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ORIGINAL ARTICLE

A homozygous loss-of-function mutation in inositol monophosphatase 1 (*IMPA1*) causes severe intellectual disability

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The genetic basis of intellectual disability (ID) is extremely heterogeneous and relatively little is known about the role of autosomal recessive traits. In a field study performed in a highly inbred area of Northeastern Brazil, we identified and investigated a large consanguineous family with nine adult members affected by severe ID associated with disruptive behavior. The Genome-Wide Human SNP Array 6.0 microarray was used to determine regions of homozygosity by descent from three affected and one normal family member. Whole-exome sequencing (WES) was performed in one affected patient using the Nextera Rapid-Capture Exome kit and Illumina HiSeq2500 system to identify the causative mutation. Potentially deleterious variants detected in regions of homozygosity by descent and not present in either 59 723 unrelated individuals from the Exome Aggregation Consortium (Browser) or 1484 Brazilians were subject to further scrutiny and segregation analysis by Sanger sequencing. Homozygosity-by-descent analysis disclosed a 20.7-Mb candidate region at 8q12.3-q21.2 (lod score: 3.11). WES identified a homozygous deleterious variant in inositol monophosphatase 1 (*IMPA1*) (NM_005536), consisting of a 5-bp duplication (c.489_493dupGGGCT; chr8: 82,583,247; GRCh37/hg19) leading to a frameshift and a premature stop codon (p.Ser165Trpfs*10) that cosegregated with the disease in 26 genotyped family members. The *IMPA1* gene product is responsible for the final step of biotransformation of inositol triphosphate and diacylglycerol, two second messengers. Despite its many physiological functions, no clinical phenotype has been assigned to this gene dysfunction to date. Additionally, IMPA1 is the main target of lithium, a drug that is at the forefront of treatment for bipolar disorder.

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INTRODUCTION

Intellectual disability (ID) is a serious neurodevelopmental disorder that is characterized by an intelligence quotient (IQ) of 70 or below, and deficiency in at least two characteristics essential for adaptive functioning, such as communication, reading, writing and self-care. This condition can usually be diagnosed before the age of 18,[1] and its prevalence is between 1 and 3%.[2] Though it can be caused by environmental insults such as infection or teratogens, with a high proportion being the result of genetic abnormalities, close to 60% of cases of ID do not have a known etiology.[3,4]

Recently, exome enrichment and next-generation sequencing have been introduced as cost-effective and fast strategies for disease-gene identification. Using this modern technology, we identified a disease-causing mutation (c.489_493dupGGGCT) within the *IMPA1* gene in a large consanguineous Brazilian family in which nine affected individuals had severe ID and disruptive paranoid behavior.

Inositol monophosphatase 1 (IMPA1: EC 3.1.3.25) is the critical enzyme for the recovery of the inositol cycle, and it is key for both the *de novo* synthesis of inositol and the recycling of inositol polyphosphates generated upon receptor activation.[5] The inositol phosphate metabolism pathway is involved in normal physiological conditions, such as insulin and PI3K/Akt signaling, endocytosis, vesicle trafficking, exocytosis, cell migration, proliferation, apoptosis, neurotransmitter release, hormone secretion, histamine release in allergic responses and in maintaining the state of homeostasis for second messengers. Thus, dysfunctions of the inositol cycle have been implicated in a variety of human diseases, including developmental defects, cancer, diabetes and neurological diseases.[6] IMPA1 has attracted much interest in the genetic studies of neuropsychiatric diseases because in therapeutic concentrations, lithium, the main pharmacological treatment for bipolar disorder, it is an uncompetitive inhibitor of IMPA1.[7,8] Therefore, *myo*-inositol is thought to have an important role in the mechanism of bipolar disorder, and has been the focus of many studies.

Although animal models and *in vitro* analysis have contributed to the understanding of the pathophysiology of IMPA1 deficiency, no human disease has been attributed to a malfunction of this protein.

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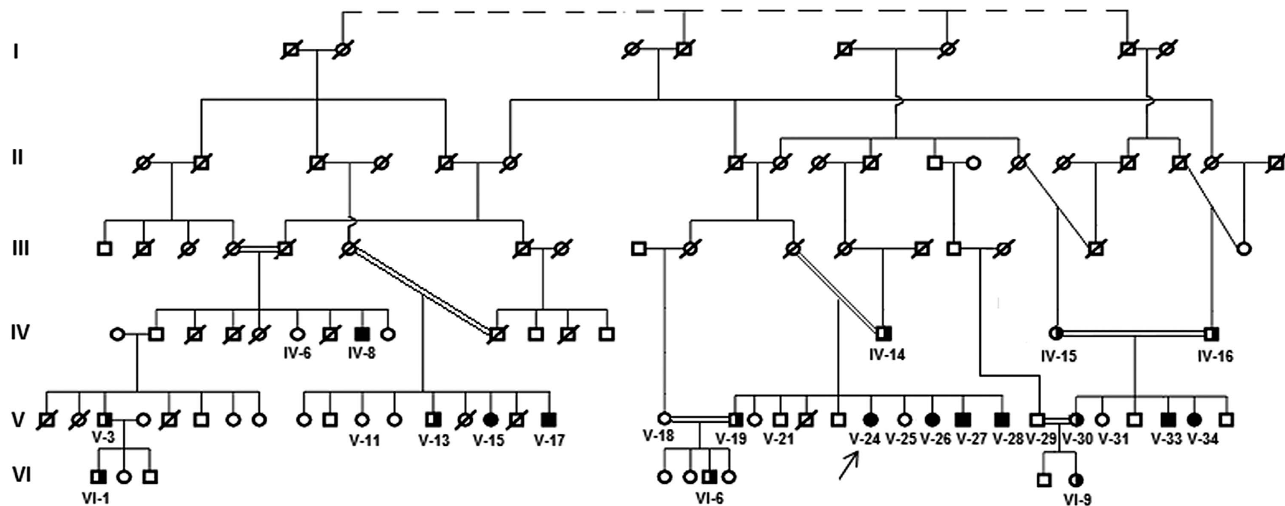

Figure 1. The six generation family pedigree with six consanguineous marriages. DNA was sampled from persons with a code, individuals with intellectual disability are represented by filled symbols and half-filled symbols indicate heterozygous individuals.

MATERIALS AND METHODS

Family ascertainment, genetic and clinical analysis

Affected individuals belonging to a small isolated community in an impoverished area of Northeastern Brazil were clinically evaluated in their hometown, as part of a larger project on prospection of neurologic disorders in highly inbred areas of the country. After obtaining written consent from the parents or legal guardians, blood and urine samples were collected from affected and healthy family members, and a pedigree was constructed on the basis of family information (Figure 1). The data sampling protocol and consent procedure were reviewed and approved by the National Committee for Ethics in Research (CONEP; http://conselho.saude.gov.br/web_comissoes/conep/index.html; Brazil).

Linkage study

Linkage study was performed using DNA samples from three affected individuals (V-24, V-26 and V-27) and one healthy member (V-21) of the same family. Genotyping was performed with the Genome-wide human SNP Array 6.0 (Affymetrix, Santa Clara, CA, USA) and genome-wide homozygosity analysis was performed by Homozygosity Mapper.[9] ALOHOMORA[10] software was used to convert the obtained data from the Affymetrix genotype platform into files for linkage analysis, and Pedcheck was used to identify Mendelian inconsistencies. Multipoint linkage analysis using MERLIN[11] software was performed assuming a fully penetrant autosomal recessive mode of inheritance with a disease allele frequency of 0.001.

Exome and Sanger sequencing

Whole-exome sequencing (WES) was performed on a DNA sample from one patient (V-24) using the Extended Nextera Rapid-Capture Exome kit (Illumina, San Diego, CA, USA) and sequenced using the Illumina HiSeq2500 system (Illumina). Exome reads were analyzed in a standard Bioinformatics pipeline using BWA for sequence alignment to the GRCh37 reference, Broad Institute GATK for genotyping, SnpEff for variant annotation and ExomeDepth for CNV detection.[12–16] Potentially deleterious variants detected in regions of homozygosity by descent, not present in 59 723 unrelated individuals from Exome Aggregation Consortium or in a Brazilian control population (1484 individuals) were selected for segregation analysis by Sanger sequencing. A 193-bp fragment harboring the candidate mutation was amplified using forward primer: 5′-CCATGAACAGGAATGCAAAA-3′ and reverse primer: 5′-GGGATACAAATGCCCTCTTC-3′. The reaction products were analyzed with an ABI 3730 DNA Analyzer (Applied Biosystems, Carlsbad, CA, USA), and the results were analyzed using Sequencher 5.0 (Gene Codes, Ann Arbor, MI).

Magnetic resonance imaging and proton magnetic resonance spectroscopy analysis

Brain magnetic resonance imaging and proton magnetic resonance spectroscopy analysis were performed on a 1.5-T whole-body Philips (Andover, MA, USA) scanner for one patient (V-17) and one healthy control.

Myo-inositol measurements in urine and plasma

To determine the total amount of myo-inositol, 100 µl of plasma or urine was incubated with alkaline phosphatase in 0.2 M Tris-HCl at pH 8.6 for 15 min at 37 °C in a total volume of 200 µl. Twenty-five microliters of 2 µM persitol solution (internal standard) was added and mixed. For determination of free *myo*-inositol, the alkaline phosphatase step was omitted. One milliliter of acetonitrile was added while vortexing, and the precipitate was removed through a 10-min centrifugation at 14,000*g* at 4 °C. The supernatant was evaporated to dryness under a nitrogen stream, and 150 µl of Tri-Sil TBT (TMSI:BSA:TMCS) reagent was added and incubated at 100 °C for 30 min. Three milliliters of hexane and 900 µl of 0.1 M HCl were added and thoroughly mixed. The hexane layer was evaporated to dryness under a nitrogen stream, and 40 µl of BSTFA+1%TMCS was added and incubated at 60 °C for 60 min. Sialylated sugar derivatives were separated on an Agilent 6890N GC with an FID detector using a CP-Sil 5 CB column. The concentration of inositol phosphates was estimated by subtracting free inositol from total inositol.

RESULTS

Clinical features

We evaluated nine individuals (five males; ages 38–59 years) who are descended from four closely related first-cousin couples. In all individuals, moderate to severe ID was detected. We further note that none of the subjects attended school, and all individuals either require close supervision or are dependent on external help for daily activities. They do not know how to manage money and are unable to name colors. Disruptive behaviors, sometimes aggressive and paranoid, were present in six of the nine affected individuals. A deceased sibling of patient IV-8, with a very similar phenotype, was kept locked in a room of his house for many years because of a history of inappropriate sexual behavior. Another seemingly affected younger sibling of patient IV-8 did not allow us to approach because of her very disruptive behavior. For that reason, we were unable to construct her genotype.

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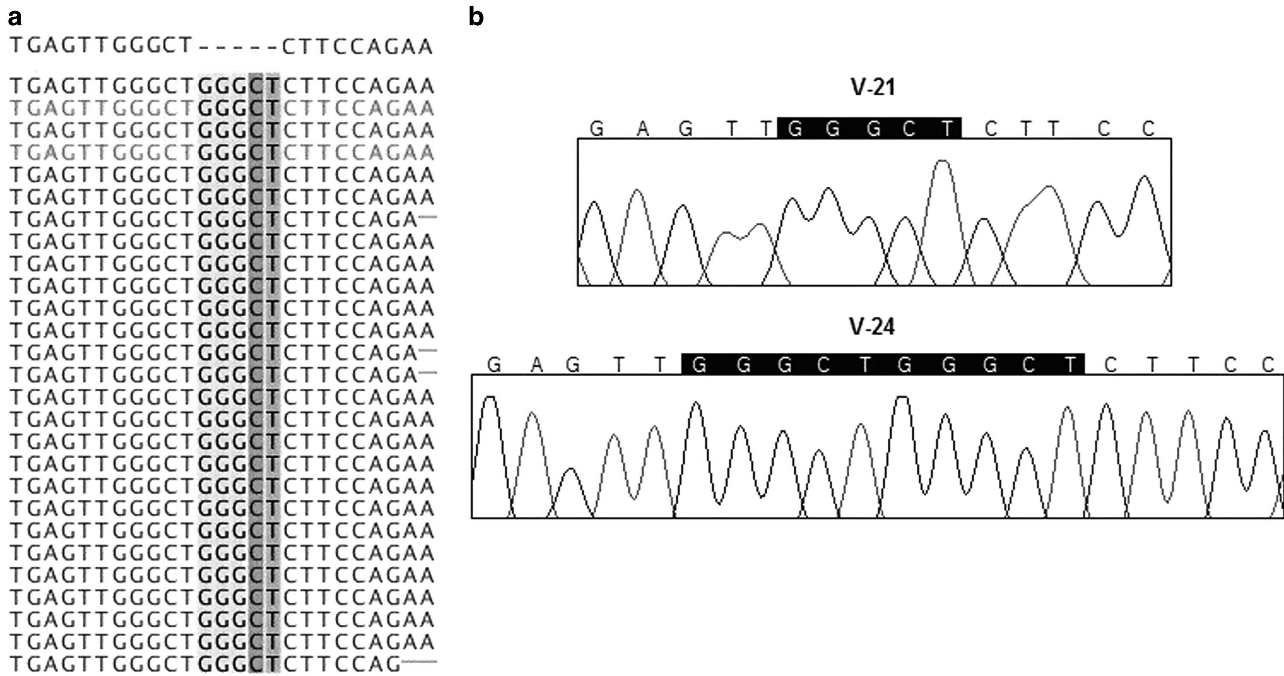

Figure 2. Mutation in *IMPA1*. (**a**) Whole-exome sequencing image of *IMPA1* sequence, highlighting the c.489_493dupGGGCT variant. (**b**) Sanger sequencing electropherograms showing homozygous control (V-21) and affected (V-24) individuals.

Linkage

Autozygosity mapping and parametric linkage analysis led to the identification of one linkage region with the maximum LOD score of 3.11 on chr8: 65,561,378-86,338,908 (8q12.3-q21.2; GRCh37/hg19). A total of 112 genes are located in the candidate region, and none were associated with autosomal recessive ID according to OMIM.[17]

Exome sequencing and Sanger sequencing of the candidate variant

The coverage of whole-exome sequencing with at least 10 reads was 96.84%, and every base was independently read an average of 80 times, as a total of 154,002,998 sequences were generated. We analyzed homozygous variants in a consensus coding transcript not present in controls, located in the linkage regions and in the following 26 genes associated with autosomal recessive ID according to OMIM:[17] *ST3GAL3, PGAP1, CRBN, PRSS12, NSUN2, MED23, GRIK2, TTI2, TUSC3, TAF2, TRAPPC9, MAN1B1, ANK3, KIAA1033, CRADD, HERC2, FBXO31, METTL23, TECR, ADAT3, KPTN, CC2D1A, NDST1, FMN2, SLC6A17* and *GPT2*. Given the target linkage region, 47 variants were identified in this region, with four of them being of low quality (filtered by GATk or erroneously genotyped as heterozygotes; Supplementary Table 1). From these 47 variants, only five were not present in the Exome Aggregation database (v0.3) (http://exac.broadinstitute.org/). Only two out these five variants are exonic coding and rare, one inside a polyP region and the other the candidate variant. The variant in the PolyP region was genotyped with a low score (<100 GATk score) and was discarded. We did not find rare variants in genes already associated with autosomal recessive ID. Therefore, the only remaining coding variant that fulfilled the criteria of possible disease-causing variant was a 5-bp duplication (c.489_493dupGGGCT; GRCh37/hg19) in homozygosis, which leads to a frameshift and premature stop codon in *IMPA1* (Figure 2). This variant cosegregated with the disease in the family (Supplementary Figure 1) and was not detected in Brazilian population controls (1484 individuals) and in 59,723 exomes from the Exome Aggregation Consortium.

Magnetic resonance imaging and proton magnetic resonance spectroscopy analysis

Brain magnetic resonance imaging was normal, as well as proton magnetic resonance spectroscopy analysis, which showed no reduction of the peak of *myo*-inositol (Supplementary Figure 2).

Myo-inositol measurements in urine and plasma

We did not detect a change in the *myo*-inositol or phosphoinositol content in the plasma or urine of patients with *IMPA1* homozygous loss of function when compared with healthy heterozygotes or normal controls (Supplementary Table 2).

DISCUSSION

Through a combination of homozygosity mapping, targeted exon enrichment and next-generation sequencing, we identified a homozygous loss-of-function variant in *IMPA1* in nine individuals with severe intellectual deficiency and disruptive behavior belonging to a large consanguineous family. The *IMPA1* gene codes for inositol monophosphatase, an enzyme active in the final step of dephosphorylation of polyphosphate *myo*-inositol. Nevertheless, we were not able to detect a change in the *myo*-inositol or phosphoinositol content in the plasma or urine of patients with IMPA1 homozygous loss of function compared with healthy heterozygotes or normal controls (Supplementary Table 1). In addition, brain magnetic resonance imaging spectroscopy did not show reduction of the inositol peak in one examined patient (Supplementary Figure 1), suggesting that levels of *myo*-inositol in biological fluids and its content in some areas of the brain are not affected by IMPA1 deficiency. Nevertheless, intracellular changes in *myo*-inositol levels or reduction of *myo*-inositol levels in specific regions of the brain cannot be ruled out.

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Over the years, the overall interest in IMPA1 function has continuously increased, as it was recognized that this enzyme is inhibited by lithium, a powerful mood stabilizer used for treatment of bipolar disorder, a psychiatric condition with high worldwide prevalence. Thus, several studies have attempted to understand the mechanism of action of lithium and its relation with IMPA1 activity.

Cryns *et al.*[8] characterized the phenotype of *Impa1* knockout mice. They observed that homozygote *Impa1*$^{-/-}$ mice died *in utero* between days 9.5 and 10.5 post coitum. However, very interestingly, it was noted that inositol supplementation of pregnant mothers rescued the lethality of *Impa*$^{-/-}$ embryos. However, an altered circadian control and hyperactivity in the forced-swim test and open-field test were observed in *Impa*$^{-/-}$ rescued mice. Berry *et al.*[18] demonstrated in mice that homozygous deletion of the sodium *myo*-inositol cotransporter-1 (*SMIT*), whose product is responsible for importing inositol into cells, caused lethality of mice shortly after birth. Ohnishi *et al.*[19] screened an ethyl-nitrosourea mutant library for *Impa1*$^{-/-}$ mutations and found a Thr95Lys missense mutation, which caused perinatal death of the mice and was also rescued by inositol supplementation. Homozygotes exhibited hyper-locomotive behavior and prolonged circadian periods. Furthermore, E.18.5 embryos displayed skeletal developmental defects. Andreassi *et al.*[20] observed that *Impa1* messenger RNA is the most abundant transcript in rat sympathetic neuron axons and that selective silencing of *Impa1* induces axon degeneration. These results highlight the importance of *myo*-inositol in the early embryonic development and survival of mice, and suggest that inositol deficiency, either by deficient synthesis, recycling or transport, is detrimental for normal development. However, the rescue of lethality in the *Impa*$^{-/-}$ mice by inositol supplementation indicates that increased diet supplementation can compensate for the defect in *myo*-inositol recycling and synthesis in the developing embryo. Interestingly, an important feature in adult rats receiving lithium during development was their hyperactivity, similar to *Impa*$^{-/-}$ mice.[21]

Up until now, only *IMPA1* and *IMPA2* are known to encode proteins with inositol monophosphatase activity in humans. Nevertheless, IMPA2 was inhibited by lithium only at high concentrations and has much lower activity towards inositol monophosphate than does IMPA1.[22] In mice, *Impa1* and *Impa2* have a different pattern of expression in different tissues. For example, expression in the brain is dominated by *Impa1*. In addition, the *Impa2* knockout mouse has no recognizable phenotype. In the search for potential compensatory mechanisms, no evidence of overexpression of *Impa2* was seen in *Impa1*$^{-/-}$ mice.[8]

IMPA1 has an essential role in maintaining neuronal polarity in the mature nervous system as demonstrated by studies on the *Caenorhabditis elegans* gene, *ttx-7*, its only gene to encode an inositol monophosphatase.[23,24] Mutations in *ttx-7* cause defects in sensory behavior and localization of both pre- and post-synaptic proteins in RIA neurons and pivotal interneurons. Both behavioral and localization defects in *ttx-7* mutants were rescued by either expression of ttx-7 in adults, forced expression of human IMPase proteins, or by inositol supplementation.[23–25] As shown by Tanizawa *et al.*,[23] the synaptic localization defects in *ttx-7* mutants occurred exclusively in RIA neurons. In addition, this study showed that inositol monophosphatase is involved in a specialized part of cell phosphatidylinositol metabolism.

Thus, we can speculate that the inhibition of IMPA1 in humans may have an effect on a specific group of neurons and/or affect a specific metabolic phosphatidylinositol pathway. The fact that we were not able to observe reduced inositol peak in one patient subjected to a brain magnetic resonance imaging spectroscopy does not rule out the possibility of inositol depletion as a mechanism of the ID. Various studies suggested the existence of several pools of inositol in the brain.[8,26] Lack of IMPA1 activity causing inositol depletion would be more likely to occur in cells with a highly active phosphatidylinositol cycle, leading to inositol depletion and causing irreversible brain damage.[8]

Several ID genes are involved in neurotransmitter release by exocytosis.[27] It has been shown that phosphoinositides, which are derived from combinational phosphorylation of phosphatidylinositol, have important roles through the Ca^{2+}-dependent mobilization of secretory vesicles to the plasma membrane.[28,29] In neurons and neuroendocrine cells, regulated secretion requires a calcium-dependent fusion of transmitter-containing vesicles with the plasma membrane. Furthermore, reduction of phosphatidylinositol 3,5-bisphosphate potentiates neuroexocytosis and leads to neuronal degeneration, a mechanism that has been linked to certain forms of Charcot–Marie–Tooth disease and amyotrophic lateral sclerosis.[30]

In short, the strategy of combining field investigation in highly inbred areas of Brazil, searching for of clusters of genetic disorders, with a state-of-art molecular approach proved once again to be successful. Using this approach, our group has recently identified, in a neighboring community, *MED25* as another gene associated with autosomal recessive ID.[16]

Now we report the identification of a novel homozygous duplication of 5 bp in *IMPA1,* in a large consanguineous family with nine individuals with severe ID and disruptive behavior. *IMPA1* encodes inositol monophosphatase 1, a key target for lithium, the leading drug for treatment of bipolar disorder. This is the first observation of a human disease involving inositol recycling and its *de novo* synthesis pathway, enhancing our comprehension of the pathophysiology of ID and psychiatric disorders. The effect of inositol supplementation in individuals with IMPA1 deficiency will be the subject of future studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)

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