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Xq11.1-11.2 deletion involving *ARHGEF9* in a girl with autism spectrum disorder

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ABSTRACT

We report an 8-year-old female with autism spectrum disorder (ASD), intellectual disability and speech delay who was found to carry a de novo 82 kb deletion of chromosome Xq11.1-11.2 involving the *ARHGEF9* gene on chromosomal microarray. So far, 11 patients with point mutations, disruptions due to chromosomal rearrangements and deletions involving *ARHGEF9* have been reported in the literature. *ARHGEF9*-related disorders comprise a wide phenotypic spectrum, including behavior disorders, autism spectrum disorder, intellectual disability, hyperekplexia and infantile epileptic encephalopathy. *ARHGEF9* encodes for collybistin which plays an important role in post synaptic clustering of glycine and inhibitory gamma-aminobutyric acid receptors along with its scaffolding partner, gephyrin. The reduction of inhibitory receptor clusters in brain has been proposed as a plausible underlying pathophysiological mechanism. With this report, we provide further evidence for the role of *ARHGEF9* in neurocognitive function, its implication in ASD, and review the clinical features of previously published individuals with *ARHGEF9*-related intellectual disability.

1. Introduction

Autism spectrum disorder (ASD) is an umbrella term for a group of neurodevelopmental disorders defined by the recently revised diagnostic criteria that include deficits in social communication and social interaction and restricted, repetitive behaviors (American Psychiatric Association, 2013). The last estimated prevalence rate for ASD was 14.7 per 1000 (one in 68) U.S. children aged 8 years (Investigators and CDC, 2014). The prevalence estimate is rapidly rising with a 29% increase over a two-year period and remains more common in males than females. About 31% of children with ASD are also diagnosed with intellectual disability. ASD is a genetically heterogeneous disorder with variation ranging from simple copy number variants (CNV), to mutations in genes involved in complex synaptic and neurodevelopmental pathways. CNVs represent relatively large deletions and duplications of genomic DNA seen in approximately 5–10% of patients with ASD (Devlin and Scherer, 2012). About 5% of ASD cases may have rare inherited loss-of-function autosomal and X-linked mutations (Stein et al., 2013).

We report an 8-year-old girl with autism spectrum disorder and Xq11.1-11.2 deletion involving the *ARHGEF9* gene. Point mutations, disruptions, and deletions of *ARHGEF9* have been previously reported and are associated with a broad phenotypic spectrum of seizures, hyperekplexia, intellectual disability, and more recently, ASD.

1.1. Clinical report

Our proposita is an 8-year-old female born to a non-consanguineous couple of Mexican ancestry. She was born at term via spontaneous vaginal delivery from an uncomplicated pregnancy. Her birth weight was 3400 gm (50th percentile for age and gender) and she had an uneventful newborn period. She walked at 16 months and spoke her first words at 2 years of age. Her behavior issues were first noticed at 3 years of age, and she was

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eventually diagnosed with ADHD at 5 years of age as per Conners' ADHD Rating Scale (Conners et al., 1998). At the age of 6 years, the patient was diagnosed with autism spectrum disorder by a developmental specialist based on the GARS-2 (Gilliam Autism Rating Scale-2 (Gilliam, 2006)). She was found to have multiple sensory sensitivities based upon the Short Sensory Profile (Dunn, 1999). She demonstrated a lack of social interaction and mild intellectual disability. The patient was evaluated at our center at the age of 6 years due to global developmental delay and most significantly, severe speech impairment. Her vocabulary was limited to about 20 words and she was unable to combine words together. She would point to communicate and was reported to be making some progress with the assistance of speech therapy. She was noted to have a poor eye contact and demonstrated hand flapping when excited. She showed poor comprehension of verbal instructions, would wander away in public places, was shy around new people, and would throw occasional temper tantrums. There was no history of seizures or hyperekplexia, and no craniofacial dysmorphism was noted on physical exam. No other medical issues were reported and the family history was noncontributory. We were unable to perform a formal IQ test.

1.2. Genetic testing

Conventional chromosomal analysis revealed a normal female karyotype, 46, XX in cultured lymphocytes from peripheral blood, and fragile X testing did not show any abnormalities. Copy number-SNP-array analysis using the Affymetrix CytoScan HD microarray platform revealed an 82 kb deletion of Xq11.1-Xq11.2 (chrX:62,970,571–63,052,696/hg19). This deletion includes the first exon and the 5′ end of each of three isoforms of the gene *ARHGEF9* (RefSeq: NM_001173479.1, NM_001173480.1 and NM_015185.2) as well as the micro-inhibitory RNA 1468 (Fig. 1). The deletion was shown to be de novo as parental microarray testing did not reveal any copy number variants. Bi-directional sequencing of the gene *ARHGEF9* was done for all coding exons and intron-exon boundaries and no variants were detected.

X-inactivation studies using the human androgen-receptor (HUMARA) gene assay on patient's peripheral blood did not indicate the presence of significant skewed X-inactivation. Random-X-chromosome inactivation ratio was less than 80:20 (data not shown).

2. Discussion

We describe a patient with de novo 82 kb, Xp11.1–11.2 deletion involving the *ARHGEF9* gene, thought to be responsible for the patient's clinical features of autism spectrum disorder and global developmental delay. This microdeletion includes two genes, *MIR1468* at the 5 prime end and exon 1 of the *ARHGEF9* gene. *MIR1468* is a novel miRNA (micro-RNA) gene, miRNAs are short noncoding RNAs involved in post translational regulation of gene expression. The function of *MIR1468* is not well understood, although a recent report suggested an association with Alzheimer's disease (Satoh et al., 2015). *ARHGEF9* (OMIM 300429) encodes for collybistin, a brain-specific guanine nucleotide exchange factor (GEF) that acts as an adaptor protein for the recruitment of gephyrin. Gephyrin and collybistin are known to work in a close-knit pathway for receptor recruitment in GABAnergic and glycinergic synapses. Several previously reported studies have elucidated the role of this pathway and its involvement in cognitive function (Harvey et al., 2004; Papadopoulos et al., 2007;

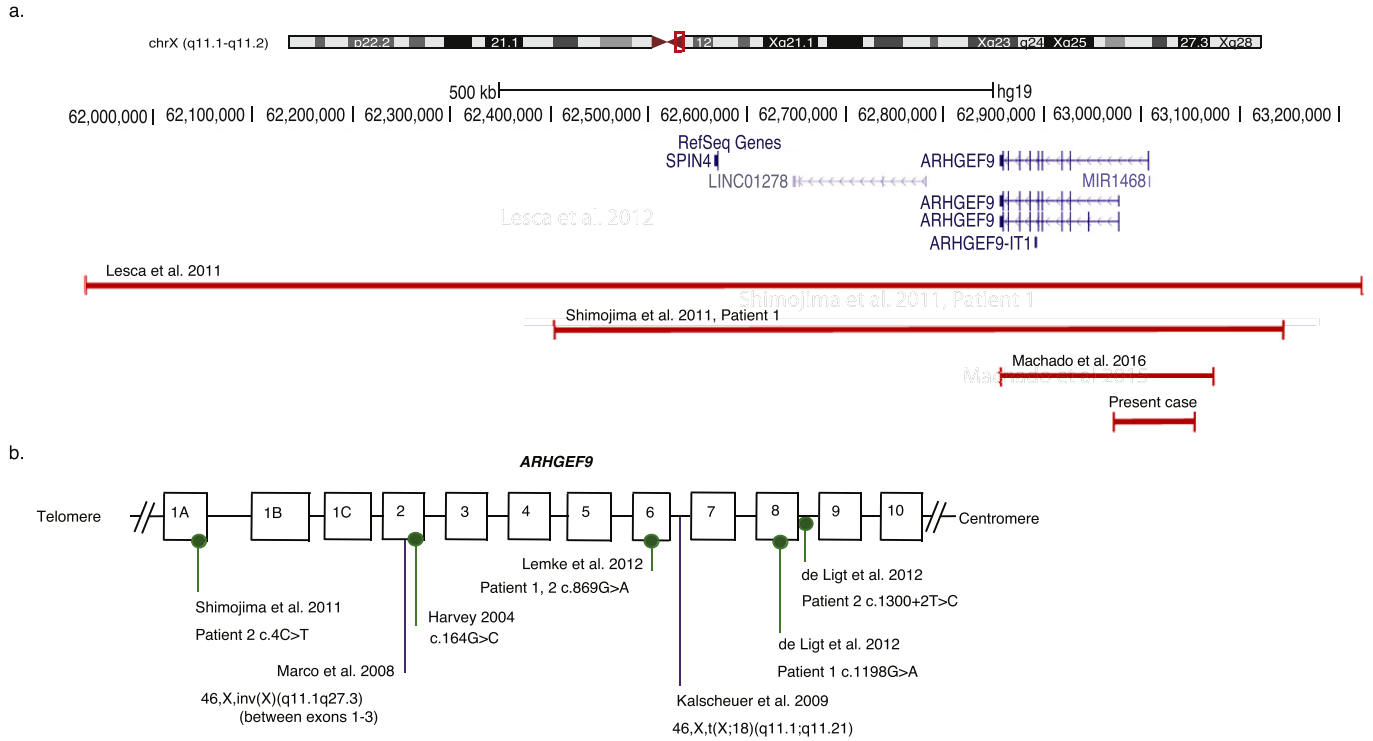

Fig. 1. . a. Genomic map of Chromosome Xq11.1-11.2 showing microdeletions in the patients with *ARHGEF9*-related intellectual disability. The overlapping chromosomal deletions in 3 previously reported patients and the current case are depicted by red bars. b. Mutations and chromosomal rearrangements leading to gene disruption in the patients with *ARHGEF9*-related intellectual disability. Green lines represent the reported loss of function variants in *ARHGEF9* and purple lines represent the chromosomal rearrangements leading. The map was plotted and downloaded from UCSC Genome Browser. NCBI genome remapping service was used to obtain GRCh37(hg19) assembly for all reported cases. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)