UNIQUE

UNDERSTANDING GENES & CHROMOSOMES

Houge-Janssens syndrome

rarechromo.org

This guide is designed to help families and healthcare professionals looking after people with Houge-Janssens syndrome. 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 condition.

What is Houge-Janssens syndrome?

Houge-Janssens syndrome (HJS) is a rare genetic condition associated with neurodevelopmental delay, varying degrees of intellectual disability, language delay, behavioural challenges, low muscle tone (hypotonia), a high risk of seizures (epilepsy) and sleep difficulties. The condition has several subtypes, and one of these (type 1) is sometimes referred to as Jordan's syndrome.

As is common with genetic conditions, each person can be affected differently. Not everyone with Houge-Janssens syndrome will have all the possible features and each person with a certain feature won't necessarily be affected by it to the same level as other people with that feature.

Houge-Janssens syndrome is caused by a change (variant) in one of several genes.

The different genes associated with HJS define its subtypes:

- HJS type 1: is caused by a variant in the *PPP2**R5D*** gene
- HJS type 2: is caused by a variant in the *PPP2**R1A*** gene
- HJS type 3: is caused by a variant in the *PPP2**CA*** gene
- HJS type 4: is caused by a variant in the *PPP2**R5C*** gene

A variant in the *PPP2**R5E*** gene has also been potentially linked to this syndrome.

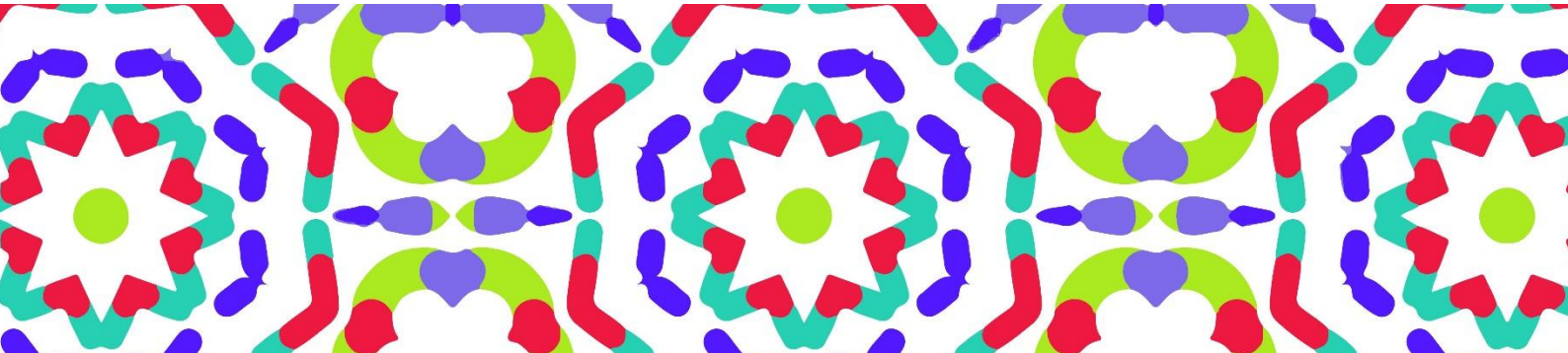
How common is Houge-Janssens syndrome?

Houge-Janssens syndrome is very rare. In early 2025, about 229 individuals with Houge-Janssens syndrome had been reported in the medical literature, but more are known to have been diagnosed.

As of 2025, the number of reported individuals for each subtype is:

- HJS type 1 (*PPP2R5D* gene): 130 individuals
- HJS type 2 (*PPP2R1A* gene): 50 individuals
- HJS type 3 (*PPP2CA* gene): 19 individuals
- HJS type 4 (*PPP2R5C* gene): 29 individuals
- HJS – PPP2R5E related (*PPP2R5E* gene): 1 individual

It is expected that more people will be diagnosed with this condition as awareness increases and genetic testing becomes more routine.



What features and symptoms do people with Houge-Janssens syndrome have?

As is common for many genetic conditions, children and adults with Houge-Janssens syndrome can have a range of features and symptoms. As more people are diagnosed, and information is shared, the range of features, and the likelihood of a child or adult having these features, will become clearer.

Common features

Most people with Houge-Janssens syndrome have:

- Some degree of developmental delay ranging from mild to severe
- Some degree of intellectual disability (ID) or learning difficulties (LD)
- Low muscle tone (hypotonia)
- Speech and language delay
- Epilepsy (seizures)
- Behavioural challenges including autism spectrum disorders (ASD)

Many people with Houge-Janssens syndrome have:

- Characteristic facial features including a broad or prominent forehead and elongated face
- Large head size (macrocephaly)
- Brain anomalies including anomalies of the bundle of fibres that connects the two halves of the brain (corpus callosum) and enlarged cavities (ventricles)

Other possible features include:

- Small head size (microcephaly)
- Eye/vision anomalies
- Joint hypermobility
- Gastro-oesophageal reflux (GERD/GORD)
- Hearing loss
- Spinal curvature e.g. scoliosis
- Heart conditions
- Tall stature (overgrowth)
- Short stature (growth delay)
- External ear anomalies

Pregnancy and birth

While most pregnancies are unremarkable and proceed without complication, concerns during pregnancy have occasionally been reported, in particular in severe forms of Houge-Janssens syndrome type 2 which can be associated with loss of the part of the brain that connects the two halves (agenesis of corpus callosum) and the fluid filled brain cavities (ventricles) being larger than expected (Lei 2023).

Some babies may have feeding difficulties after birth, related to low muscle tone (hypotonia). This can affect a newborn's ability to suck and swallow, and may be complicated by gastroesophageal reflux (GERD/GORD – when food readily returns up the food passage).

Birth weights are usually average. Head circumferences are usually within the standard range or larger than expected (macrocephaly), but in a few more severely affected children, a small head size (microcephaly) can be found. Other challenges for newborns are usually only associated with the most severe forms of the syndrome, and include early onset seizures.

I had a completely normal pregnancy and our daughter was always a very healthy baby. We did not recognise any issues until she was about 6 months old. Which started off with a health worker noticing that her head was very small. It was in the 0.5 percentile, also around this time we started to notice her development was a little bit behind where my other two older kids would have been." Age 4 years, HJS type 2

"Our daughter was born small and floppy (she had hypotonia) and had significant feeding difficulties. At just five days old, she was re-admitted to hospital with failure to thrive. We were reassured that she would improve, prescribed medication for reflux, and discharged home. No further investigations were undertaken." Age 10 years, HJS type 3

Appearance

Certain facial features are found more often in children with Houge-Janssens syndrome than in other children. This may mean that you see similarities between your child and others with Houge-Janssens syndrome. The most common characteristic features include a broad or prominent forehead (frontal bossing), a long or elongated face, an unusually large head (macrocephaly) or, in a few children, unusually shaped ears, which may be small (microtia). Mild eye conditions and anomalies can also occur, as described below.

Other physical characteristics may include variations in height, with some individuals having tall stature while others may have short stature. Many individuals have bendy (hypermobile) joints and some have an atypical curvature of the spine (scoliosis).

In retrospect, there were subtle facial features that may only have been recognised by a clinician. These included a flat nasal bridge, thin upper lip, elfin ears, and large corneas." Age 10 years, HJS type 3

Development

Gross and fine motor skills

So far (2026), developmental delay has been reported in most children with Houge-Janssens syndrome. The degree of delay ranges from mild to profound and the clinical severity can be related to the specific gene change (variant). Developmental 'milestones', including walking, using cutlery, using zips and buttons, are often delayed, although there is a wide range of eventual ability, with some children acquiring mobility and other skills around the same age as 'typical' children and others showing more obvious delay. Difficulties in movement and coordination of facial and throat muscles (oral motor dysfunction) can contribute to feeding difficulties.

Low muscle tone (hypotonia) is common and may affect mobility. Prolonged or long-lasting hypotonia is a core feature in all types of this syndrome, especially in types 1 and 2 (Houge 2025). Some children may have an unusual gait when walking because of balance issues (known as ataxia). For some, independent walking may not be achieved, with the age of walking ranging from 18 months to nine years, and some individuals remaining unable to walk at ten years of age. There is also a risk for ea rly-onset parkinsonism (symptoms that affect muscles, movements and coordination) in HJS type 1, which has been reported to begin in the mid-20s.

An assessment of 48 individuals with HJS type 1 found that most had low adaptive levels. An area of greatest difficulty was personal daily living skills, while a relative strength was noted in domestic daily living skills and fine motor skills (Oyama 2023).

Unique publishes separate guides to Therapies and Toilet training and continence

"As time moved on it was really obvious how hyper mobile our daughter was and also the hypotonia. She did not walk until almost 3. But we got there after lots and lots of physio. Also she has some coordination issues. As she is getting older she is dealing with these really well and we're hoping with time and work this will all work itself out to some point." Age 4 years, HJS type 2

"Our son is a happy, affectionate and determined seven-year-old with Houge-Janssens Syndrome type 1, also known as PPP2R5D-related neurodevelopmental disorder or Jordan's Syndrome. He is autistic, nonspeaking and, although not officially diagnosed, is suspected by LD CAMHS (Learning Disability Child and Adolescent Mental Health Service) to have a mild learning disability. He also has diagnoses of macrocephaly (noted in utero at our 20-week scan), hypotonia, significant sensory processing difficulties, and an anxiety disorder with related significant sleep disturbances." Age 7 years, HJS type 1

"Our daughter's syndrome affects her in all areas of development. Milestones take longer for her to achieve, and are a joy when she reaches them. For example, she has recently started using a walking frame, which has been wonderful to see." Age 3 years, HJS type 1

"During infancy, our daughter was unusually quiet and didn't coo as a typical child of that age would. She cried frequently and had significant delays in achieving gross motor milestones. She did not sit, crawl or walk within the expected developmental timeframe, achieving independent walking at 26 months. Her gait was unsteady, with poor balance and coordination. She continues to have significant motor difficulties and requires assistance with all activities of daily living. Although she achieved continence at six years of age, she still requires adult support with toileting." Age 10 years, HJS type 3

Intellectual development and learning

Most children with Houge-Janssens syndrome have learning (intellectual) disability (LD/ID) or learning difficulties. Neurodevelopmental delay is a universal feature, and when intellectual disa bility is present, it can range from mild to severe. The severity of the condition is highly variable and can depend on the specific genetic variant involved. Most children will require significant additional support with their learning throughout their education. These learning difficulties have a significant functional impact on daily living and adaptive skills.

> ***Our daughter has a mild intellectual disability." Age 4 years, HJS type 2***

"School was difficult for our daughter, as it was too structured and she displayed a lot of complex behaviours. She has since left school and is in adult day care which is fabulous. She loves it, she has made lots of friends and is always out and about. Her behaviours, although not gone, are a lot less which is brilliant for us." HJS type 1

"Our son needs support with every aspect of daily life, including personal care, communication, mobility, continence, safety and emotional regulation. He is doubly incontinent, has very limited danger awareness and requires continuous supervision. He has an EHCP and attends a specialist school, where he receives 2:1 support to help keep him safe. He also travels to and from school alone because shared transport causes severe anxiety and dysregulation." Age 7 years, HJS type 1

Unique publishes separate guides to Education and Further education, training and work

Speech and language

Children with Houge-Janssens syndrome typically experience some degree of speech and language delay, which is often moderate to severe. It is a very common feature, reported in 75-100% of individuals with HJS types 1, 2 and 4, and 50-74% of individuals with HJS type 3 (Houge 2025). Expressive language difficulties are a prominent finding. The eventual range of achievement is broad, but a few people may remain non-verbal (Douzgou 2022). Those who do develop speech may achieve single words, short phrases or basic sentences and some go on to develop conversational skills and a broader vocabulary. For example, one ten-year-old individual has been reported to use only two words with poor articulation, while a fifteen-year-old could use 100-200 words and form short sentences (Mirzaa 2019). An assessment of 48 individuals with HJS type 1 found an area of greatest difficulty was expressive communication while relative strengths were noted in receptive communication (Oyama 2023).

Unique publishes a separate guide to Communication

Our daughter's greatest challenge at the moment is her speech. Her comprehension and understanding does not match her speech so this can be very frustrating for her. She has found other ways to communicate and people always say even without her speech they knew exactly what she wanted. She has about 20 basic words but I do think with time this will also come. Also she can not sit still and can not concentrate on anything for more than a minute or two but with pre school we are slowly extending this." Age 4 years, HJS type 2

"We have learned that our daughter's receptive language is far greater than her expressive communication; she is pre-verbal, but uses a small range of Makaton signs and sounds (such as snoring when she sees a bed)." Age 3 years, HJS type 1

"By two years of age, our daughter remained non-verbal. When we first raised concerns, they were frequently dismissed, and we were often reassured that she would develop in her own time. It took persistent advocacy before our concerns were acknowledged. Speech and language therapy was initiated but later discontinued because she was considered "not ready." When she started nursery at three years old, she had only a limited vocabulary, with much of her communication consisting of repeating what she had heard (echolalia). She is now highly very verbal, but her speech remains repetitive and is often difficult for unfamiliar people to understand. She has a speech sound disorder, is unable to produce certain sounds, and continues to have significant expressive language difficulties, often becoming frustrated when she cannot make herself understood." Age 10 years, HJS type 3

"Our son communicates through gestures, vocalisations, Makaton and a personalised picture communication book. He understands far more than he can express and does best when people presume competence, give him plenty of processing time and communicate with him in a consistent and accessible way." Age 7 years, HJS type 1

Feeding

Feeding issues in the new-born period are common, reported in approximately half of affected individuals, and are more common in those with a more severe clinical presentation. These challenges often stem from difficulties with the coordination of muscles in the mouth (oral motor dysfunction), which can cause sensory-related feeding problems and specific swallowing difficulties that lead to gagging or choking with solid foods. A high-arched roof of the mouth (high-arched palate) has also been noted as a possible contributing factor. The combined effect of these feeding and gastrointestinal problems can impact growth and nutrition, often leading to poor weight gain.

Some babies also suffer from gastro-oesophageal reflux (GERD/GORD) (in which feeds return readily up the food passage); reflux has been reported in 25-49% of individuals with HJS type 1 (Houge 2025) and feeding difficulties have been reported in around 50% of those with HJS type 2 (Douzgou 2022) and around 60% of those with HJS type 3 (Reynhout 2019). Other gastrointestinal problems are also seen, with constipation and/or diarrhoea reported in 24% of individuals (Mirzaa 2019). In some cases, specific gastrointestinal issues have been linked to certain genetic variants. For example, in a study of individuals with HJS type 4, constipation was linked to two specific variants (called p.Arg177Trp and p.His133Pro), as was frequent or chronic diarrhoea (linked to variants called p.Glu122Lys and p.Ala130del). Intermittent bloating and bowel incontinence have also been reported (Verbinnen 2025).

Unique publishes a separate guide to Feeding

Growth and stature

Growth in children with Houge-Janssens syndrome is highly variable, although nearly 90% of children described in the medical literature so far (2026) have a height within the standard range (Houge 2025). Some children may have short or tall stature, and many have a head size that is larger or smaller than expected (macrocephaly or microcephaly). These features can differ depending on the specific gene change involved:

- In HJS Type 1 (*PPP2R5D* gene variants), tall stature is seen in a small number of individuals (5-24%) and a larger head size (macrocephaly) is common (50-74%) (Houge 2025)
- In HJS Type 2 (*PPP2R1A* gene variants), short stature is reported in a small number of individuals (5-24%), and both larger (macrocephaly) and smaller (microcephaly) head sizes are also seen (25-49% each) (Houge 2025)
- In HJS Type 3 (*PPP2CA* gene variants), both tall and short stature are seen in a small number of individuals (5-24%), while a smaller head size (microcephaly) is more common (25-49%) than a large one (Houge 2025)
- In HJS Type 4 (*PPP2R5C* gene variants), a larger head size (macrocephaly) is reported in some individuals (25-49%) (Houge 2025)

Behaviour

Behavioural difficulties are a core feature of Houge-Janssens syndrome. The prevalence of behavioural features (including autism spectrum disorder (ASD)) varies depending on the HJS type, ranging from 25-49% in individuals with HJS types 1 and 3, to 50-74% in those with HJS types 2 and 4 (Houge 2025).

Children with Houge-Janssens syndrome typically tend to have behaviour in keeping with their overall degree of developmental delay. Some children have an autism diagnosis or traits (in one study of 72 individuals, 16% had a clinical diagnosis of autism and a further 16% were considered borderline autistic (Mirzaa 2025). In another study specifically looking at HJS1, 26% of individuals (19 out of 72) had an autism diagnosis (Oyama 2023). Other behaviours including attention deficit hyperactivity disorder (ADHD), anxiety, self-harming, aggressive behaviours and sensory processing differences have also been reported. Other reported behaviours include being withdrawn, attention-seeking, tantrums, difficulties with impulse control and emotional regulation, destructive behaviours and repetitive actions such as teeth grinding. A need for routine and structure is also common.

Understanding this complex profile is key to providing effective support. Management strategies should focus on addressing the root causes of challenging behaviours - such as providing sensory supports, using strategies to manage anxiety and creating structured environments to help with attention. Sensory-related feeding issues may be addressed with feeding therapy from an occupational or speech therapist. Efforts to take into account and introduce strategies to tackle communication and other difficulties may also be beneficial.

Unique publishes a separate guide to Challenging Behaviour

Our daughter can not sit still and can not concentrate on anything for more than a minute or two but with pre school we are slowly extending this. It's very easy to talk about the challenges and the worries that we have with our daughter, sometimes it can cast a shadow over all the positives. However, she lights up every single room she walks in to. When we walk down the street, she fist pumps everyone on the way and everyone every where seems to know her name. She loves life she loves fun and she loves everybody. I think we could learn a lot from her and from kids with Houge Janssens syndrome." Age 4 years, HJS type 2

"When our son is overwhelmed, in pain or unable to communicate what he needs, he can become extremely distressed and display significant self-injurious behaviour. This includes hitting or punching his head, head-banging, biting himself, nipping himself, and dropping to the floor. He is supported by Learning Disability CAMHS, has a Positive Behaviour Support Plan and takes 8mg Fluoxetine daily for his anxiety disorder. Age 7 years, HJS type 1

"Our son has a wonderful sense of humour and loves water play, swimming, trampolining, sensory activities, being outdoors, music and dancing. Music is a huge source of joy for him. He responds strongly to familiar songs, rhythm and repetition, and often shows his happiness through movement, laughter and vocalisation. Age 7 years, HJS type 1

Sleep

Some children have sleep disturbances, such as frequent awakenings, but this has not yet been systematically assessed.

Unique publishes a separate guide to Sleep

Sleep is a major challenge. Our son takes 8-10mg of melatonin each night and uses a specialist safe-space bed because he wakes frequently and cannot remain safe independently overnight." Age 7 years, HJS type 1

Puberty

There is limited information available about puberty in children with Houge-Janssens syndrome. We do know that some boys and/or girls appeared to be go through puberty early (precocious puberty), although a specific age of onset has not been established. The specific features of puberty may vary depending on the HJS type.

Unique publishes a separate guide to Puberty

unique

Some families of children with genetic disorders and behavioural difficulties or learning disability can be particularly concerned at their daughter's ability to cope with menstruation, and for some discussing menstrual regulation options with a paediatrician may be beneficial.

Simons Searchlight publishes a guide to Navigating Menstruation

Adulthood

Experiences of adulthood are likely to vary considerably and will depend on many factors. These include the level of any LD/ID, possible on-going medical concerns and improvements in early intervention and therapies/treatments. Information on the natural history of Houge-Janssens syndrome into adulthood is limited, however, it is understood that core neurodevelopmental features persist and some specific health concerns may emerge over time.

A significant risk for individuals with HJS type 1 is the development of early-onset parkinsonism. This has been reported in 25-49% of individuals (Houge 2025). Curvature of the spine (Scoliosis) can also develop over time, which has been reported in 5-24% of individuals with HJS types 1 and 2.

The long-term health profile is characterised by HJS type:

- HJS type 1 (*PPP2R5D*): The most frequent features (seen in ≥75% of individuals) are neurodevelopmental delay, language delay and low muscle tone (hypotonia). A large head size (macrocephaly) affects 50-74% of individuals. Other features include epilepsy, behaviour difficulties, enlarged ventricles in the brain, eye conditions and gastroesophageal reflux (affecting 25-49%)
- HJS type 2 (*PPP2R1A*): Highly prevalent features (seen in ≥75% of individuals) include neurodevelopmental and language delay and low muscle tone (hypotonia). Epilepsy and structural brain anomalies are also seen in many individuals (50-74%). Both a large head size (macrocephaly) and a small head size (microcephaly) are common (25-49%)
- HJS type 3 (*PPP2CA*): Neurodevelopmental delay is seen in almost all individuals (75–100%), with language delay and low muscle tone (hypotonia) affecting 50–74%. Other common features include epilepsy, behaviour difficulties and a small head size (microcephaly) (25-49%)
- HJS type 4 (*PPP2R5C*): The most frequent features (seen in ≥75% of individuals) are neurodevelopmental and language delay. Low muscle tone (hypotonia), epilepsy and behaviour difficulties affect 50–74% of individuals, with a large head size (macrocephaly) being a common finding (25-49%)
- *PPP2R5E*: The single reported adult with a variant in this gene presented with neurodevelopmental delay, low muscle tone (hypotonia), behaviour difficulties, hearing loss and scoliosis

Unique publishes a separate guide to Transition

She loves being outside. She enjoys going to the circus, bowling, cinema and being out and about. Her happy place is at our caravan by the sea." Age 19 years, HJS type 1

Medical concerns

The following medical concerns have been found in children with Houge-Janssens syndrome. They are not found in all children with HJS so not all children with Houge-Janssens syndrome will be affected.

Heart

Mild heart malformations (structural anomalies present at birth) have been found in some people with Houge-Janssens syndrome. The prevalence of heart conditions is estimated to be between 5-24% in individuals with Houge-Janssens syndrome types 1, 2 and 3. Heart anomalies are not considered to be a typical feature of HJS type 4. Severe heart conditions have not been recognised as part of the spectrum of this condition.

It remains to be seen if some heart anomalies are more common in HJS than in children in general (almost 1% of all babies have a heart malformation). Such anomalies found in children with HJS can include:

- A hole between the top two chambers of the heart (atrial septal defect (ASD)), a hole between the bottom two chambers of the heart (ventricular septal defect (VSD)), or the persistence of a small flap-like opening between the top two heart chambers (patent foramen ovale)
- Mild narrowing of the vessel carrying blood from the heart to the lungs (pulmonary stenosis)
- Narrowing of the veins carrying blood from the lungs to the heart (pulmonary vein stenosis)
- Failure of closure of the tube that carries blood between the aorta and the pulmonary artery when the baby is growing in the womb (during the foetal period)(persistent ductus arteriosus (PDA))
- A change in one of the heart valves, for example, a mitral valve defect, a bicuspid aortic valve, dysplastic pulmonary and aortic valves, or leaking of the heart valves (mild to moderate tricuspid and mild mitral valve regurgitation)
- An underdeveloped (hypoplastic) part of the main artery of the body (aortic arch)
- Narrowing of the main artery of the body (coarctation of the aorta)

Brain

Many children with HJS have a structural brain anomaly, which can be detected by MRI (magnetic resonance imaging) or a CT (computerised tomography) scan of their brain. The changes seen vary but include:

- An unusually large head (macrocephaly) or small head (microcephaly)
- Underdevelopment (hypoplasia) or partial/complete absence (agenesis) of the white matter connecting the two halves of the brain (corpus callosum)
- A build-up of fluid within the brain (hydrocephaly) or what appears to be hydrocephalus due to large brain size with enlarged fluid-filled cavities. There is so far little evidence that true hydrocephalus (caused by obstructed fluid drainage from the brain) is associated with HJS
- Enlarged fluid-filled cavities in the brain (dilated ventricles/ventriculomegaly)
- Underdevelopment of parts of the brain: the pons and cerebellum (pontocerebellar hypoplasia)
- A delay in the process of coating nerve fibres with a protective sheath (delayed myelination)
- Damage to the white matter around the fluid-filled cavities of the brain (periventricular leukomalacia)

The specific type and frequency of these brain anomalies often depend on the gene involved:

- HJS type 1 (*PPP2R5D* gene variants) is mainly associated with an unusually large head (macrocephaly), seen in 50-74% of individuals, and enlarged ventricles, seen in 25-49% (Houge 2025)
- HJS type 2 (*PPP2R1A* gene variants) is associated with a high frequency of significant anomalies, including underdevelopment or absence of the corpus callosum (50-74%) and enlarged ventricles (50-74%). Both large and small head sizes are common findings in this HJS type (Houge 2025; Douzgou 2022)
- HJS type 3 (*PPP2CA* gene variants) most frequently presents with an unusually small head (microcephaly), seen in 25-49% of individuals (Houge 2025)
- HJS type 4 (*PPP2R5C* gene variants) is associated with an unusually large head (macrocephaly) in 25-49% of individuals (Houge 2025)

"Our daughter's brain MRI shows there was a reduction in the cerebral white matter and the corpus callosum is present but extremely thin. This lead to genetic testing when paired with all the other symptoms which eventually came to our diagnosis." Age 4 years, HJS type 2

Seizures

Frequently children with Houge-Janssens syndrome experience some form of seizure (a sudden and unexpected change in the electrical activity in the brain), with approximately half of all affected individuals developing epilepsy. The prevalence varies significantly by HJS type, affecting 25-49% of individuals with HJS types 1 and 3 and 50-74% of those with HJS types 2 and 4. The risk for developing epilepsy is often associated with moderate-to-severe intellectual disability and the presence of microcephaly. However, an exception is noted in HJS type 3, where severe epilepsy can also occur in individuals with mild intellectual disability.

Depending on the part(s) of the brain affected, symptoms vary, but include temporary confusion, uncontrollable jerking movements and loss of consciousness or awareness. Age of onset can vary considerably, with a mean of 2.3 years (reported range from birth to 17.8 years) (Oyama 2023), while seizures may be isolated to a single incident or occur more regularly. More than one type of seizure may be present in the same individual.

Seizure types reported in a study of 33 individuals with Houge-Janssens syndrome (Mirzaa 2019) include:

- Focal seizures: this type of seizure begins in one side of the brain and was previously called partial seizures. This category includes multifocal and complex partial seizures. Focal onset seizures are the most common type of seizures experienced by people with epilepsy
- Infantile spasm: this type of seizure usually occurrs in clusters in babies between 3-10 months (also referred to as generalised epileptic spasms). Spasms are seen most often when a baby wakes and may be obvious or subtle
- Generalised tonic-clonic seizures: at the onset of this type of seizure, the abnormal electrical activity involves both sides of the brain. The seizure involves a phase of stiffening followed by jerking of the body
- Myoclonic generalised seizure: this type of sezure involves jerky or shock-like contraction of different muscles anywhere in the body but usually the arms or legs. Each myoclonic seizure lasts for a fraction of a second or a second at most

"Our daughter started to suffer with what they call breath holding spells and would faint, so we were constantly being monitored to see if these were seizures. This has stopped now and we are still not sure what these were." Age 4 years, HJS type 2

Movement Disorders

Some individuals with Houge-Janssens syndrome have a movement disorder. These movement disorders can be highly variable in frequency, duration and type, and are often seen as involuntary movements and/or spasms in parts of their bodies and may be sudden and repetitive.

The movement disorders reported have included:

- Involuntary muscle movements and twisting or tightening in altered postures (dystonia)
- Early-onset parkinsonism, which has so far been seen in individuals with Houge-Janssens syndrome type 1 (with a 25-49% prevalence in this subgroup) and can begin in an individual's mid-20s (Mirzaa 2019)
- Uncoordinated or unsteady walking (ataxic gait)
- Difficulties with controlling the muscles of the mouth and face used for speaking and eating (oral motor dysfunction)

Constipation

Constipation is common among children with Houge-Janssens syndrome. Gastrointestinal issues such as constipation and/or diarrhoea are reported in 24% of individuals (Mirzaa 2019). In some cases, constipation has been specifically linked to certain genetic variants (p.Arg177Trp and p.His133Pro variants in the *PPP2R5C* gene).

ERIC is a children's bladder and bowel charity providing trusted resources and support

Hormones

Children with Houge-Janssens syndrome may have conditions that affect their hormones, and the specific signs can vary depending on the genetic cause of the condition. These conditions include early (precocious) puberty, poor weight gain and low blood sugar (hypoglycaemia). Growth and final height (stature) can also be affected, though this varies between individuals. It is important to note that unlike some similar conditions, advanced bone age is not a typical feature of Houge-Janssens syndrome.

Ears and Hearing

Some children with HJS have a hearing impairment, but hearing is unaffected in most children. Hearing loss is a recognised feature in 5-24% of individuals with HJS type 2, 3 and 4, but is not considered a typical feature of HJS types 1. A hearing loss may be sensorineural, where there are problems with the inner ear.

Structural anomalies of the ear are not typical in most types of HJS. However, anomalies of the external ear are seen in 5-24% of individuals with HJS type 2. These can include small ears (microtia) or underdeveloped ears (hypoplastic ears).

Unique publishes a separate guide to Hearing

Eyes and sight

Eye and vision anomalies, usually mild, are not uncommon in children with Houge-Janssens syndrome. Known concerns include short-sightedness (myopia), astigmatism (reported in 17% of individuals in one study (Mirzaa 2019)), a squint, where one or both eyes turn inward, outward, up, or down (strabismus, reported in 28% of individuals in one study (Mirza 2019)), and a 'lazy eye' (amblyopia). Other reported features include a drooping eyelid (ptosis), damage to the brains visual processing centres (cortical visual impairment), an enlarged cornea (megalocornea) and underdevelopment of the optic nerve (optic nerve hypoplasia).

Our daughter has a strong prescription for her glasses and has remained under ophthalmology follow-up for several years. She has also been diagnosed with mild megalocornea (large corneas). Age 10 years, HJS type 3

Breathing

Babies and children with Houge-Janssens syndrome tend to have a higher rate of respiratory concerns, which may become less frequent with age and maturity, although they can persist throughout childhood. Several features of the syndrome may contribute to these respiratory difficulties. These include low muscle tone (hypotonia), which is a core feature seen in 75-100% of individuals with HJS type 1 (from a study of 130 people (Houge 2025)) and HJS type 2 (from a study of 50 people (Houge 2025)), and 50-74% with HJS type 3 (from a study of 19 people (Houge 2025)) and HJS type 4 (from a study of 29 people (Houge 2025)). Curvature of the spine (scoliosis) and developmental delay can also be contributing factors. Other issues may include sleep apnoea (when there is an abnormal breathing pattern during sleep), which has been documented in at least two individuals with Houge-Janssens syndrome. Other reported respiratory issues include sleep-disordered breathing and events related to aspiration (when food or liquid enters the airway), which can lead to aspiration pneumonia.

Hands and feet

Children with Houge-Janssens syndrome can have anomalies of the hands and feet, e.g. fingers or toes that curve inwards (clinodactyly), overlapping toes, single or incomplete creases across the palm (transverse palmar creases) and flat feet (pes planus), but none of these findings are specific for HJS.

Spine

Some babies are born with or develop a spinal curvature, either a sideways curve of the spine (scoliosis), which is reported in 5–24% of individuals with HJS types 1 and 2. Scoliosis has also been seen in the one individual reported so far with a change in the *PPP2R5E* gene. To date (2026), there is no information available about how common scoliosis is in individuals with HJS types 3 and 4.

Joints

Joint anomalies are a known feature of Houge-Janssens syndrome. These include loose (hyper-mobile) joints, which can present during infancy or childhood, (seen in 5-24% of individuals with HJS type 2 (due to *PPP2R1A* variants) and HJS type 3 (due to *PPP2CA* variants)). Information for other genetic subtypes is currently lacking. Some children have a degree of hip dysplasia, in which the hip joints are easily dislocated.

Teeth

Information on dental health in Houge-Janssens syndrome is limited, but if a high-arched palate is present, that may be associated with dental crowding.

Unique publishes separate guides to Looking after your child's teeth and Teeth: common concerns

"She has distinctive pointy teeth on either side at the front and when she smiles with that big smile she would melt anyone's heart." Age 4 years, HJS type 2

Palate

Anomalies of the roof of the mouth (palate), ranging from those that may be invisible to the casual onlooker such as a high/arched palate to more obvious conditions such as a cleft palate have been reported. A high arched palate is a recurrent feature, having been noted in a study of up to 16 individuals (Reynhout 2019). A much rarer finding is a submucosal cleft palate, which has been reported in one individual. Anomalies of the palate, particularly clefting, can cause difficulties in feeding, and a high palate may also be associated with dental crowding.

CLAPA (Cleft Lip and Palate Association) offers support for people affected by cleft lip and palate

Genitals

Minor anomalies of the genitals in boys have been reported rarely, like hypospadias, where the hole normally at the end of the penis lies on the underside, and undescended testes (cryptorchidism).

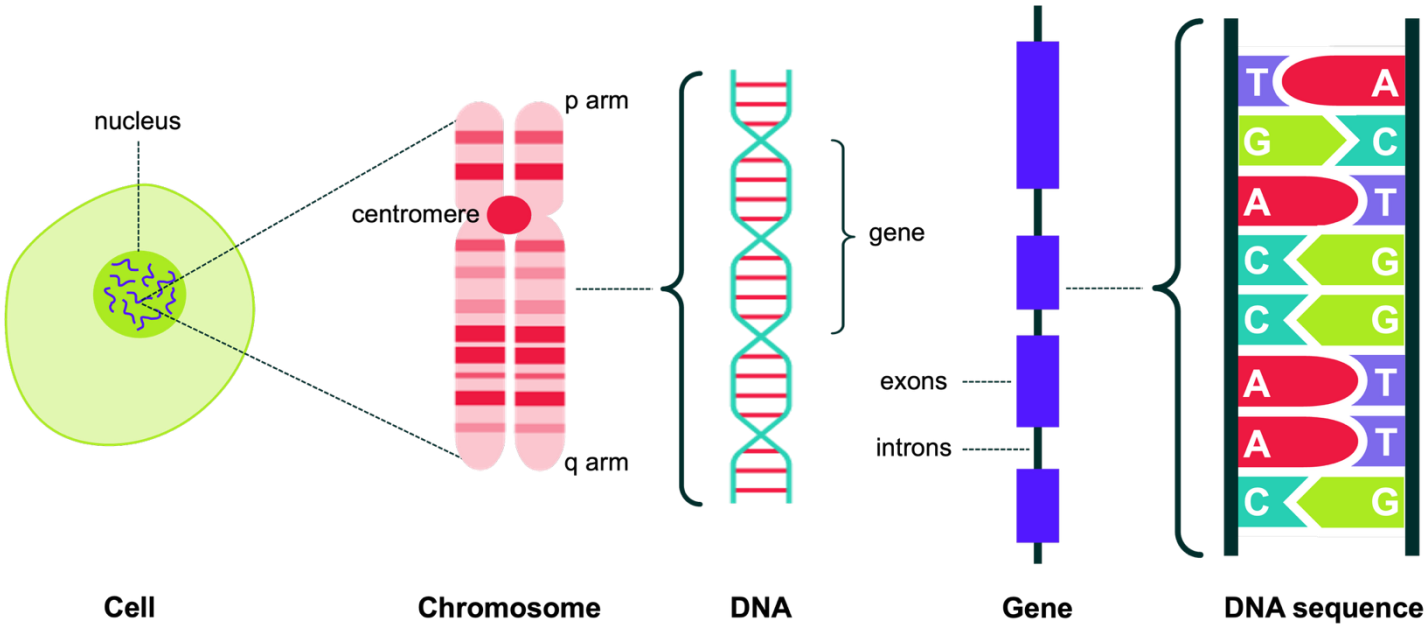
"Our son has a history of recurrent ear infections, two grommet insertions, adenoid removal, recurrent upper respiratory infections, acute rhinitis and hayfever. His medical history also includes an insufficient response to the Haemophilus influenzae type B vaccine, borderline or low ferritin levels and ongoing gastrointestinal difficulties, including constipation, diarrhoea, blood in his stools, abdominal discomfort and feeding-related issues. He is also currently under investigations for Haemophilia C, or Factor II Deficiency." Age 7 years, HJS type 1

This section includes some more complicated scientific terms and concepts - don't worry if it's a lot to take in, you can always come back to this section later if you want to.

Genes and chromosomes

Genes are instructions which have important roles in our growth and development. They are made of DNA and are incorporated into organised structures called chromosomes. Chromosomes therefore contain our genetic information. Chromosomes are located inside our cells, the building blocks of our bodies. In people with genetic conditions, one or more of their genes don't instruct the body as expected, which can lead to changes in how their body works.

DNA is made up of building blocks called 'bases' or 'nucleotides'. There are four DNA bases which can be abbreviated to the letters A, C, G, and T. These DNA bases are paired up in the DNA structure into 'base-pairs'. The full sequence of our DNA is over three billion base-pairs long. There are changes in the DNA sequence (variants) present in everyone's genes. It is variants in our genes that make each one of us unique individuals.



What causes Houge-Janssens syndrome?

Houge-Janssens syndrome is caused by a specific change (known as a pathogenic variant) to the DNA sequence of one of several genes: *PPP2R5D*, *PPP2R1A*, *PPP2CA*, *PPP2R5C* or *PPP2R5E*. Houge-Janssens syndrome can also be caused by the loss of one of these genes due to a chromosome deletion.

The *PPP2R5D* gene is located in the short 'p' arm of chromosome 6 in a region called 6p21.1.
The *PPP2R1A* gene is located in the long 'q' arm of chromosome 19 in a region called 19q13.41.
The *PPP2CA* gene is located in the long 'q' arm of chromosome 5 in a region called 5q31.1.
The *PPP2R5C* gene is located in the long 'q' arm of chromosome 14 in a region called 14q32.31.
The *PPP2R5E* gene is located in the long 'q' arm of chromosome 14 in a region called 14q23.2.

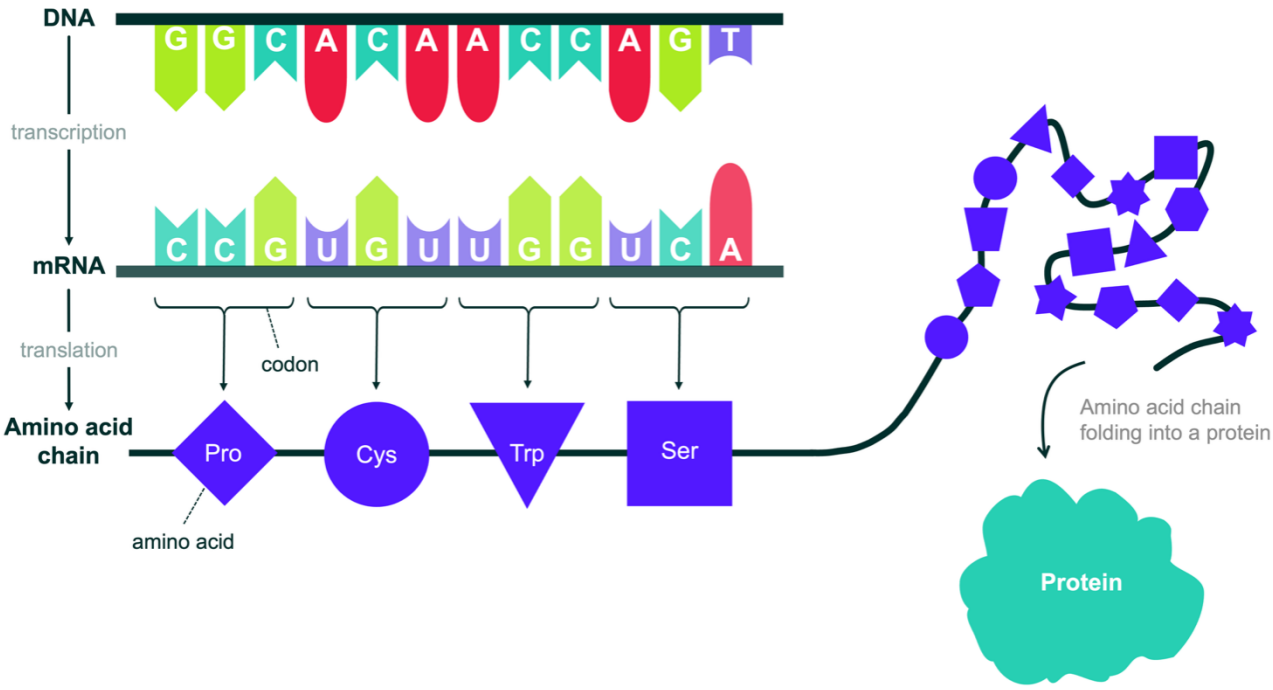
We have two copies of each of these numbered chromosomes in our cells and so two copies of each of these gene. Houge-Janssens syndrome occurs when only one copy of a gene is affected; the second copy is fully functional. This is known as autosomal dominant since all numbered chromosomes are called autosomes and genetic conditions that occur when only one copy of an autosomal gene is affected are known as dominant.

Unique publishes a separate guide to single gene disorders – autosomal dominant inheritance

Genes and proteins

Most genetic conditions are caused by changes to genes that provide instructions for making proteins; these are called protein-coding genes. The genes that cause HJS are five out of around 20,000 protein coding genes in total.

Proteins are molecules that are made up of long chains of chemicals called amino acids and play critical roles in the body. This is because proteins are essential for lots of processes such as breaking down food, moving our muscles, and growing the body's organs and making sure they function properly. To make these amino acids a copy of the DNA sequence is created, called messenger RNA (mRNA). mRNA uses the same A, C and G bases as DNA, but the 'T' bases are swapped to 'U' bases. Within a gene, each three-letter sequence (codon) of mRNA bases provides the instructions for one amino acid. Changes to the amino acid sequence can affect the function of the protein.



The role of the PP2A (phosphatase type 2A) protein

The *PPP2R5D*, *PPP2R1A*, *PPP2CA*, *PPP2R5C* and *PPP2R5E* gene sequences are used to make different parts (subunits) of a group of proteins called the Protein Phosphatase type 2A (PP2A) protein complex. This protein complex is important because it regulates a wide array of processes within cells, which are essential for cell growth and brain function. The main role of the PP2A enzyme is to remove chemical groups (called phosphate groups) from other proteins (a process called dephosphorylation), which is essential for regulating protein function and thereby cell function.

The PP2A protein complex is made of different parts (subunits) that work together. Changes in the genes that make the different parts of the PP2A protein complex can cause it to not work correctly. This can happen in two main ways: either the protein is not active enough, or it holds on too tightly to other proteins it is meant to be working on, stopping them from doing their job (a process called substrate trapping).

Different types of genetic changes

The specific type of genetic change in the genes associated with Houge-Janssens syndrome is an important factor that could influence an individual's symptoms and features. Research suggests that different types of changes to the gene sequence (variants) can affect the protein phosphatase type 2A (PP2A) protein complex in different ways, which might account for the variability in symptoms and features, or their severity, in different people with Houge-Janssens syndrome. In a few individuals with HJS type 3, one entire copy of the gene is missing (deleted).

Unique publishes a separate guide to deletions and microdeletions

Gene Sequence Variants, Loss of Function (LOF): People with Houge-Janssens syndrome are more commonly found to have a gene sequence variant, most often a missense variant, but variants include:

- Missense variants: Where one amino acid is replaced by another, producing an altered protein. This is the most common variant type in Houge-Janssens syndrome regardless of subtype
- In-frame deletions: This is where a small part of the DNA sequence is deleted, but the rest of the code can still be read. This leads to a change in amino acid composition, just like the missense variants, and such variants may be pathogenic in all types of HJS.
- Nonsense variants: Where the amino acid change results in a premature 'stop' signal, stopping protein production too early, leading to degradation of the RNA molecule made from the gene or a shorter, unfinished (truncated) protein. Examples of this variant type have been reported in the *PPP2CA* gene
- Frameshift variants: Where the DNA coding sequence is shifted by the addition or deletion of individual DNA bases which means the incorrect amino acid sequence is generated, often ending in a premature 'stop' signal. This type of variant may be pathogenic (causing the syndrome) in the *PPP2CA* gene

In HJS Type 3, variants in *PPP2CA* are often referred to as 'null' variants if they result in a loss of function only. In all forms of HJS, the main types of pathogenic variants lead to a change in the amino acid composition of the protein (missense variants and in-frame deletions). This may not only cause reduced protein function but also interference with substrate binding (like blocking of phosphate removal from other proteins), or interference with the function of other subunits in the protein phosphatase 2A (PP2A) complex. This is known as a dominant-negative effect. When this dominant-negative effect concerns many different types of PP2A subunits, the result is a clinically more severe type of HJS.

Genetic Tests

Houge-Janssens syndrome is caused by gene sequence variants that can be identified by a type of genetic test called sequencing, such as whole exome sequencing (WES) or whole genome sequencing (WGS). Gene deletions can also be identified by a whole genome sequencing test or a different type of genetic test called a chromosome microarray (CMA), such as an arrayCGH or SNParray.

Unique publishes separate guides to DNA sequencing, arrayCGH and SNParrays

Genetic Test Results

The results of genetic (genomic) testing are likely to be provided by a geneticist, a genetic counsellor or the clinician who ordered the test. Depending on the test that was carried out, someone with Houge-Janssens syndrome might have results that look like the following example:

Result of trio exome sequencing: *PPP2R1A*(NM_014225.5): c.544C>T, p.(Arg180Trp) *dn*

Trio exome sequencing means that the sequence of the child's DNA has been compared to the sequence of parental DNA samples. This is done to discover spontaneous alterations in the DNA sequence of the child (called *de novo* variants, abbreviated *dn*), and such de novo variants are the main cause of Houge-Janssens syndrome.

PPP2R1A	the gene that has been identified as having a variant
NM_014225.5	this is the code for the reference sequence, i.e. the version of the *PPP2R1A* gene that the result refers to. A gene can have many versions, and if the version is changed, then the nucleotide and amino acid position numbers (see below) will also change
c.544C>T	signifies the base pair position of the change within the gene sequence (the position where the C nucleotide has been replaced by the T nucleotide). c stands for complementary DNA, and refers to a DNA copy of the mRNA transcript of the gene
p.(Arg180Trp)	signifies the change to the protein: the amino acid arginine (Arg or R) has been replaced by the amino acid histidine (Trp or W) at position 180 in the sequence of amino acids that make up this version of the protein. The parenthesis indicates that this amino acid change is a prediction based on the nucleotide sequence (cDNA) change. In HJS it is common to use single-letter amino acid codes instead of 3-letter amino acid codes, e.g. R180W instead of Arg180Trp

"Our daughter was diagnosed with the syndrome when she was 2. We were very grateful to have the diagnosis because we found a community of other children and parents who have similar experiences to us." Age 3 years, HJS type I

"We have had to fight all the way with our daughter. She was undiagnosed until she was 9. We found that very difficult as we didn't know what the future held. When we received the diagnosis there was nothing known about it as she was the 4th in the world found. We had an appointment with geneticist and they told us to join Unique, where a few months later a family in America found us, along with the other two families we founded a Facebook group with the four of us, spent our time comparing the kids. Age 19 years, HJS type 1

Why did this happen?

When children are conceived, their parents' genetic material (DNA) is copied in the egg and sperm that makes a new child. The biological copying method is not perfect, and random changes occur in the genetic code of all children that are not seen in the DNA of their parents. This happens naturally and is not due to the parents' diet, environment or lifestyle. Most of these DNA changes have no obvious effect. But in rare instances these random DNA changes can lead to health issues or affect development. When such a random change disrupts the function of the *PPP2R5D*, *PPP2R1A*, *PPP2CA*, *PPP2R5C* or *PPP2R5E* gene then a child will have Houge-Janssens syndrome. These genes provide instructions for making parts of a crucial enzyme called PP2A, and dysfunction of this enzyme leads to the clinical features of the syndrome.

Houge-Janssens syndrome follows a dominant inheritance pattern. This means a pathogenic variant in only one of the two copies of a gene is sufficient to cause the condition.

In almost all people identified so far with Houge-Janssens syndrome, the genetic change was a random (or 'de novo') change, meaning the change occurred for the first time in that family in the affected individual. Rarely variants in the HJS genes are inherited from an affected parent (typically the parent has mild features/ID). Very rarely (the exact risk is unknown, but is estimated to be less than 1%) one parent may have the same change (variant) in some of their egg or sperm cells and pass it on to their child (this is known as germline mosaicism). However, it is important to recognize that no one should be blamed for variants in their DNA and no parent is at fault when a new DNA change occurs in their child.

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 almost everyone reported with Houge-Janssens syndrome so far, the genetic alteration has been found to be de novo (dn), which means neither parent was found to have the same gene change as their child. Therefore, the chance of having another child with Houge-Janssens syndrome is usually less than 1%.

One reason why there is some residual chance of recurrence is due to the rare phenomenon called germline mosaicism that was mentioned above. This is when a parent carries a genetic change, but it is limited to some of their egg or sperm cells. The genetic change would not, therefore, be detected in the parents' blood tests. In HJS germline mosaicism must be very rare otherwise affected siblings would have been reported.

In families where a gene variant has been inherited from a parent (not through germline mosaicism), the possibility of having another child - either a girl or a boy - with Houge-Janssens syndrome rises to 50% (1 in 2) in each pregnancy. A parent may carry the variant and be affected themselves, or they may be unaware they have the variant because they are only mildly affected. This can be due to the wide range in severity of symptoms seen in Houge-Janssens syndrome, from severe to very mild (this is known as variable expressivity), or in rare instances, because an individual carrying the gene variant shows no clinical signs of the condition (which is known as reduced penetrance).

Unique publishes a separate guide to Variable expressivity and reduced penetrance

Because of these possibilities, genetic testing for both parents is necessary to establish an accurate recurrence risk, especially in people who have clinically milder features. However, the effect on a child's development, health and behaviour cannot be reliably predicted. Your genetics centre should be able to offer counselling before you have another pregnancy.

If your child with a *PPP2R5D*, *PPP2R1A*, *PPP2CA*, *PPP2R5C* or *PPP2R5E* variant goes on to have children of their own, the chances of passing on the variant to their child are 50% in each pregnancy.

A clinical geneticist or a genetic counsellor can provide specific advice for each family about the chance of having further children with Houge-Janssens syndrome.

Unique publishes separate guides to Planning your next child, Prenatal genetic testing and diagnosis, A clinical genetics appointment and Supporting siblings of children with a rare genetic condition

Can Houge-Janssens syndrome be cured?

There is currently no cure for Houge-Janssens syndrome. Some effects of the genetic change took place during a baby's formation and development, like many of the anomalies that may be found in the brain, and those cannot be reversed. Hypothetically, other effects of the genetic change could possibly be treated, but that requires a better understanding of the disease mechanism and how lack of dephosphorylation might be corrected. Research on this is still in its infancy. However, knowing the diagnosis means that appropriate monitoring and interventions can be put in place. Current treatment focuses on managing the specific symptoms and providing supportive care to improve quality of life.

> ***We visit the states every couple of years as we are taking part in finding a 'cure' which we have been doing since the start in 2017. We went into this so it would hopefully help other families in the future. We feel that if it helps our daughter at least 20% in the future then that is great. Human clinical trials have now started in the states." Age 19 years, HJS type 1***

Management

No clinical practice guidelines for Houge-Janssens syndrome have been published (2026). The following suggestions have been provided by clinicians, who have personal experience of managing/treating individuals with Houge-Janssens syndrome, to improve quality of life and reduce complications.

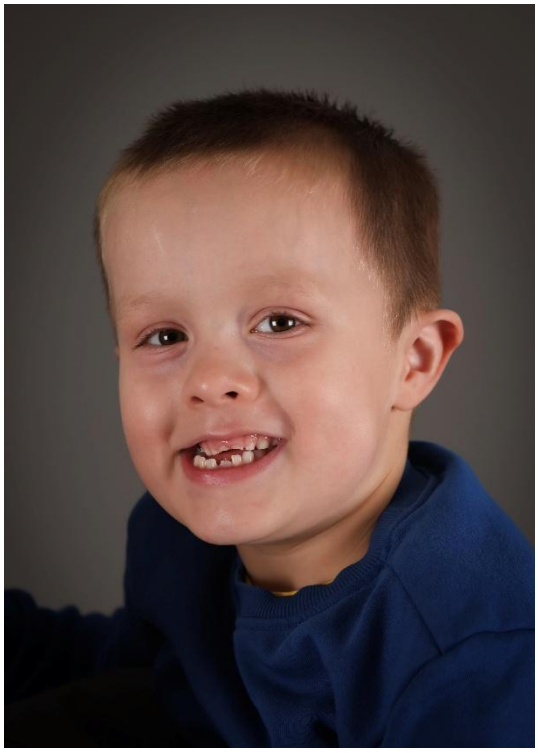
Children and adults with Houge-Janssens syndrome should be under the care of a multidisciplinary team. The team should include a geneticist and paediatrician (for children) who can oversee care so that development and behaviour can be monitored, and the best help given in the form of different therapies. Individuals may also have evaluations with various specialist doctors.

Immediately following diagnosis

When not carried out as part of the diagnostic process, an evaluation of the features of Houge-Janssens syndrome that are present in the child or adult who has been diagnosed with this genetic condition is recommended. This can determine which of the features of Houge-Janssens syndrome are present and how severe they are.

The following assessments are recommended:

- A physical examination to look for low muscle tone (hypotonia) and joint hypermobility
- A growth assessment, including measurement of height, weight, and head circumference
- A cardiac assessment, including an echocardiogram, to look for congenital heart malformations
- An audiological (hearing) assessment to determine the severity of hearing loss and ensure early in
- tervention
- An ophthalmology (eye) assessment to check for vision issues, strabismus and astigmatism
- A neurologic assessment to determine whether conditions such as seizures, movement disorders and learning (intellectual) disability are present. An electroencephalogram (EEG) is recommended to assess for seizure activity. Brain magnetic



resonance imaging (MRI), a technique that can be used to visualise the brain, should be carried out to look for structural brain anomalies such as underdevelopment (hypoplasia) or absence (agenesis) of the corpus callosum and enlarged ventricles

- A developmental assessment to get a baseline of motor, language, cognitive, social and adaptive skills
- An assessment by a speech and language pathologist to evaluate the extent of any language delay and to consider whether augmentative and alternative communication (AAC) may be helpful
- A feeding assessment by a gastroenterologist or feeding team to look for issues such as feeding difficulties, difficulty swallowing (dysphagia), gastroesophageal reflux (GERD) or constipation
- An orthopaedic assessment to evaluate for skeletal issues, such as curvature of the spine (scoliosis)
- A neuropsychiatric assessment for the management of significant behavioural concerns, such as aggressive behaviour, sleep issues, or features of autism spectrum disorder (ASD)

Genetic counselling for affected individuals and their families should also be offered together with the provision of signposting to family support and resources. Referrals for therapies, such as physical, occupational and speech therapy, as well as early intervention programmes and planning for an education plan should be considered.

> ***Our son receives the higher-rate care component of Disability Living Allowance and higher-rate mobility under the severe mental impairment criteria. He also receives 10 hours of respite each week during term time, 15 hours during school holidays and two overnight stays each month, with 2:1 support in the community at all times." Age 7 years, HJS type 1***

Supportive care

A central coordinator, such as a developmental paediatrician or geneticist, is beneficial to integrate care plans from various specialists. How a person with Houge-Janssens syndrome is cared for is likely to require co-ordinated care by a multidisciplinary team of specialists, which may include a/an:

Developmental paediatrician – a doctor who specialises in the physical, mental and social health of children from birth to young adulthood. They often act as the central point of contact, monitoring overall development, managing complex medical issues and coordinating referrals

Clinical geneticist / genetic counsellor – confirms the diagnosis, provides information about the specific genetic variant and its implications, and offers counselling to the family

Neurologist – a doctor who specialises in conditions of the brain, spinal cord and nervous system who manages symptoms such as epilepsy and movement disorders

Cardiologist – a doctor who specialises in heart conditions

Ophthalmologist – a doctor who specialises in conditions affecting the eyes

Audiologist and otolaryngologist (ENT) – health care professionals who diagnoses, treats and helps manage conditions that involve hearing, balance or the ear

Gastroenterologist / nutritionist – health care professionals who manages feeding difficulties, gastro-oesophageal reflux (GERD) and poor weight gain

Orthopaedist – a specialist who monitors and treats musculoskeletal issues such as scoliosis and joint hypermobility

Occupational therapist (OT) – a health care professional who uses activities to aid self-management of a condition and can provide equipment, focusing on fine motor skills and activities of daily living

Physiotherapist/physical therapist (PT) – a health care professional who uses exercise, movement, manual therapy, education and advice to help with the body's strength and mobility, addressing motor delays and low muscle tone (hypotonia)

Speech and language therapist (SALT) – a health care professional who helps with speech, language communication and sometimes feeding/swallowing difficulties. They may evaluate for augmentative and alternative communication (AAC) devices

Psychologist / Psychiatrist / Behaviour Analyst – addresses behavioural challenges and provides management strategies

Specialist nurses and/or other healthcare professionals may need to systematically and comprehensively plan a child or adult's treatment.

Treatments and therapies

Early intervention can be beneficial and formal testing to assess specific, individual needs is recommended. An education, health and care plan (EHCP) in the UK, individualized education plan (IEP) in the US, or equivalent document in other countries, may be issued after a child has undergone an assessment, to help ensure that the educational, health and social provisions deemed necessary to support the child's needs are delivered.

Treatment will depend on the specific features and symptoms experienced by the person with HJS but may include:

Physiotherapy for low muscle tone (hypotonia) and gross motor delays, which usually includes exercises to build core strength, improve balance and enhance coordination to help children achieve motor milestones like sitting, crawling, and walking and to improve overall mobility and reduce the risk of later orthopaedic complications such as scoliosis, contractures and hip dislocation.

Occupational therapy for fine motor skill delays and sensory sensitivities, which can include activities to improve hand strength and coordination for daily tasks (e.g. feeding, dressing, grooming and writing) and sensory integration therapy to help individuals better process and respond to sensory information from their environment.

Speech therapy for a range of speech and language delays or difficulties and feeding/swallowing difficulties. For children with moderate to severe difficulties, this can include regular sessions focusing on Augmentative and Alternative Communication (AAC) methods (e.g. sign language, picture exchange systems and high-tech communication devices) and provides a functional means of communication for individuals who are non-verbal or have very limited speech.

Behavioural therapy for features of autism, ADHD and anxiety, which can include structured therapies like Applied Behaviour Analysis (ABA) to help manage challenging behaviours, improve social skills and develop coping strategies.

Medications may be prescribed such as anti-seizure medications (ASMs) to help control or prevent seizures; baclofen, tizanidine and Botox® injections to manage atypical muscle tone; melatonin for sleep difficulties, stool softeners and/or laxatives for constipation; and levodopa for early-onset parkinsonism (in HJS type 1).

Medical equipment such as wheelchairs, walkers, orthotics or adaptive strollers may be recommended to aid mobility and positioning.

Diet, such as a high-fibre diet may be recommended to help relieve constipation. In some cases, a ketogenic diet may be used to help control seizures.

Surgery, such as the placement of a nasogastric (NG) or gastrostomy tube (G-tube) for severe feeding difficulties to ensure adequate nutrition, or procedures to correct a squint (strabismus) to improve vision.

Surveillance

It is recommended that the following evaluations are carried out/considered to monitor an individual's existing symptoms, how they respond to care and treatment and whether any new symptoms emerge over time:

- Monitor for growth (including head circumference, stature and weight) and adequate nutritional intake at each visit
- Neuropsychiatric and learning assessments to monitor developmental progress in motor, adaptive, cognitive and speech-language skills and to screen for behavioural concerns (such as anxiety, depression, attention issues and features of autism spectrum disorder in individuals over 12 months) at each visit
- Consider a neurologic review (including an EEG, if seizures are suspected)
- Assessment for movement disorders, including parkinsonism, and of fine and gross motor skills to determine the need for physical or occupational therapy, as needed
- Consider a skeletal review to assess for scoliosis, with radiographs as needed
- An initial examination by an ophthalmologist to assess for conditions such as astigmatism and strabismus, with on-going reviews as needed or as recommended by the specialist
- Consider regular meetings with an endocrinologist to assess for signs of precocious puberty (annually throughout early childhood)
- Monitor for constipation, diarrhoea, symptoms of gastro-oesophageal reflux disease (GORD) and food sensitivities at each visit
- Consider the need for a sleep study to investigate any sleep problems
- Assessment of the need for social support, such as social work support, local resources, respite care, home nursing care and care coordination

Research into new treatments for Houge-Janssens syndrome

The genetic change causing Houge-Janssens syndrome affects development of the brain and other parts of the body before birth. Therefore, a complete cure is unlikely, even in the future, since the brain has already formed by the time a diagnosis is made. However, research into improved treatments and management for various features of Houge-Janssens syndrome is ongoing. In addition, although Houge-Janssens syndrome is a relatively rare condition, the *PPP2R5D*, *PPP2R1A*, *PPP2CA*, *PPP2R5C* and *PPP2R5E* genes are the subject of a lot of research. Research into the underlying molecular mechanisms of HJS is paving the way for potential future treatments that aim to restore the function of the PP2A enzyme. These strategies are currently in conceptual, preclinical or early clinical stages and include:

- Small molecule therapies to address specific molecular changes, such as correcting protein misfolding or alleviating substrate trapping (where an affected part of the enzyme traps molecules, preventing the enzyme from working)
- Pharmacologic kinase inhibitors to target cellular pathways that become overactive due to PP2A dysfunction
- PP2A activators, which are drugs designed to directly activate the PP2A enzyme and cross the blood-brain barrier
- Repurposed drugs

Details of clinical trials related to a particular condition or gene can be found at **ClinicalTrials.gov** and **EU Clinical Trials Register**.

Families say ...

"For anyone who has just received a diagnosis. Just remember a diagnosis does not define anyone. These kids are still their own person and make the world a happier place. Have patience and celebrate small wins. There is a reason these special kids were placed into our families and we need to embrace it." HJS type 2

"Our son is significantly delayed in most areas of development, but he surprises us all the time. He is an affectionate boy who is generally happy and has a very infectious giggle." HJS type 1

"Our daughter is very engaged in the world around her; she loves animals and books. She is also very sociable and has recently learned to hug. She has a special bond with her big sister and brings us all so much joy." HJS type 1

"Receiving the diagnosis brought both relief and heartbreak. It finally provided an explanation for our daughter's difficulties, but little practical guidance followed. There were no established care pathways, evidence-based management guidelines, or clear expectations for her future. Despite these uncertainties, our daughter is a spirited, imaginative and affectionate child. She adores her siblings, loves unicorns and anything pink, and has a wonderfully quirky sense of humour." HJS type 3

"For new parents I would tell them to go and meet other parents as that is where you get all your information from. I have made great friends and now our kids are all adults but we still meet up. Unless you live it no one truly understands and don't always agree with the professionals as majority of the time they are ticking boxes (maybe that's me being cynical as we have been in this world for a long time)." HJS type 1

"Despite the considerable challenges he faces, our son brings enormous joy to everyone who knows him. He is loving, funny, resilient and entirely unique. His personality is expressed through his smile, laughter, dancing, movement, affection and the strong connections he forms with trusted people. He reminds us every day of the importance of looking beyond spoken language and conventional measures of ability. Greater awareness and research into Houge-Janssens Syndrome are essential to improving understanding, treatment, support and quality of life for our chil and other individuals living with the condition." HJS type 1

Sources

The information in this booklet is drawn from the published medical literature and information from Unique members. In 2026, Unique had 26 members with Houge-Janssens syndrome. The first-named author and publication date for articles in the medical literature are given to allow you to look for the abstracts or original articles on the internet in **PubMed**.

References

Baker E (2022). PPP2R1A neurodevelopmental disorder is associated with congenital heart defects. Am J Med Genet., 188A: 3262–3277. **Link to article**

Douzgou S (2022). PPP2R1A-Related Neurodevelopmental Disorder. GeneReviews®. **Link to article**

Houge G (2025). Houge-Janssens syndrome. European Journal of Human Genetics. **Link to article**

Jiang Y (2024). Thirteen New Patients of PPP2R5D Gene Mutation and the Fine Profile of Genotype–Phenotype Correlation Unraveling the Pathogenic Mechanism Underlying Macrocephaly Phenotype. Children, 11(8): 897. PMID 39201832. **Link to article**

Lei T 2023. Prenatal Diagnosis of PPP2R1A-Related Neurodevelopmental Disorders Using Whole Exome Sequencing: Clinical Report and Review of Literature. Genes (Basel). 2023;14(1):126. PMID 36672867. **Link to article**

Lenaerts L (2021). The broad phenotypic spectrum of PPP2R1A-related neurodevelopmental disorders correlates with the degree of biochemical dysfunction. Genetics in Medicine, 23(2): 352–362. PMID 33106617. **Link to article**

Mirzaa G (2019). PPP2R5D-Related Neurodevelopmental Disorder. GeneReviews®. **Link to article**

Oyama N (2023). Clinical, neuroimaging and molecular characteristics of PPP2R5D- related neurodevelopmental disorders: an expanded series with functional characterisation and genotype–phenotype analysis. J Med Genet, 60(5): 511–522. PMID 36216457. **Link to article**

Reynhout S (2019). De Novo Mutations Affecting the Catalytic Ca Subunit of PP2A, PPP2CA, Cause Syndromic Intellectual Disability Resembling Other PP2A-Related Neurodevelopmental Disorders. The American Journal of Human Genetics, 104(1): 139–156. PMID 30595372. **Link to article**

Shang L (2016). De novo missense variants in PPP2R5D are associated with intellectual disability, macrocephaly, hypotonia, and autism. Neurogenetics, 17(1): 43–49. PMID 26576547. **Link to article**

Verbinnen I (2021). Protein Phosphatase 2A (PP2A) mutations in brain function, development, and neurologic disease. Biochemical Society Transactions, 49: 1567–1588. **Link to article**

Verbinnen I (2022). Clinical and molecular characteristics of a novel rare de novo variant in PPP2CA in a patient with a developmental disorder, autism, and epilepsy. Frontiers in Cell and Developmental Biology, 10. **Link to article**

Verbinnen I (2025). Pathogenic de novo variants in PPP2R5C cause a neurodevelopmental disorder within the Houge-Janssens syndrome spectrum. The American Journal of Human Genetics, 112: 554–571. **Link to article**

unique

Inform Network Support

Rare Chromosome Disorder Support Group
The Stables, Station Road West, Oxted, Surrey, RH8, 9EE, UK
Tel: +44(0)1883 723356
help@rarechromo.org I rarechromo.org

Join Unique for family links, information and support:

Become a member

Please help us to help you!

Unique is a charity without government funding, existing entirely on donations and grants.
If you can, please make a donation:

Donate via our website

Websites, Facebook groups and other links:

- Jordan's Guardian Angels
- PPP2CA Pathways

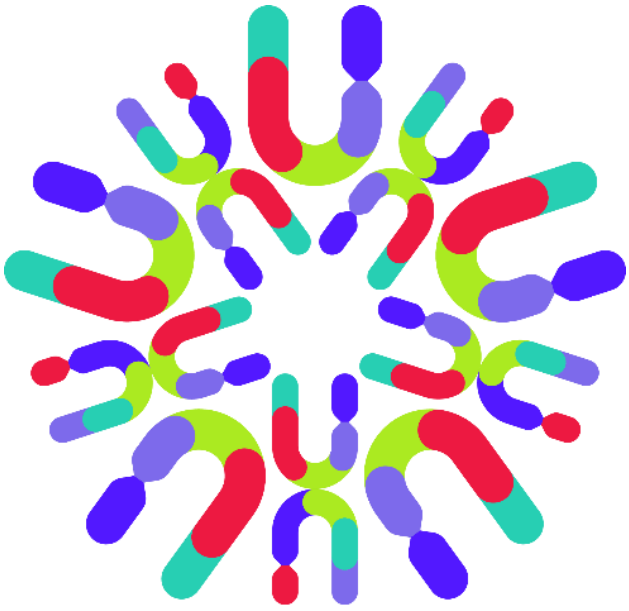
This guide was reviewed by Dr Gunnar Douzgos Houge, MD PhD.

This guide was produced as part of a collaborative project between the Manchester Rare Condition Centre, Shorthills AI and Unique (AP/CA). We thank the North West Genome Medicine Service Alliance for supporting the project.

Version 1 (AP/CA) [2026]

Rare Chromosome Disorder Support Group
Registered in England and Wales

Charity Number 1110661
Company Number 546041



unique

UNDERSTANDING GENES
& CHROMOSOMES

rarechromo.org