## What causes USP7-related disorder?

The *USP7* gene is located on chromosome 16. We have two copies of chromosome 16 and therefore two copies of the *USP7* gene. USP7-related disorder is caused by one copy of the *USP7* gene not functioning as expected. This may be due to a change (known as a variant) within the gene which disrupts its function, or to the loss (deletion) of the gene or part of it. The other copy of the *USP7* gene is unaffected and so can carry out its usual function. This type of genetic change is called autosomal dominant, since the change occurred on an autosome (chromosomes 1-22) and symptoms are apparent with only one altered copy (dominant).

The *USP7* gene has multiple roles in the genetic control of our development and functioning. The USP7 protein has many functions including controlling the activity of other genes (transcriptional regulation), immune response, and the process of recycling protein in our cells. Not all functions are fully understood but knowledge in these areas will progress as research continues. USP7 is also known to have a role in functioning of the brain.

## Why did this happen?

When children are conceived their parents' genetic material is copied in the egg and sperm that makes a new child. The biological copying method is not perfect and occasionally random, rare changes occur in the genetic code of children that are not seen in the DNA of their parents. USP7-related disorder occurs when one of these random changes affects the *USP7* gene. These types of change happen naturally in everyone and are not due to lifestyle or anything that anyone did prior to or during pregnancy. It's only when one of these changes affects an important gene that health and/or development are affected.

## 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 all families reported in the medical literature so far (2021), this genetic change has happened for the first time in the child with USP7-related disorder. This is called a '*de novo* variant'. When the parents are unaffected, the chances of having another child with the same condition are very low. Very rarely, a parent may be identified as having germline mosaicism, which means the gene variant can be present in the egg or sperm but is not detected in a standard blood test. Each family situation is different and a clinical geneticist or genetic counsellor can offer family specific advice.

## Families say ...

"He is always smiling, he's happy go lucky and enjoys everything to do with farming & building sites! He gives the best cuddles and is a fantastic brother." - Age 11 years

"His diagnosis has not changed anything for us, apart from linking all his issues together." - Age 11 years

## Inform Network Support


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Websites:
Foundation for USP7-Related Disorders: https://www.usp7.org/
Facebook groups:
https://www.facebook.com/FoundationUSP7/
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# USP7 - related disorder

## Hao-Fountain Syndrome (HFOUS)

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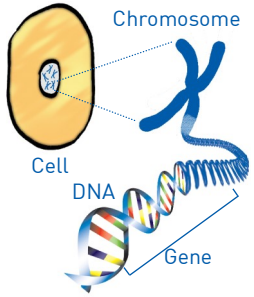
## What is USP7-related disorder?

USP7-related disorder is caused by changes (known as variants) in, or a deletion of, the *USP7* gene. This gene is located on the short 'p' arm of chromosome 16 in a region called 16p13.2. Its name is an abbreviation of the protein it codes for - Ubiquitin-specific protease 7.





USP7-related disorder is also known as Hao-Fountain Syndrome (HFOUS). Children with USP7-related disorder have neurodevelopmental difficulties. They have developmental delay with learning difficulties or intellectual disability. Their speech and language is affected and they can have difficulties with their behaviour. USP7-related disorder affects boys and girls, and there are both mildly and more significantly affected individuals of both sexes.

### Most children have:

- Language and speech difficulties, delay or absence
- Developmental delay
- Moderate to severe learning difficulties or intellectual disability (ID)
- Unusual findings during brain MRI
- Low muscle tone/floppiness (hypotonia)
- Eye anomalies (strabismus, myopia, nystagmus, or other)
- Behavioural difficulties (e.g. autism)
- Significant feeding problems
- Underdeveloped genitalia in boys (hypogonadism)
- Mild facial features

### Some children have

- Seizures (abnormal electrical activity in the brain)
- A slightly unusual way of walking (abnormal gait)
- Short stature
- Difficulty gaining weight
- Chronic constipation or diarrhoea
- Shortened muscles or joints (contractures)

## How common is USP7-related disorder?

USP7-related disorder is extremely rare, there are reports in the medical literature for about 25 individuals who have been identified worldwide (2021). Many more individuals with a USP7 variant or deletion are known to have been diagnosed and many are likely to remain undiagnosed.

## Development

### Physical development

Children with USP7-related disorder learn to walk alone, but this may be delayed slightly. Hypotonia and/or joint hyper-flexibility may play a role in delay. Approximately 44% of children have an abnormal gait.

### Learning

Children with USP7-related disorder typically have learning difficulties and are often given a diagnosis of intellectual disability (ID). Some children require special education and others may remain in a mainstream school with an Educational Health Care Plan (EHCP).

### Behaviour

Children with rare chromosome and gene disorders often have behavioural, social and/or communication difficulties and vulnerability in these areas means that children should be monitored and families offered early support. Over half of the children with USP7-related disorder have been identified as having autism or autistic-like behaviours such as hand flapping, skin picking or repetitive behaviour. Some are described as having aggressive behaviour, temper tantrums, impulsivity, compulsivity, stubbornness or manipulative behaviour.

### Speech

For the majority of children with USP7-related disorder identified so far, speech is delayed and limited; some children are non-verbal. Language abilities may also be linked to the level of learning disability or ID for each child.

### Growth

A third of children with USP7-related disorder are reported to have short stature.

### Facial appearance

Various minor facial appearances have been reported in children with USP7-related disorder such as deep set eyes and a prominent nasal septum extending below the wings of the nostrils. However, every child's appearance is different and will change with age.

## Medical concerns

The medical concerns experienced by children with USP7-related disorder are extremely variable and impossible to predict. Below are some of the more common features that a child may experience:

### Brain imaging and seizures

The majority, but not all, children with USP7-related disorder reported so far (2021) have unusual brain imaging results following an MRI. However, only 44% of these children have developed seizures.

### Eyes and eyesight

Children with USP7-related disorder may be more likely to have a squint (strabismus), where the eyes do not look in the same direction. Treatment can include patching, exercises, glasses, and surgery to bring the eyes into line. Children can also be short sighted (myopic) or have involuntary eye movements (nystagmus).

### Gastrointestinal problems

Just over half of the children described in the medical literature have some form of feeding difficulty such as reflux or vomiting. Chronic constipation/diarrhoea has also been described.

### Reduced growth

Approximately a third of children with USP7-related disorder have short stature. Some children might benefit from growth hormone (GH) therapy.

### Hypogonadism

Over half of the boys with UPS7-related disorder have a small penis, underdeveloped scrotum or small testes. Testes may not be descended into the scrotal sac at the time of birth (cryptorchidism).

## Management recommendations

- Early input from speech and language, physio– and occupational therapists is important
- An assessment of special educational needs should be carried out so that extra help can be put in place at school
- An assessment by an ophthalmologist
- An assessment by a gastroenterologist
- Input from a neurology/neurodevelopment team may be required
- A brain MRI to assess for brain abnormalities
- Seizure activity may need monitoring
- Screening for growth hormone deficiency