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Case Report Open Access

Infant Spinocerebellar Ataxia Type 27: Early Presentation Due To a 13q33.1 Microdeletion Involving the FGF14 Gene

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Abstract

Spinocerebellar ataxia type 27 (SCA27) is caused by mutations in FGF14 and is associated with developmental delays, tremors, and ataxia, which is typically adult onset and slowly progressing. We report here the first case of a de novo microdeletion of 13q33.1 involving only the FGF14 gene in a child presenting with symptoms of SCA27 includes mild developmental delays, abnormal gait, and tremors beginning in the first year of life. Our observations confirm the role of FGF14 in the development of SCA27 and document a partial deletion of FGF14 inducing SCA27 symptoms at an early age. This report highlights the importance of considering spinocerebellar ataxias even in young children with mild neurologic symptoms and emphasize the utility of array CGH analysis as a diagnostic tool and further elucidating the phenotypic spectrum that can be seen with SCA27.

Keywords: FGF14; SCA27; Spinocerebellar ataxia; 13q33; Microdeletion; Ataxia; Fibroblast growth factor; Chromosome 13

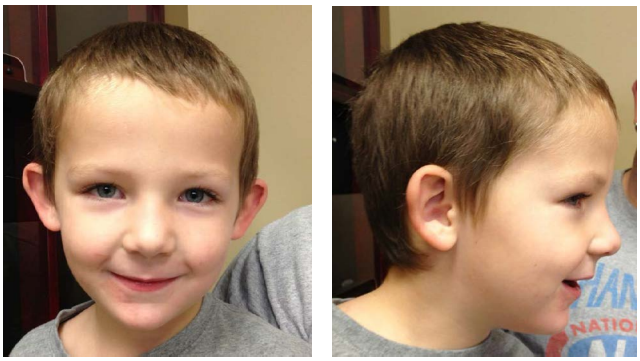
Introduction

Recognition of the natural history and phenotypic spectrum of a specific disorder is of extreme clinical importance and a difficult task unless a detailed description of multiple individuals is reviewed and available in published literature. Symptoms of SCA27 typically include general cerebellar dysfunction including gait disturbances, tremors, mental retardation and/or developmental delay, dysarthria, and gaze-evoked nystagmus. The age of onset is from childhood to young adulthood, with most individuals having a very slowly progressive adult onset of symptoms beginning with tremors [1-4].

We report here a 4 year old male with a de novo microdeletion of 13q33.1 involving the FGF14 gene who presented with symptoms in the first year of life. This case provides further information on the clinical variability of SCA27 and adds information on the natural history of SCA27 due to the unusual early presentation seen in this case. We review the currently available literature on FGF14 and SCA27 as well as discuss the clinical significance of the FGF14 gene in addition to the importance of utilizing array CGH as a diagnostic tool for SCA27.

Case Report

Our proband is a male patient born at 36 weeks gestation with a birth weight of 3.45 kg (75% percentile). The pregnancy was uncomplicated except for preterm labor of unknown etiology (Figure 1). The perinatal period was uncomplicated. Though his delays began at less than 1 year of age, he presented to our clinic at 4.5 years of age because of motor skill delays, speech delays, tremors, an awkward but not truly ataxic gait, stuttering, and occasional drooling. His medical history is significant for an admission to the hospital for "overactive airway disease" and **respiratory syncytial virus** (RSV) at four months of age. He has a history of a few staring episodes and headaches (at least one following a period of intense crying) but no confirmed seizures. He has had frequent ear infections and failed a behavioral audiogram. After placing myringotomy tubes he had marked improvement with speech. At 4 years and 7 months of age a developmental evaluation was performed utilizing the Kaufman Brief Intelligence Test and Bruininks-Oseretsky Test of Motor Proficiency. His verbal IQ score was 76 while the nonverbal score was 86, for a composite IQ score of 77 (below average) and age equivalent below 4 years of age. The Bruinicks-Oseretsky Test standard score was 44 (27th percentile). The patient knows his colors and shapes, but struggles to recognize letters and to count past 6. He attends a developmental preschool and receives speech, occupational, and physical therapies. Cranial nerve examination, muscle tone and strength, coordination, and deep tendon reflexes are all unremarkable. He is mildly dysmorphic, with mild acrocephaly, prominent cupped ears with ear lobe creases, epicanthal folds, a smooth philtrum with thin upper lip, and a broad forehead. The family history is unremarkable with the exception of migraines for his



Dysmorphic features include mild acrocephaly, prominent cupped ears with ear lobe creases, epicanthal folds, a smooth philtrum with thin upper lip, and a broad forehead.

Figure 1: Proband at 5 years and 2 months of age.

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mother. He has two full siblings and paternal half siblings all of whom are alive and well with no similar symptoms.

Evaluations have included a brain MRI, EEG, lactatic acid, and fragile X tricleotide repeat analysis which were all normal. 180K Agilent oligonucleotide array indicated an approximately 97kb microdeletion (arr [hg18] 13q33.1 (101171175-101268228)×1) involving a significant portion of the FGF14 gene (Figure 2). No other genes appear to be involved in this deletion and parental oligonucelotide arrays were performed confirming this is a de novo deletion. This is the smallest cytogenetic abnormality to be associated with SCA27.

Discussion

More than 20 different types of spinocerebellar ataxia (SCA) have been described in the literature with a prevalence of approximately 1 to 4 per 100,000 individuals [5-7]. Ataxia is the primary symptom shared among all SCAs. There are other symptoms which can be type specific, such as mental retardation, seizures, oculomotor involvement such as nystagmus and/or tremors which can develop over time [5,6]. The majority of spinal cerebellar ataxias (SCA) have been associated with trinucleotide repeats with the exception of 6 different types including type 27 [5]. SCA27 is a rare autosomal dominantly inherited SCA caused by mutations in FGF14 on chromosome 13.

FGF14 belongs to the fibroblast growth factor (FGF) family and is known to be expressed in both the developing and adult central nervous systems [8]. The phenotypic similarity between mice and reported human cases make it an excellent model for SCA27 [9,10]. The Fgf14-/- knockout mice were anatomically normal and fertile, but developed both a paroxysmal hyperkinetic movement and ataxia as well as reduced dopamine antagonist responses [9]. This study further demonstrated that Fgfr14 is widely expressed in the central nervous system but does not appear to be critical for structural brain formations [9]. In addition, FGF14 has been found to interact with MAP kinase scaffold protein interacting protein 2 and may play a role in vesicle trafficking in axons of the central nervous system [9].

Only 6 distinct families, including 1 family with at least 14 affected individuals, have been reported in the literature with SCA27 as the result of confirmed abnormalities in FGF14 [1-4,11-13]. Most of these previously reported individuals have mutations in FGF14 and typically present with general cerebellar dysfunction including gait disturbances, tremors, mental retardation and/or developmental delay, dysarthria, and gaze-evoked nystagmus. The age of onset is from childhood to young adulthood, with most individuals having a very slowly progressive adult onset of symptoms beginning with tremors. Multiple individuals reported an increase in symptoms during times of emotional stress and/or physical exercise. These individuals also report a tendency for outbursts, depression, aggressive behaviors, and memory loss. [1-4]. In two families the etiology is determined to be a translocation disrupting the FGF14 gene. The probands in these families present with symptoms at less than 1 year of age [4,12]. One male child presents with episodic involuntary movements including ataxia and tremors. He is found to have a de novo 13:21 translocation which disrupts the FGF14 gene [12]. The other, a female, presents with microcephaly, developmental delays, gait ataxia, and tremors. Her mother, also affected, has significantly milder features including seizures as a child, mild learning difficulties, and ataxia (only while her eyes are closed). These two individuals are found to have a 5:13 translocation also disrupting the FGF14 gene [4]. The first reported case involving only a deletion of 13q33 was in a young boy with mild ataxia and abnormal eye movements whose symptoms worsen during times of a fever. This individual, as well as his mother who also has an abnormal gait and abnormal eye movements, and his maternal grandmother who has postural tremor all have a 202 kb deletion involving the FGF14 gene as of the submission of this article, the publication is still in print and unavailable for a full review [13].

The mechanism by which FGF14 causes the observed phenotype is not clearly understood. Based on the aforementioned knock out mouse model, a loss of function etiology is possible. However, a separate mouse model based on the specific missense mutation identified in the largest known family with SCA27 demonstrated that the abnormal Fgf14 interferes with interaction between the wild type Fgf14 and the neuronal sodium channel. This then results in reducing the neuronal excitability and is likely the explanation for the observed phenotype induced by a possible dominant negative effect [10].

It will be critical to continue to assess affected families to fully understand the implications of FGF14 in human disease and particularly how FGF14 affects dopamine responses and neuronal excitability changes. The mechanism by which FGF14 disrupts these aspects of signaling/trafficking pathway within the brain is of particular interest since individuals; including our patient seem to have worsening symptoms in times of emotional stress. This may lead to more targeted treatments for patients with SCA27 and will be an important area of

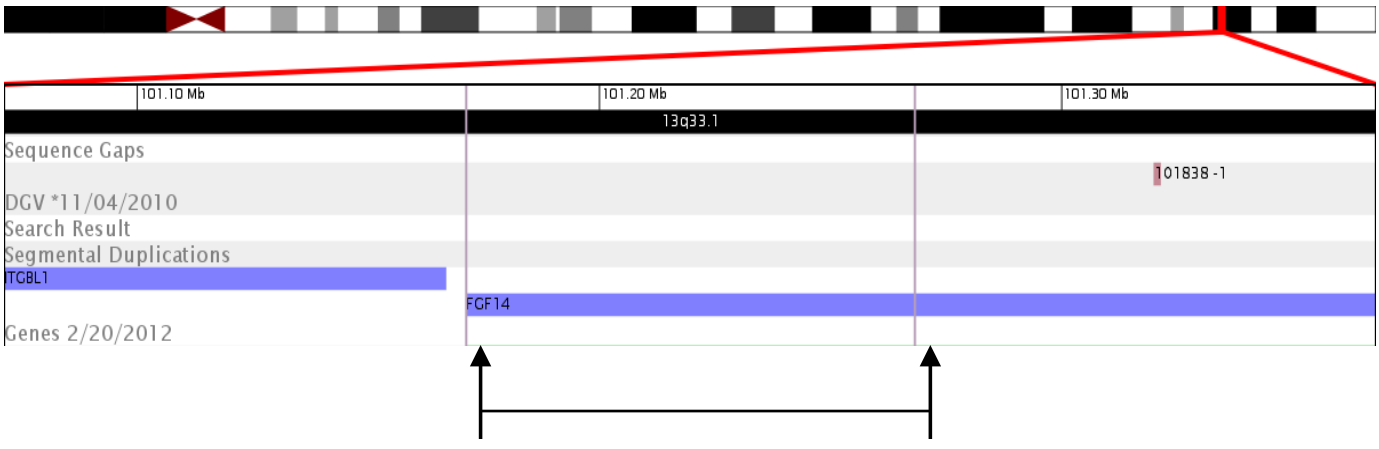

Figure 2: Ideogram of the 13q33.1 deletion (arr [hg18] 13q33.1 (101171175-101268228)×1) identified in our patient which appears to only encompass a portion of the FGF14 gene.

further research. It is clearly possible that different abnormalities within the FGF14 gene may result in varied phenotypes due to a difference in the molecular interactions of FGF14 and the neuronal trafficking pathways. In reviewing both the Database of Genomic Variants and DECHIPER, we were unable to locate copy number variants similar to the one observed in our patient or the previously reported patient discussed here [13-18]. Larger deletions involving 13q33 have been reported in over 20 different primary literature publications and as with other large chromosome abnormalities are known to be associated with an increased risk for intellectual disabilities and/or structural birth defects. The cases reviewed here allow for a clearer delineation of the phenotypic spectrum for individuals with SCA27 due to point mutations, translocations, or small deletions involving only the FGF14 gene.

Conclusion

Because many SCAs are adult onset and progressive, this group of disorders can be overlooked in cases of a child presenting with isolated unexplained tremors or ataxia. Our case is the first reported with a deletion of the FGF14 gene further confirming the role of FGF14 in the development of SCA27 and demonstrates a deletion of even a portion of FGF14 is pathogenic. Though reports are limited, disruptions/partial deletions of the gene may have the potential for a younger age of onset while certain missense mutations may lead to later onset of symptoms. Finally it is important to highlight the importance of considering array CGH in addition to molecular testing as a diagnostic tool for children and infants without striking dysmorphology and only mild gait anomalies or tremors to avoid delaying diagnosis and more thoroughly define the phenotypic spectrum which can be seen with SCA27.

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