Late-onset gain of skills and peculiar jugular pit in an 11-year-old girl with 5q14.3 microdeletion including *MEF2C*

Siren Berland[a,b] and Gunnar Houge[b,c]

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[a]Department of Clinical Genetics, St. Olavs Hospital HF, Trondheim, [b]Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen and [c]Department of Clinical Medicine, University of Bergen, Norway

Correspondence to Dr Siren Berland, MD, Department of Clinical Genetics, St Olavs Hospital, N-7006 Trondheim, Norway
Tel: +47 728 22450; fax: +47 728 22452;
e-mail: siren.berland@helse-bergen.no

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List of main features

MEF2C deletion
Severe mental retardation
Microcephaly
Stereotypic movements
Poor eye contact
Seizures
Precocious puberty
Hypotonia
Absent speech
Sternal fistula

Clinical summary

The patient, now 11 years old, is a girl born by elective cesarean section after an uneventful pregnancy. Neonatal findings were normal. She has two healthy siblings and healthy parents. Lack of eye contact was noted at 6 weeks of age, and strabismus, intermittent nystagmus, and mild hypotonia were noted at 4 months of age. Some febrile tonic–clonic seizures were observed between the ages of 1 and 7 years. Several atypical seizures with myoclonic jerks were also noted. Standard electroencephalographic (EEG) record was normal at the age of 1 year, but a few months later a generalized epileptiform pattern was present. Repeat EEG attempts at the ages of 6 and 8 years were unsuccessful because of lack of cooperation. The patient's epilepsy was never troublesome and no recurrences have been noted after the cessation of low-dose valproate treatment at the age of 8 years. The patient's psychomotor development has been severely retarded. She sat at the age of 3 years, crawled and walked with support from the age of 4 years, and first learned to walk unaided at the age of 11 years. Fine motor skills are better than gross motor skills. No verbal language is present, but she mimics sounds. She does not produce proper hand signs, but make use of body language. She uses a picture exchange communication program whereby she chooses, for example, an activity or type of food and delivers the picture to the instructor. She also enjoys simple computer games with touch screen. Receptive language skills are better than expressive, and she can follow instructions. Her height has followed the 97.5 centile (tall family), and her head circumferences have been on the 2.5 centile. She resembles her sisters, who also have long and upslanted palpebral fissures and everted lower lids. More nonfamiliar features are mild brachycephaly, wide forehead, short and wide philtrum with an everted upper lip, and short and broad chin (Fig. 1). She has mild clinodactyly and short and narrow feet. Ankle stabilization surgery has been performed. At consultation at the age of 11 years, poor eye contact and stereotypic movements were the most obvious features. A peculiar finding was a pit in the jugular fossa. She is usually a happy and joyful child, has no panic attacks but is easily scared of loud sounds, is

Fig. 1

The proband at the age of 10 years. Note brachycephaly, everted upper lip, and a short, broad chin. The pit in the jugular fossa is not clearly visible in this image, but the darker skin area surrounding the pit can be seen. The localization of the pit is marked by an arrow.

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seldom sick, and has normal appetite, breathing, and sleeping patterns. Autistic features are present, but less now than before, as she has recently begun seeking social contact. At a younger age, she was fascinated by water and bright objects and had typical hand washing stereotypies. These movements are now replaced by flipping stereotypies, for example, flipping corners of carpets or a page of a magazine. Puberty has occurred early, with menarche at the age of 8 years and 10 months.

Results of investigations

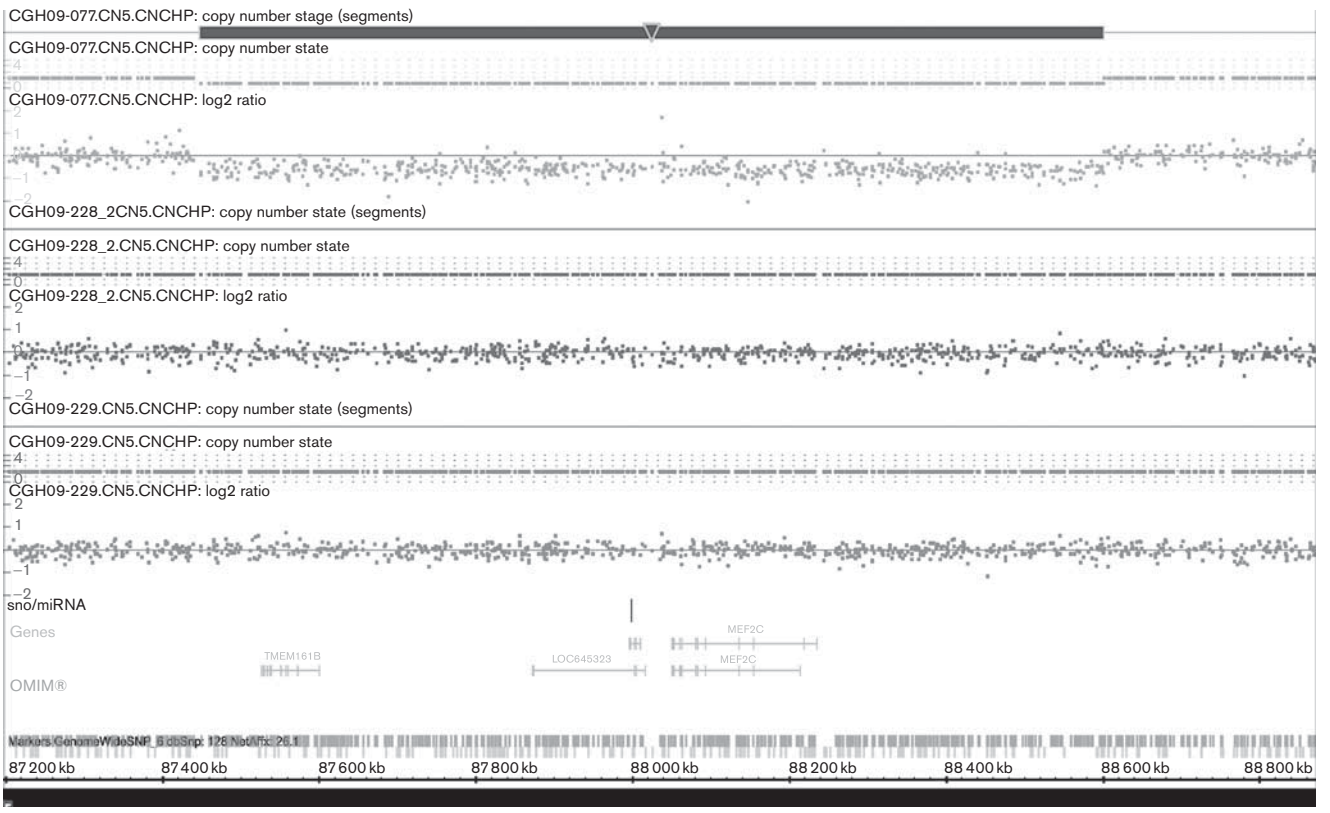
Brain MRIs at ages 1 and 8 years were normal. The patient has normal vision and hearing. EEG showed nonspecific epileptic changes. G-banded chromosome analysis and DNA analysis for fragile X, Angelman, and Rett syndromes were normal. An Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, California, USA) analysis identified a de-novo 1.15 Mb deletion in band 5q14.3, and accordingly the patient's karyotype was 46,XX.arr 5q14.3(87449860-88600147)x1 (nucleotide positions are according to National Center for Biotechnology Information Build 36) (Fig. 2). This deletion contains only two protein coding genes, *MEF2C* and *TMEM161B*. *MEF2C* haploinsufficiency was postulated to be the main cause of the patient's developmental delay because of high expression in the brain and a function as a transcription factor. Shortly after Le Meur *et al.* (2010) reported five patients with partial or complete deletions involving *MEF2C* and one patient with a stop mutation in the gene.

Discussion

Our findings support the reported *MEF2C* deletion phenotype of severe mental retardation, hand stereotypies, poor eye contact, absent speech, and epilepsy (Cardoso *et al.*, 2009; Engels *et al.*, 2009; Le Meur *et al.*, 2010; Nowakowska *et al.*, 2010; Novara *et al.*, 2010; Zweier *et al.*, 2010). Le Meur *et al.* (2010) also reported a somewhat atypical patient with a nonsense *MEF2C* mutation in exon 7 and regression of skills from the age of 5 months. This patient was able to walk unaided. One patient with a truncating *MEF2C* mutation walked at the age of 2 years and 8 months (Zweier *et al.*, 2010).

Our patient is older than most of the patients reported earlier. She has had a remarkably positive development at late age with cessation of epilepsy, gain of ability to walk

Fig. 2



The Affymetrix 6.0 SNP array result with a deletion including *MEF2C*: the uppermost dotted line indicates the patient's copy number state and the solid bar above signifies the deletion. The normal log2 ratios after testing DNA samples from the father (darker dotted line in the middle) and mother (lower dots) can be observed below. At the bottom, genes and RNA transcripts removed by the deletion are displayed.

unaided (at age of 11 years), better communication skills, and social contact, indicating that physiotherapy and language training may be beneficial for these patients. To date, she is the first reported patient with a deletion of the entire gene who has learned to walk unaided. The suprasternal or jugular pit (a small sinus located in the jugular fossa) could be a characteristic clinical sign, as such an unusual finding was also noted in at least one other patient (patient 1 in the study by Le Meur *et al.* (2010); Alice Goldberg, personal communication).

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