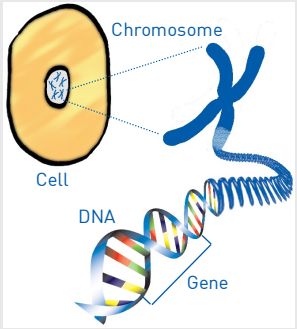
Why did this happen?



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.

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Unique
Understanding Chromosome & Gene Disorders

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www.rarechromo.org/donate
Please help us to help you!

Websites, Facebook groups and other links

http://humandiseasegenes.nl/mef2c/
This website provides information on patients with mutations in the *MEF2C* gene, including clinical data, molecular data, management and research options with the intention of creating an on-line registry for patients with *MEF2C* haploinsufficiency syndrome.

Unique lists external message boards and websites in order to be helpful to families looking for information and support. 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. The text was written by Dr Sofia Douzgou, MD, PhD, FRCP and Dr Florence Riccardi, MD, Manchester Centre for Genomic Medicine, Central Manchester University Hospitals, NHS Foundation Trust, UK, and the guide was compiled by Unique (CA).
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Unique
Understanding Chromosome & Gene Disorders

MEF2C haploinsufficiency syndrome

(*MRD20*/chromosome 5q14.3 deletion syndrome)

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 from14 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.