Neurogenetics (2009) 10:371–374
DOI 10.1007/s10048-009-0197-x

SHORT COMMUNICATION

SCA27 caused by a chromosome translocation: further delineation of the phenotype

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Received: 24 February 2009 / Accepted: 28 April 2009 / Published online: 27 May 2009

Abstract We report of a spinocerebellar ataxia (SCA)27 in a daughter and her mother whose karyotype is 46, XX t(5;13)(q31.2;q33.1). The translocation breakpoint is identical in both patients, disrupting the gene-encoding fibroblast growth factor 14 isoform b (*FGF14-1b*). Clinically, both show signs of SCA, although the daughter is the most affected with early onset cerebellar ataxia, microcephaly, and severe mental retardation. FGF14-1b is the predominant isoform in brain, where it interacts with the voltage gated Na channel. $Fgf14^{-/-}$ mice develop ataxia and paroxysmal dyskinesia and have cognitive deficits. One missense and one non-sense mutation in *FGF14* have previously been linked to SCA27. Truncation of one allele in our patients suggests that haploinsuffiency of *FGF14* can cause SCA27.

Keywords Cognitive impairment · Inherited translocation · *FGF14* · Microcephaly · SCA27

Introduction

We report of a spinocerebellar ataxia (SCA)27 in a daughter and her mother carrying a translocation between chromosomes 5 and 13, disrupting the gene encoding the fibroblast growth factor 14 isoform b (*FGF14-1b*) [1]. Two previous reports have described autosomal dominant SCA27 caused by *FGF14* point mutations [2–4]. Patients exhibit signs of cerebellar dysfunction, extrapyramidal tremors and dyskinesia, peripheral neuropathy, impairment of positional sensation, and academic underachievement.

Electronic supplementary material The online version of this article (doi:10.1007/s10048-009-0197-x) contains supplementary material, which is available to authorized users.

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Fig. 1 Picture of the proband at 5.5 years

Onset is usually in early adulthood with gait unsteadiness and upper limbs tremors.

Clinical report

The proband (Fig. 1) is a 5.5-year-old girl with psychomotor delay and microcephaly since birth. Signs of cerebellar dysfunction, noted as truncal unsteadiness in the first year of life, progressed to include gait ataxia, axial tremor with titubation of head and neck, action and intention tremor, and dysarthria (Electronic supplementary material E-Video 1). Nystagmus was absent. Her mouth was open with drooling. She occasionally displayed dyskinetic jerky movements in the neck and arms. Deep tendon reflexes were slightly increased, and there was suspicion of extensor plantar responses. Other features included a short neck, fifth fingers clinodactyly, and high arched feet. Testing with Wechsler Preschool and Primary Scale of Intelligence, VMI, Leiters test and parts of Bayleys Scale gave a mental age of about 2 years, which corresponds to severe mental retardation. Cerebral MRI, nerve conduction velocities, and electromyography were normal.

The mother, age 42, works as a cleaner. As a child, she was pharmacologically treated for seizures. She went to a special school for learning disabilities. On examination, she became unsteady while standing with her eyes closed (Electronic supplementary material E-Video 2). She was unable to keep her balance standing on one foot catching a ball. She managed to stand on a roller board for 3 s (reference value >11 s) with open eyes. Sensory modalities were normal. Deep tendon reflexes were slightly increased, whereas plantar reflexes were equivocal. She had high arched feet. EMG was normal. F-responses and nerve conduction velocities were reduced (lower limbs 44.3 m/s), suggesting mild degree of demyelination. EEG was normal. She did not consent to be examined with cerebral MRI. Testing with the Wechsler Abbreviated Scale of Intelligence and VMI gave an IQ of approximately 2 SD below average. The mother has healthy parents, which are not available for analysis. She has one 16-year-old son and three brothers; one has 1 daughter, one has two sons, and one does not have children. All these family members are healthy.

Results

The karyotype of the proband and her mother was defined by G-banding as 46, XX t(5;13)(q31.2;q33.1) (Fig. 2a). Array comparative genomic hybridization (44k oligo array, Agilent Technologies, Santa Clara, CA, USA) in the proband was normal. The translocation breakpoint was mapped by fluorescence in situ hybridization (FISH) on the patient and her mother, using genomic clones selected at the UCSC Genome Browser (NCBI Build 36.1; Electronic supplementary material E-Table 1). The breakpoints were located within probe G248P80273D7 on der(5) and between two partly

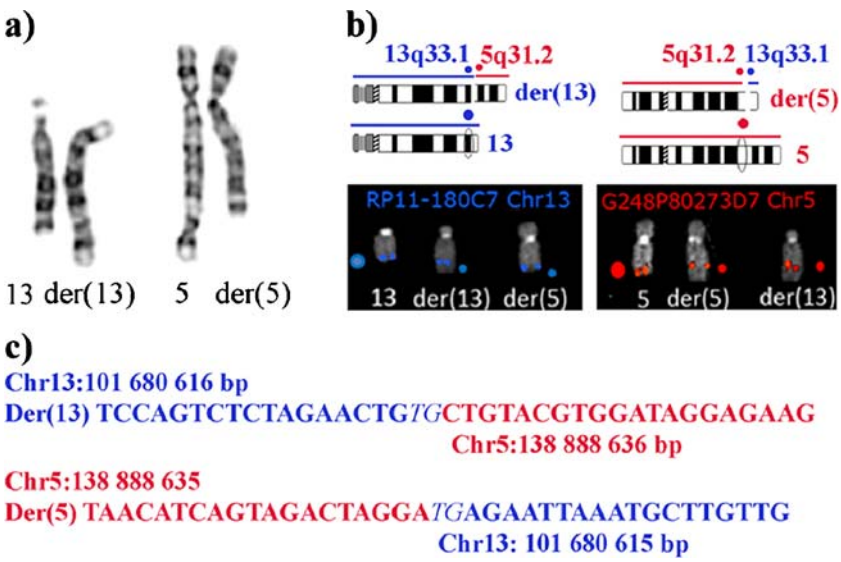

Fig. 2 Significant results from chromosome breakpoint analysis. **a** Detail of the proband's karyotype (only aberrant chromosome pairs are shown). **b** relevant FISH results in the proband. RP11-180C7, Cy5, (chr13:101,579,849–101,742,909 bp) overlaps the breakpoint on chr13. G248P80273D7, Cy3, (chr5:138,866,024–138,903,543 bp) identifies the breakpoint on chr5. **c** Sequence at the chromosome breakpoints. The di-nucleotide duplication from chr13 is in *italic*

overlapping fosmids, G248P89496F6 and G248P85958H1, on der(13) (Fig. 2b and Electronic supplementary material E-Table 1). Analysis of fibroblasts from the mother gave no indication of mosaicism for the t(5;13) chromosome. We designed a panel of PCR primers spanning the candidate region on der(5) and der(13) (Electronic supplementary material E-Table 2). Sequencing of the PCR products revealed that both breakpoints are identical in mother and daughter. On der(5), the fusion is between chr5:138888635 base pair (bp) and chr13:101680615 bp, and the der(13) fusion is between chr13:101680616 bp and chr5:138888636 bp. The breakpoint on der(13) was located between exon 1 and 2 of the gene encoding the isoform 1b of FGF14, disrupting this gene. At the breakpoint (Fig. 2c), a di-nucleotide duplication (chr13:10168015–101680616 bp) was detected, and no significant sequence similarity between chromosome 5 and 13 was found, suggesting that the translocation resulted from a non-homologous end-joining. All five exons of both alleles of *FGF14-1b* in mother and daughter were sequenced (Electronic supplementary material E-Table 3) and no mutations were detected.

Discussion

Both the proband and her mother demonstrated features of SCA. Increased tendon reflexes and possible extensor plantar responses indicated pyramidal tract involvement in both. The daughter was the most affected with early onset cerebellar ataxia, microcephaly, and severe mental retardation (Table 1).

SCA27 was described in a Dutch pedigree with a missense mutation in *FGF14* exon 4 [2, 4] and in a German patient carrying a frameshift mutation in *FGF14* exon 5 [3]. In our family, the identical translocation breakpoint in the mother and daughter disrupts the gene-encoding FGF14-1b on der(13). The only difference between the genes encoding FGF14-1b and FGF14-1a is an alternative exon 1 in the latter [1], which is unaffected by the translocation in our patients. Tremors were noted in the first two reports of SCA27, and in the Dutch family. This was an early sign of the disease, while ataxia became evident later. In our proband, tremor and ataxia were already evident at age 2. The mother exhibits milder dysfunctions without tremors, which may be attributed to phenotypic variation in SCA27 as the same genomic aberration was detected in both. FGF14-1b is the predominant isoform in brain, with cerebellum showing highest expression, followed by hippocampus, amygdala, cerebral cortex, striatum, and thalamus [5, 6]. In human and mouse, FGF14 interacts with the voltage-gated Na channel [7], and loss of FGF14 function has been shown to reduce excitability of hippocampal neurons. $Fgf14^{-/-}$ mice [7] develop ataxia and paroxysmal dyskinesia and have

Table 1 Comparison of clinical features in three SCA27 families

	Daughter (proband this report)	Mother (this report)	Previous patients (n=15; described in [2, 3])
Age at tremor onset (y)	<2.5	−	6–20
Age at ataxia onset (y)	<2.5	Not recorded	18–50
IQ/education	SMR	SS	PS n=7; SS n=4; SE n=3
Nystagmus	−	−	15
Tremors	+	−	13
Gait ataxia	+[a]	+[b]	12
Dysarthria	+	−	11
Writing disability	+	−	9
Dyskinesia	+	−	8
Titubation	+	−	7
Pes cavus	+	+	1[c]
Upper motor neuron involvement	+	+	Not recorded
Cerebellar atrophy (MRI)	−	Not examined	2/8 examined
Etiology	46,XX, t(5;13)(q31.2;q33.1)	46,XX, t(5;13)(q31.2;q33.1)	F145S or Asp163fsX12 mutation in *FGF14*

Summary of clinical features in the SCA27 families

n number, *SMR* severe mental retardation, *PS* primary school, *SE* secondary education, *SS* special school, *y* years, *(+)* feature present

[a] See Supplementary movie E-video 1

[b] Gait ataxia with eyes closed (see Supplementary movie E-video 2)

[c] Not assessed in the family described by Brusse et al. [2]

cognitive deficits [6, 8]. Truncation of one allele in a previous SCA27 patient [3] and in our patient suggest that haploinsuffiency of *FGF14* can cause SCA27.

Acknowledgments We thank the family for their collaboration and contribution to this study. We are indebted to Eli Ormerod who performed the G-banding. This work was founded by project support from the University of Oslo. DM and EF were supported by "Sigurd K. Thoresens Foundation", "University of Oslo Research Fund (UNIFOR)", and "Ullevål University Hospital Research Fund (VIRUUS)".

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