, gave us options with pros and cons to each one and helped us make a plan that is hopefully the best plan for our child." Age 10 years

Adults

There is not much information as yet regarding adults with BRPS. The eldest person reported in the medical literature is a 47 year old man with an ASXL3 mutation and suspected BRPS (Verhoeven 2018). Unique's eldest member is 20 years old and the ASXL3 support groups eldest member is 40 years old. There are now also reports of adults with ASXL3 loss of function mutations who have children of their own, so a milder outcome is emerging.

Other observations

A few families have mentioned that temperature regulation and perception may be slightly altered in their child with BRPS. Parents mention their child is insensitive to cold and/or overheats. Some families have also mentioned their child appears to have altered pain perception, such as a high pain threshold. Such observations are often reported in children with rare chromosome or gene variations. As more information is gathered we will be able to identify if this is particularly common in children with BRPS, or not. There are also three reports in the medical literature mentioning children with BRPS who have a tendency to hyperventilate. More information is required to assess if these observations are particularly common in children with BRPS.

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 BPRS.
- Monitoring weight gain in infancy is important. Feeding difficulties and reflux are common and 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 from occupational therapy is important.
- Sleep disturbance may improve with melatonin.

Families say ...

“ All children are different, as I have two children with BRPS, I can say that there are just a few things they have in common. The most important thing is to love them a lot ,to support them all the time and to be patient. They are treasures.”

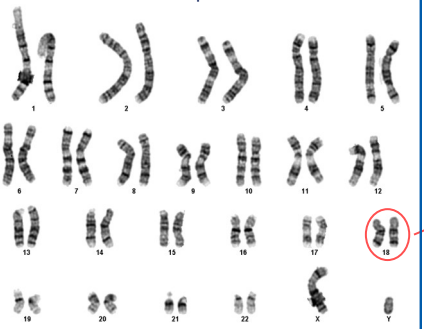
“ She loves to be on her iPad watching YouTube, she can manoeuvre the iPad as well as any child her age. She likes to watch animals so we make frequent trips to the pet store. She loves playing with water and she likes swimming (only in the shallow end where she can stand) and she likes taking a bath and showers. She loves listening to music, her favorite activity is going to the movies. ”
Age 10 years.

Caitlin Calder: founder of www.ASXL3.com and the ASXL3/BRPS facebook group. “ Dr. Bainbridge contacted me a few years ago and asked if I would be willing to become a point person for the newly diagnosed. I agreed and set up an email address and then waited. By the end of the first year I had been in contact with 3 families. It was so amazing to hear their stories and be able to say "My kid does that too!" After 2 years we had 20 families. As of 5/2017 we have close to 100 families in our Facebook ASXL/Bainbridge-Ropers Syndrome group. I never would have thought we would reach this point. For so many years I was alone and now when I talk to parents of newly diagnosed, I always tell them "You aren't alone anymore!" Parents in the group are so open and willing to share their experience and advice. It's a great place to vent frustrations and to also share in our kid's accomplishments. These parents celebrate even the smallest gains because they know how hard it was to get there! I tried to create a group and site that I would have loved to have when my daughter was diagnosed. ”

Chromosomes, genes and proteins

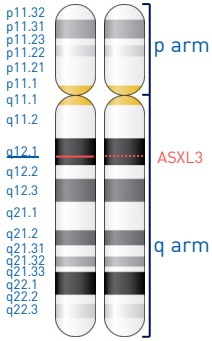
Chromosomes

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 ASXL3 gene is located on chromosome 18, (chromosome 18 pair is circled in red).



Chromosome 18 and ASXL3

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).



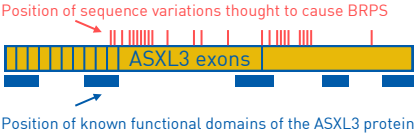
Each chromosome 18 contains a copy of the ASXL3 gene. It is located on the q arm within band 12.1 so it's location is referred to as 18q12.1.

Children with BRPS have one unaffected copy of ASXL3 and one copy with a 'loss of function (LOF) truncating' mutation.

The ASXL3 gene

The ASXL3 gene contains 12 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 ASXL3 protein. This protein has different regions (domains, coloured blue below) of different functional significance. (It is also thought that shorter proteins may be produced from the same gene by using fewer exons).

The red lines in the diagram below show the positions of known sequence variations in the ASXL3 exons thought to be responsible for Bainbridge-Ropers Syndrome. There is no link between the severity of BRPS and the variation position. (Some people have been identified with ASXL3 mutations but do not have BPRS or any obvious outcome).



The ASXL3 protein

Most of the BRPS causing ASXL3 sequence variations identified to date (2018) are called 'truncating mutations' which means, if a protein were to be made from the sequence, it would be shorter than it should be (truncated). Since proteins are 3D structures, a sequence variation could 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.

Another possibility is that this type of sequence variation leads to 'nonsense-mediated decay' which means a protein is not made from the sequence with a variation. Since one chromosome 18 has a functional ASXL3 gene, and the other does not, only half the amount of protein is presumed to be produced and this could have an effect on the individual concerned.

There are also reports of healthy unaffected people with an ASXL3 sequence variation that alters the protein sequence. This may mean that the protein is still able to function with certain alterations. It is also possible that other factors may effect the outcome of having an ASXL3 sequence variation such as when the mutation arose, a persons own unique genetic back ground or additional unidentified mutations.

Inform Network Support

Rare Chromosome Disorder Support Group
The Stables, Station Road West, Oxted, Surrey RH8 9EE, UK
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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!

Research, Websites and Facebook groups

Most families with an ASXL3 mutation are eligible to participate in the Simons VIP research project:
https://www.simonsvipconnect.org/what-we-study/single-genes.html?id=550
Simons VIP also have a closed facebook group for families with Bainbridge–Ropers Syndrome and ASXL3 mutations:
https://www.facebook.com/groups/svip.asxl3/

There is a support group with it's own website and facebook group set up by a family who have a daughter with Bainbridge-Ropers syndrome:
https://www.asxl3.com/
https://www.facebook.com/groups/288227234667517/

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 *Unique* (AP) and reviewed by Dr Meena Balasubramanian MBBS, DCH, FRCPCH, MD, Consultant Clinical Geneticist, Sheffield Clinical Genetics Service.

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