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Duplication of *OCRL* and Adjacent Genes Associated with Autism but not Lowe Syndrome

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Abstract

Disturbances in the form of microduplications and microdeletions have been found throughout the genome and have been associated with autism, intellectual disability, and recognizable malformation syndromes. In our study of 187 probands with autism, we have identified a duplication in Xq25 including full gene duplication of *OCRL* and six flanking genes. Activity of the enzyme gene product in fibroblasts was elevated to over twice the level in control fibroblasts. The boy had no somatic or neurological findings reminiscent of Lowe syndrome.

Keywords

X chromosome; autism; microduplication; *OCRL*; Lowe syndrome

INTRODUCTION

Whole gene duplications are found as disease associated alterations and as innocent variations within the genome. In some cases, disease associated duplications may produce phenotypes identical or similar to those caused by point mutations or deletions. Such is the case for duplications of *PLP1*, the gene responsible for Pelizaeus-Merzbacher disease. Other disease associated duplications produce phenotypes very different from those caused by point mutations or deletions. Deletions or loss-of-function mutations of *MECP2* in females cause Rett syndrome while duplications in females are relatively benign, exemplifying a different phenotype with duplication, although these duplications cause a severe neurological disability in males.

Within the South Carolina Autism Project, array-based comparative genomic hybridization analysis identified one proband with a copy number gain of *OCRL* and six flanking genes. The somatic, neurologic, cognitive, and behavioral phenotype of this boy is in no aspect reminiscent of Lowe syndrome caused by loss-of-function mutations of the gene.

CLINICAL REPORT

CMS 18509, a boy, is the only child of healthy white parents (Fig. 1). The pregnancy was associated with gestational diabetes managed by diet. Rho-Gam was administered at 7

months gestation. Delivery was at 38.5 weeks, the birth weight was 3.3 kg, and the newborn period was uneventful.

At age 10 months he had a febrile seizure and 2–3 months later developed complex partial seizures which were controlled with anticonvulsives and brain surgery (left frontotemporal resection at age 5 years).

He walked at 12 months and developed age-appropriate speech, but both motor and language development plateaued at age 18–20 months and then began to regress. His fine motor skills lagged behind, social skills also lagged, and play preference was with younger children. He exhibited echolalia, avoided eye contact, seemed to have very sensitive hearing, and developed routines in his activities. He also seemed to have good memory, spelling skills, and mechanical skills.

At age 6 9/12 years, he had a height of 112 cm (5th centile) and head circumference of 51.3 cm (40th centile). His facies appeared expressionless with widely opened eyes and Cupid's bow upper lip. The occiput was flattened. Deep tendon reflexes were more brisk at the knees than elsewhere.

At age 16 7/12 years, he had height of 164 cm (5–10th centile) and head circumference of 56.4 cm (50–75th centile). He had good vision and hearing and no cataracts were present. No seizures had occurred in the past three years. He was schooled in a self-contained classroom where he read on a second grade level.

Autism and intellectual disability was based on CARS, ADI-R, PL-ADOS, Vineland Adaptive Behavior Scales, and Stanford-Binet Intelligence Scale: Fourth Edition. The IQ was 60 at age 17 years. Chromosome analysis, plasma amino acids, urine metabolic screen, urine amino acids, urine organic acids, *FMRI*, *AFF2*, and serum adenylosuccinate lyase activity were normal. Platelet serotonin was elevated. Brain MRI showed no structural abnormality, EEG showed epileptic discharges localized to the left fronto-orbital area.

The patient is a proband in the South Carolina Autism Project: A Search for Causes, which was prospectively reviewed and approved by the Self Regional Healthcare Institutional Review Board [Schroer et al. 1998].

MATERIALS AND METHODS

Fluorescence in situ Hybridization Analysis

Fluorescence in situ hybridization (FISH) analysis in lymphoblast cell line from the patient using a probe specific for *OCRL* gene (RP11-137A15) and the RP11-137H15 clone, a specific probe for chromosome X. DNA for home-brew FISH probes was extracted and directly labeled according to the manufacturers' instructions (Abbott Molecular, Abbott Park, IL).

Exon-Focused Microarray Analysis

DNA samples from the South Carolina Autism Project were tested for deletions or duplications using an exon-focused microarray. This was a custom Agilent 44K X 4 platform for array comparative genomic hybridization (CGH) containing probes across exonic and intronic regions of 326 candidate genes that are highly expressed in the brain, involved in neuronal/synaptic function, and/or were implicated in intellectual disability. The analysis was performed using genomic DNA isolated from lymphoblast cell line for the patient, his mother, and two healthy maternal uncles.

Deletion Mapping by High-Resolution Oligonucleotide Array

Further characterization of the deletions was performed utilizing the Agilent 244K Whole Human Genome CGH arrays (Agilent Technologies, Inc, CA, USA) containing 236,000 probes. The procedures for DNA digestion, labeling, hybridization, and data analysis were performed essentially according to the manufacturer's protocol (Agilent Technologies, Santa Clara, CA) as described previously [Ou et al. 2008].

RESULTS

The exon microarray for the patient showed a gain of all probes covering the *OCRL* gene (data not shown). This duplication was inherited from the mother and was not found in two healthy maternal uncles. Analysis with the Agilent 244 K array revealed that the duplication was approximately 615 kb in size extending from nucleotides 128,252,539-128,868,225 (UCSC Freeze March 2006) on Xq25 (Fig. 3). The duplication includes the following Ref. Seq. genes from centromere to telomere: *SMARCA1*, *OCRL*, *APLN*, *XPNPEP2*, *SASH3*, *ZDHHC9*, and *UTPI4A*. Maternal X-inactivation was within the range that qualifies as random (75:25). FISH evaluation of lymphoblast cell line from the patient showed 2 strong *OCRL* signals (Fig. 3), consistent with a duplication of this chromosomal region.

In order to test the functional significance of this duplication, *OCRL*1 phosphatase activity on skin fibroblasts was obtained and showed activity of 13.9 nmol/min/mg protein as compared to 4.3 and 4.7 in two normal controls (normal range 2–9).

DISCUSSION

Duplication of *OCRL* and six adjacent genes is in this case associated with nonsyndromic autism with intellectual disability. Lowe syndrome caused by loss-of-function mutations in *OCRL* is the best defined genetic disorder associated with this genetic interval (OMIM 300535, 309000). With the exception of short stature, the phenotype does not have any of the key manifestations of Lowe syndrome [Stevenson et al. 2012]. Specifically, cataracts, renal tubular dysfunction, progressive renal disease, hypotonia, and areflexia were not present. Although female heterozygotes with Lowe syndrome can have mild features of the disorder, the mother of this patient had random X-inactivation in lymphoblasts and had no clinical abnormalities. She was a college graduate and taught in secondary school. Whether the autism should be attributed to the *OCRL* duplication or to duplication of the flanking genes cannot be determined. A variant in the gene for X-prolyl aminopeptidase 2 (*XPNPEP2*) is reported to be associated with angioedema induced by angiotensin I-converting enzyme inhibitors (OMIM 300145) [Duan et al. 2005]. Mutations in *ZDHHC9*, which encodes a palmitoyltransferase are reported to cause X-linked intellectual disability (OMIM 300646) [Raymond et al. 2007]. The other four genes in the duplicated interval do not have known phenotypic or disease variations (*SMARCA1*, OMIM 300012; *APLN*, OMIM 300297; *SASH3*, OMIM unassigned; and *UTPI4A*, OMIM 300508).

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Fig. 1.
Partial pedigree of CMS 18509. III-1 and his mother, II-2, had the duplication. Normal males, II-3 and II-4, were negative for the duplication.

Fig. 2.
Patient CMS 18509 at age 6 9/12 years, showing normal craniofacial proportion and Cupid's bow upper lip.

A

B

Fig. 3.

A) An output profile of the Agilent 244 K array hybridization showing the 615 kb duplicated region on the long arm of chromosome X in the patient. B) FISH on lymphoblast cell line using the RP11-137A15 clone as a probe specific for the *OCRL* gene (red). The green signal is a specific X chromosome probe (RP11-137H15) used as a control. The patient has two red signals consistent with duplication at Xq25.