A Novel De Novo Microdeletion Spanning the SYNGAP1 Gene on the Short Arm of Chromosome 6 Associated With Mental Retardation

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Received 28 March 2010; Accepted 19 May 2010

TO THE EDITOR:

Point mutations in the SYNGAP1 gene were described recently as a relatively frequent cause of mental retardation, present in about 3% of nonsyndromic individuals with mental retardation [Hamdan et al., 2009]. We ascertained a carrier of a deletion encompassing SYNGAP1 among 300 patients with mental retardation studied by 1 Mb array-comparative genomic hybridization (a-CGH). Data on the patient were deposited in the DECIPHER database (Database of Chromosomal Imbalances and Phenotype in Humans using Ensembl Resources, http://www.sanger.ac.uk/PostGenomics/decipher). Informed consent for publishing results and photos was obtained from the patient’s legal guardians.

The boy (DECIPHER USP002265) was the only child of non-consanguineous healthy parents, and no other cases of mental impairment were known among first- or second-degree relatives. He was born at term by caesarean; his birth weight was 3,315 g (between 25th and 50th centiles) and length 47 cm (<3rd centile). Motor development was considered slightly delayed: he sat up without support at 6 1/2 months, and walked at age 16 months. Sphincter control was present at age 5 1/2 years. At examination at age 6 years and 9 months, he appeared to have moderate mental retardation; he was hyperactive with attention deficit. He had severe speech impairment, and was able to articulate only a few isolated words. His height was 115 cm (<3rd centile), and head circumference 53 cm (between 2nd and 50th centiles); he had a long face, a high forehead, and hypoplastic auricles; a slightly depressed sternum; retractile testes; general joint hyperextensibility/dislocation; single palmar creases; flat feet. Basically, the boy presented a clinical picture of mental retardation associated with severe speech impairment and apparent connective tissue abnormalities. Brain computerized tomography showed no abnormalities. Audiometric evaluation (BERA) did not show hearing impairment. He had a normal G-banded karyotype and a negative fragile-X molecular test.

DNA was extracted from peripheral blood leukocytes. A heterozygous deletion at 6p21 was first detected by a-CGH, using a 1 Mb platform, as described previously [Rosenberg et al., 2006]. To further map the deletion, we performed oligonucleotide a-CGH using a 4x44K whole-genome platform [NGRL Wessex Constitutional Array, design 017457 (http://www.ngrl.org.uk/Wessex/arraycgh.htm), Agilent Technologies, Santa Clara, CA], hybridized according to the manufacturer’s protocols. Oligonucleotides mapped to a 812.77 kb segment on 6p21.31–21.32 (chr6:33,273,955–34,086,729; 4,086,729; Human GRCh37 Assembly, hg19) were found to be deleted; the distal breakpoint was mapped to a 14.3 kb interval (chr6:33,259,651–33,273,955); the proximal breakpoint was located on a ~123 kb segment (chr6:34,086,729–34,209,880) (Fig. 1).

Grant sponsor: FAPESP; Grant numbers: CEPID—Center for the Study of the Human Genome, CEGH 98/14254-2 and 2009/00898-1; Grant sponsor: CNPq.

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Published online 3 August 2010 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/ajmg.a.33554
Scattered copy number variants within this genomic region are documented in the Database of Genomic Variants (http://projects.tcag.ca/variation), but they cover a minor part of the entire deleted segment described here. Fluorescent in situ hybridization on peripheral blood metaphases using a BAC clone mapped to the deleted segment (RP3-468B3) demonstrated that the imbalance was not present in either parent of the propositus, indicating its de novo origin (data not shown).

This novel deletion at 6p21.3 encompasses up to 18 known genes, one predicted gene (C6orf125), and one provisional pseudogene (LYPLA2P1) (Human GRCh37 Assembly, hg19). Twelve of the known genes are shown to be expressed in brain (TAPBP, ZBTB22, DAXX, PHF1, CUTA, SYNGAP1, ZBTB9, BAK1, ITPR3, IP6K3, LEMD2, and GRM4), and, excepting for SYNGAP1 and GRM4, also expressed in connective tissue. These genes are, therefore, functional candidates contributing to the impairment of the central nervous system and/or connective tissue in our patient. However, data that allow a clinical evaluation of the presumptive haploinsufficiency effect are available for just a few of these deleted genes. Among them is the DAXX gene, encoding a multifunctional protein (death-associated protein 6) that functions in the nucleus as a transcription regulator. One of its interacting proteins in the nucleus is ATRX [Tang et al., 2004], an ATP-dependent chromatin remodeling protein that is mutated in X-linked mental retardation (OMIM 301040; OMIM 309580). DAXX mutations are not known in humans. Part of GRM4 is mapped to the proximal breakpoint interval, and this gene might be entirely deleted or otherwise disrupted. It codes for the metabotropic glutamate receptor 4 (mGluR4), a G-protein-coupled receptor that mediates inhibition of neurotransmitter release and is highly expressed in the cerebellum. In its absence, mice showed impaired spatial learning and memory [Gerlai et al., 1998], one study finding learning deficits only in the homozygous but not in the heterozygous mGluR4 knockout mice [Pekhlebtsi et al., 1996].

SYNGAP1 (synaptic RAS-GTPase activating protein 1) is a component of the NMDAR (N-methyl-D-aspartate receptor) complex and blocks the insertion of AMPAR ( α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) at the postsynaptic membrane by inhibiting the RAS-ERK pathway [Rumbaugh et al., 2006]; the phenotype of mice heterozygous for a null Syngap1 allele documents the role of the protein in synaptic plasticity and cognition [Komiyama et al., 2002]. Under the hypothesis that autosomal genes involved in synaptic plasticity are a common cause of mental retardation, Hamdan et al. [2009] screened 94 patients with nonsyndromic mental retardation for SYNGAP1 mutations by direct sequencing, and found two transversions and one intragenic deletion in heterozygosis in three patients. These de novo mutations resulted in premature stop codons, and the produced proteins would lack important functional domains; in addition, mRNA nonsense-mediated decay remained a possibility. The carriers had moderate to severe mental retardation and severe language impairment, two of them presenting generalized forms of mild epilepsy. Therefore, SYNGAP1 haploinsufficiency might be the main cause of mental retardation and severe speech impairment associated with the novel 6p deletion described here.

ACKNOWLEDGMENTS

This work was supported by FAPESP (CEPID—Center for the Study of the Human Genome, CEGH 98/14254-2, and 2009/00898-1) and CNPq.
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