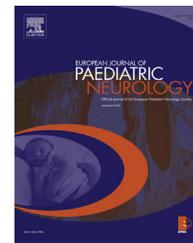




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Case study

A new variable phenotype in spinocerebellar ataxia 27 (SCA 27) caused by a deletion in the FGF14 gene



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ABSTRACT

We present a young boy whose mild ataxia and abnormal eye movements repeatedly deteriorated with fever, making him unable to sit or walk during fever episodes. SNP-array analysis identified a 202 kb deletion in chromosome 13q33.1 containing the fibroblast growth factor (FGF)14 gene, which is associated with spinocerebellar ataxia (SCA) 27. This 13q deletion was also present in the proband's mother and grandmother. The mother was unable to perform tandem gait walking and had abnormal eye movements but had never sought medical attention. The grandmother predominantly had a postural tremor. FGF14 regulates brain sodium channels, especially in the cerebellum. Sodium channels can be fever sensitive. This family demonstrates phenotypic variability of FGF14 deletions (SCA 27), fever sensitivity of ataxia and the added value of SNP-array analysis in making a diagnosis.

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1. Introduction

Spinocerebellar ataxias (SCA) are neurodegenerative syndromes. SCA 27 is a rare cause of familial ataxia. A F145S missense mutation in exon 4 of the gene FGF14 was first described in a Dutch family with a progressive ataxia phenotype, a condition later named SCA 27.^{1,2} SCA 27 as a result of a deletion of FGF14 has not been described before. Five previous reports have described clinical manifestations of alterations in the FGF14 gene,^{1–3} [esupp 1–2]. The original SCA 27 family typically presented with childhood onset postural tremor, progressive ataxia from adolescence, low IQ, memory and

executive function disturbances, dyskinesias (predominantly orofacial) and head titubation. In this report, we describe a family with a deletion of FGF14 and a variable SCA phenotype including gait instability, nystagmus and febrile episodic ataxia.

2. Case study

The proband presented at the age of two years with delayed walking. In subsequent years, his mild gait disorder due to poor axial balance became more apparent with

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dysdiadochokinesis and dysmetria. He showed dysmetric saccadic eye movements, intrusive square wave jerks and horizontal and vertical gaze-evoked nystagmus. He has slight dysarthric speech. There were no postural tremor, chorea, polyneuropathy or dyskinesia. During three fever-related episodes (up to 40 °C) with mild respiratory infections, he presented with acute severe deterioration of all symptoms and signs, being unable to sit and walk. These clinical deteriorations fluctuated with the intensity of his fever. His IQ was within normal limits, with better verbal than performal scores. At the age of 6 years his height, weight and head circumference were normal.

The family's pedigree is shown in Fig. 1. The proband's mother shows the same abnormal eye movements and is unable to perform tandem gait walking, but had never sought medical attention. The mother's brother is reported to have similar symptoms and signs (coordination disorder and abnormal eye movements) but has not visited a doctor. The mother's mother first noticed a head tremor at age 49 and postural hand tremor at age 66 with mild cerebellar (especially gait) ataxia on physical examination, and was diagnosed with essential tremor by a movement disorders neurologist. Two of her sisters and her mother were also reported to have similar problems. All family members had normal intelligence.

During the first episode of fever-related neurological deterioration, an MRI of the brain and CSF analysis were normal in the proband. Laboratory investigations showed normal renal and liver function, electrolytes, full blood count, lactate, ammonia and basic metabolic investigations in plasma and urine. Electroencephalography recordings during and after a febrile episode were normal. In the grandmother and mother, brain MRI showed no abnormalities. Clinically, there was an episodic ataxia syndrome with interictal nystagmus and postural imbalance. There were some similarities in the proband to a family with episodic ataxia type 2, caused by a *CACNA1A* mutation.⁴ Sequencing of the *CACNA1A* gene in our proband, however, did not show any abnormalities. However his mother and grandmother did not have episodic ataxia and his episodes lasted days. Because of the low clinical suspicion of EA2, no MLPA of the *CACNA1A* gene

was performed, so small deletions in the gene cannot completely be ruled out.

GeneChip Human Mapping 250K SNP-array (Affymetrix) showed an interstitial deletion on chromosome 13q33.1 with a maximum size of 201,8 kb (20 SNP probes), from 102.334.036 bp to 102.535.807 bp (Ensembl release 67) (see Fig. 2). It includes the last four exons of the protein coding gene *ITGEBL1* (Integrin beta-like protein 1 precursor) and the first four exons of the fibroblast growth factor 14 (*FGF14*) gene. This deletion was also present in the proband's mother and grandmother and absent in his father. In our laboratory, performing around 1500 SNP-array analyses per year, no deletions including the *FGF14* gene have been detected so far in patients without a SCA phenotype. No other abnormalities were found in the proband on SNP-array analysis.

3. Discussion

We found a novel familial deletion of 202 kb containing part of the *FGF14* and *ITGEBL1* genes, associated with a variable cerebellar ataxia phenotype. *FGF14* abnormalities are a rare cause of cerebellar ataxia. Deletions of (part of) this gene have not been described before. The resolution of the SNP-array platform we used was such that other very small, yet clinically relevant genomic deletions or duplications of other loci could have been missed. No information is available on the function of the *ITGEBL1* gene. A contribution of this gene to the clinical phenotype in this family appears unlikely, but cannot be excluded.

SCA 27 caused by *FGF14* aberrations appears to be rare. In literature there are several studies that have investigated SCA patients for mutations in the *FGF14* gene. Dalski et al.³ performed molecular genetic analyses of the five exons of *FGF14* in 208 unrelated familial ataxia cases and 208 control samples in Germany. They detected a novel single base pair deletion in exon 4 (c.487delA) leading to a frameshift mutation in one patient. This 18-year-old male had mild mental retardation (IQ 70). From age 12 years, he had progressive truncal and gait ataxia, small-amplitude hand tremor, gaze-evoked nystagmus, pes cavus, memory loss, and a depressive mood. Misceo et al. [esupp 1] described a translocation between chromosome 5 and 13, disrupting *FGF14*, in a mother and daughter from Norway. Clinically, both showed signs of SCA, although the daughter was most affected with early onset cerebellar ataxia, microcephaly, and severe mental retardation. A Japanese group described a *FGF14* disruption caused by a de novo reciprocal chromosomal translocation between chromosomes 13 and 21 in a patient with paroxysmal non-kinesigenic dyskinesia (PNKD). The patient had mild mental retardation and showed involuntary gross movements of the extremities, associated with choreic movements of the head and trunk at the age of four, with no clear progression [esupp 2]. In 53 SCA (of unknown origin) patients from France, no mutations were found in *FGF14* [esupp 3] and neither did the discoverers of SCA 27 find any additional mutations in 38 SCA patients. Zhao et al. found no mutations in exon 4 of the *FGF14* gene either in 90 suspected SCA and 15 childhood onset postural tremor cases in Singapore [esupp 4]. By only focusing on exon 4, however, they might have missed mutations in

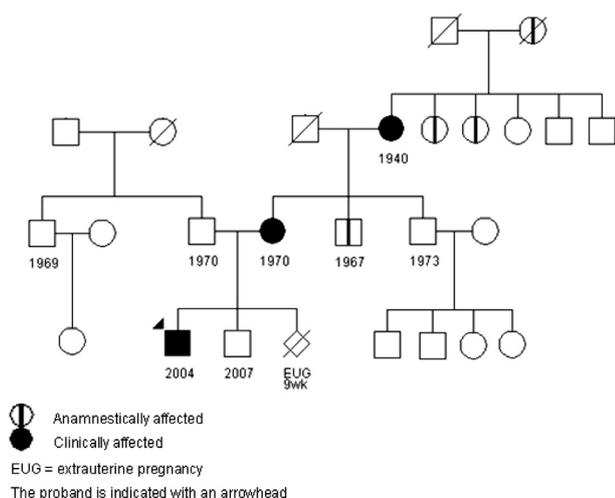


Fig. 1 – Pedigree of the proband's family.

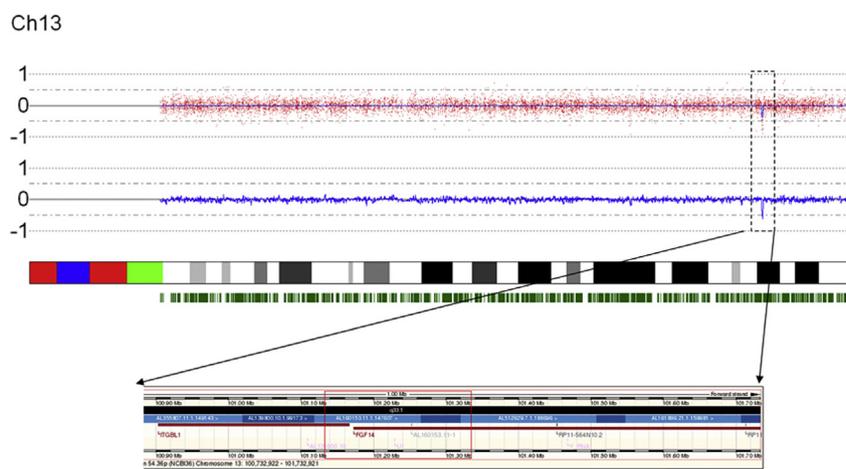


Fig. 2 – SNP-array results of the proband.

other exons. None of these studies, however, looked for deletions of the *FGF14* gene.

Brusse et al. hypothesized that the symptoms in SCA 27 are caused by loss of function of the *FGF14* protein, rather than protein aggregation, as is the case in other SCA's. This could explain the lack of significant progression of symptoms in SCA 27. Laezza et al.⁵ demonstrated that mutated *FGF14* reduces sodium channel subunit expression at the axon initial segment and alters neuronal excitability. Other genetic disorders of different organ specific sodium channels such as *SCN1A* in generalized epilepsy with fever-triggered seizures (GEFS+) [esupp 5], *SCNA5* in Brugada syndrome [esupp 6], and *SCN9A* in primary erythromalgia [esupp 7] are known to be fever-sensitive.

This current study supports previous findings that alterations in *FGF14* cause phenotypic variability with apparent complete penetrance with the prominent symptoms of nystagmus and ataxia. In addition, it supports suggestions of the role of *FGF14* in regulating cerebellar activity through *Nav1.2* and *1.6* α -subunits [esupp 8], the functions of which seem to be sensitive to fever.

Furthermore, it shows that SNP array analysis can help diagnose unexplained neurological disorders and broaden the phenotypic and genotypic spectrum in known syndromes, in this case SCA 27. Mutations in *FGF14* seem to be rare, but perhaps other episodic or cerebellar ataxia syndromes can be explained by alterations in *FGF14* or related genes.

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Competing interests

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejpn.2013.10.006>.

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