Why did this happen?
When children are conceived the parents’ genetic material is copied in the egg and sperm that make a new child. The biological ‘copying’ mechanism 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. MEF2C haploinsufficiency syndrome occurs when one of these changes affects the MEF2C gene. This happens naturally in plants and animals and is not due to your lifestyle or anything you did. For MEF2C haploinsufficiency syndrome, the changes that cause the syndrome have occurred out of the blue (de novo).

How common is it?
Mutations in the MEF2C gene that cause this syndrome are rare. Sixty individuals have been reported in the medical literature, so far (2018). It is likely, however, that there are still undiagnosed individuals.

Can it happen again?
The possibility of having another child affected by a rare gene disorder depends on the genetic code of the parents. To the best of our knowledge, all the affected people are the first person in their family to have the pathogenic gene variant (2018).

For MEF2C haploinsufficiency syndrome, since the parents do not have the changes in the MEF2C gene that cause the syndrome, their chances of having another affected child would be considered very small (<1%).

There is still a small risk due to a rare phenomenon known as germline mosaicism, which is when a small number of egg or sperm cells carry the genetic change but the rest of the body’s cells do not.

This disorder has as an “autosomal dominant” pattern of inheritance, which means that if a person with MEF2C haploinsufficiency syndrome has children, each child has a 50% chance of being affected.

A clinical geneticist or genetic counsellor can give you specific advice for your family.

Can it be cured?
There is no cure since the effects of the genetic variant took place during development in the womb; however, a diagnosis means that appropriate monitoring and treatment can be put in place.
What is MEF2C haploinsufficiency syndrome?

MEF2C haploinsufficiency syndrome is a genetic condition which affects body development, in particular development of the brain. The condition is also known as "mental retardation, autosomal dominant 20" (MRD20) or "chromosome 5q14.3 deletion syndrome".

MEF2C haploinsufficiency syndrome was first described in 2009. People with this syndrome have variable degrees of developmental delay, hypotonia (low muscle tone), seizures, stereotypic movements and characteristic (though subtle) facial features.

Why did this happen?
The human body is made up of billions of cells. These cells are important for carrying out different functions in the body as well as housing the vital "instructions" that enable our body to work properly, contained within the DNA that make up our genes. Each person has several thousand genes, one copy inherited from their father and one copy inherited from their mother, grouped along thread-like structures called chromosomes, which are packaged to fit inside our cells.

MEF2C haploinsufficiency syndrome is caused by changes (mutations) in the MEF2C gene, located on chromosome 5.

The function of the MEF2C gene is to control and regulate other genes during the development of the human body. The MEF2C gene plays an important role in brain development and is also important in the development of the face, skeletal muscle, blood vessels, heart and immune system.

The MEF2C gene is located on chromosome 5 in band 5q14.3 at base pairs 88013975-88199922 [hg19 genome assembly]. In MEF2C haploinsufficiency syndrome one copy of the MEF2C gene does not function normally. This may be due to a change (mutation) within the gene or deletion of some of the gene, which disrupts its function.

Most common features

- Developmental delay in motor milestones e.g. walking
- Severely impaired or absent speech
- Stereotypic movement e.g. repetitive hand movements
- Hypotonia (low muscle tone)
- Seizures

AFFECTED people will not necessarily have all of these features, but they have been found to be the most common. The condition affects boys and girls in the same way.

Development

- **Physical development**
  Most children (98%) have a delay in reaching their motor milestones e.g. sitting, crawling, cruising and walking, compared with other children of the same age. Ability to walk is affected, but a minority of children do learn to walk. The average age for sitting without support is 16 months (ranging from 8 to 36 months) while the average age for walking independently is 42 months (ranging from 14 months to 11 years).
- **Speech and learning**
  Most people (89%) with MEF2C haploinsufficiency syndrome have severely impaired or absent language. A few people have developed some limited speech and communication abilities.
- **Learning**
  Most children require support with their learning, focused on non-academic and daily living skills. A proportion may attend a special school. One person with a chromosome 5q14.3 microdeletion was reported with only mild learning difficulties and normal speech.
- **Behaviour**
  Children frequently have autistic features (53%) and stereotypic behaviour. Most children (70%) have repetitive hand movements e.g. hand flapping, clapping, mouthing or biting while some demonstrate head rocking. Problems with sleep have been frequently reported (57%).
- **Growth**
  Most babies are usually born with an average head size, weight and length and continued to grow appropriately. A few babies (18%) have a significantly reduced head size, this is called ‘microcephaly’.

Management recommendations

- Genetic counselling to explain genetic test results, recurrence risk and suggest an appropriate management schedule.
- Paediatric MDT assessment for developmental delay, ASD/ADHD and complex behavioural patterns, including educational support where required.
- Electroencephalogram (EEG) where seizures are suspected and regular assessment by a neurologic paediatrician.
- Magnetic resonance imaging (MRI) scan of the brain.
- Hearing and eyesight (ophthalmology) reviews.
- Baseline echocardiogram (ECG) and further follow-up with a cardiologist if heart abnormalities are detected.

Medical concerns

Not all people with MEF2C haploinsufficiency syndrome have the same features. Those with a chromosome 5q14.3 microdeletion that also affects other genes can have an increased likelihood of medical problems compared to those with mutations or deletions limited to the MEF2C gene.

A key clinician (hospital or community paediatrician or GP) should oversee care so that development and behaviour can be monitored and the best help can be given early if required [See Management recommendations].

- **Hypotonia**
  Most babies (95%) have low muscle tone (hypotonia), commonly known as ‘floppy baby syndrome’.
- **Seizures**
  Most people (83%) have a type of epilepsy, although they can also be seizure-free. The average age of the first seizure is 15 months, ranging from 1 day to 6 years. Most of the time, the seizures respond well to medication. Febrile seizures are also common (41%).
- **Feeding**
  Most children have feeding difficulties (75%) and constipation (55%) in early childhood and infancy.
- **Eyesight**
  The majority of children (88%) have poor eye contact. Ametropia, which includes a range of disorders of the eye that mean the eye is unable to focus correctly e.g. myopia (short-sightedness); hyperopia (long-sightedness); astigmatism; and strabismus (crossed-eyes) are common.
- **Skin conditions**
  Hemangiomas [non-cancerous growths of blood vessels] are a common and characteristic feature in people with MEF2C haploinsufficiency syndrome (50%). They usually disappear without treatment. Approximately one third of people have a small and subtle skin defect at the bottom of the neck called “jugular pit” or “sternal fistula”.
- **Heart conditions**
  Anomalies of the heart have been reported in two people, although it is not yet clear whether this is a definite feature of the condition.
- **Breathing problems**
  Recurrent respiratory infections are frequent (63%). Some patients have episodic breathing abnormalities.