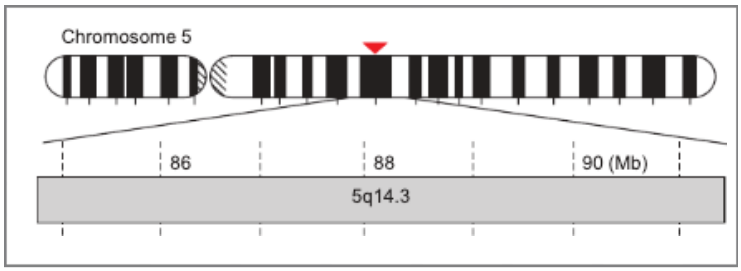
5q14.3 Deletion (MEF2C Deficiency Syndrome)

The segment 5q14 in the proximal part of the long arm of chromosome 5 contains many important neural genes, including the MEF2C gene, located at 5q14.3. Deletions of this gene causes a complex of neurodevelopmental problems including intellectual disability, developmental delay and seizures.



MEF2C, a key gene involved in 5q14.3 deletions, is known to code for a transcription factor that is essential for the proper development of the brain, face, heart, and overall vascular development[1]. It is important in developing neurons and synaptic formations as well as maintaining homeostatic control of excitatory synapse number during neural development and memory storage[2]. As a result, patients with this deletion have severe intellectual disabilities, severe developmental delays, epilepsy, stereotypic movements, and mild dysmorphic facial features.

These deletions are basically sporadic and non-recurring, meaning most deletions are unique. The size of deletions may vary from 0.2 Mb (actually covering only the MEF2C gene) to 8 Mb (and involving several other genes). However, even in patients with relatively large deletions, loss of the MEF2C remains the main factor causing clinical problems. The sex ratio among affected patients is almost equal (1:1).

Every patient who has a 5q14.3 deletion will present with intellectual disabilities as well as developmental delays. One way these disabilities and delays manifest in individuals is speech. Individuals will have little to no speech or expressive language skills. Those who can communicate can only do so with a couple words here and there. No patient is able to speak fluent sentences. Patients will also have very delayed gross motor skills. Skills like

sitting unaided, crawling, and pulling to stand can take up to 18 months, 5 years, and 7 years respectively[1]. Many children with the deletion are unable to walk unaided. However, some have the ability to maneuver a wheelchair as their source of transport[3].

Epileptic seizures are another common manifestation of 5q14.3 deletions. Epilepsy affects most patients (80%) and can begin as early as infancy. About half of those who develop seizures will have their first seizure within their first year of life. The overall severity and type of an individual's epilepsy can vary. It can range from daily seizures to only occasional ones and includes generalized, combined, and focal epilepsies. Many patients, however, can be treated for epilepsy and become seizure free. About 50% of patients who receive a median of two anti-epileptic drugs will become seizure free[4].

Another main manifestation of 5q14.3 deletions is stereotypic movements. This includes behaviors such as hand flapping, clapping, mouthing, head rocking, and hand biting[1]. These behaviors can be best characterized as hyperkinesis and tend to come out when the patient is excited. Hyperkinesis tends to decrease and moderate over time as the patient progresses through childhood[5]. A high pain tolerance is another remarkable sign presented by many individuals, as well as sleeping problems. Up to 40% of patients experience sleep problems (both falling asleep and staying asleep). Many patients with this syndrome are also diagnosed with autism.

Some patients will also have dysmorphic facial features as a result of the deletion. This can include a broad forehead, up slanting palpebral fissures, a flat nasal root and bridge, a small, upturned nose, small mouth, large ears, small chin, and strabismus. These features may not all be present in individuals and can range in how strongly they are presented[6].

Point mutations in the MEF2C gene leading to its haploinsufficiency produce the same clinical picture as the deletion. Sometimes in the literature we can read about the MEF2C deficiency syndrome. Actually more than 60% of known patients with this condition have deletions, and other have mutations. However, it should be mentioned that diagnostics of deletions is not so difficult as diagnostics of mutations: molecular cytogenetic examination, which may be ordered for most patients with developmental delay, will reveal all types of chromosomal imbalance. Finding a mutation, however, requires either whole exome sequencing or special examination for the MEF2C gene (which may be ordered if there is an idea that the patient may have defect of this gene).

Receiving an official diagnosis of a 5q14.3 deletion (or MEF2C deficiency) can be challenging. Patients with this condition present many of the same characteristics as several other syndromes such as Pitt-Hopkins, Angelman's and Rett's syndromes. There are very few distinguishing characteristics between these diagnoses - making them difficult to reach without looking at the patient's DNA to search for specific deletions or mutations[1].

REFERENCES

[1] Vrečar I., Innes J., Jones E.A., et al. Further clinical delineation of the MEF2C haploinsufficiency syndrome: report on new cases and literature review of severe neurodevelopmental disorders presenting with seizures, absent speech, and involuntary movements. J Pediatr Genet 2017, v. 6, 129-141.

[2] Nowakowska B.A., Obersztyn E., Szymańska K., et al. Severe mental retardation, seizures, and hypotonia due to deletions of MEF2C. Am J Med Genet B Neuropsychiatr Genet. 2010, v. 153B, 1042-1051.

[3] Le Meur N., Holder-Espinasse M., Jaillard S., et al. MEF2C haploinsufficiency caused by either microdeletion of the 5q14.3 region or mutation is responsible for severe mental retardation with stereotypic movements, epilepsy and/or cerebral malformations. J Med Genet. 2010, v. 47, 22-29.

[4] Raviglione F., Douzgou S., Scala M. et al. Electroclinical features of MEF2C haploinsufficiency-related epilepsy: A multicenter European study. Seizure 2021, v. 88, 60-72.

[5] Paciorkowski A.R., Traylor R.N., Rosenfeld J.A., et al. MEF2C haploinsufficiency features consistent hyperkinesis, variable epilepsy, and has a role in dorsal and ventral neuronal developmental pathways. Neurogenetics 2013, v.14, 99-111.

[6] Hotz A., Hellenbroich Y., Sperner J., et al. Microdeletion 5q14.3 and anomalies of brain development. Am J Med Genet. 2013, v. 161A, 2124-2133.