ORIGINAL ARTICLE

Homozygous missense mutation in *MED25* segregates with syndromic intellectual disability in a large consanguineous family

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ABSTRACT

Background Intellectual disability (ID) is a highly heterogeneous condition affecting 2% of the population worldwide. In a field study conducted in a highly inbred area of Northeastern Brazil, we investigated a consanguineous family in which seven adults presented syndromic ID.

Methods Genome-Wide Human SNP Array 6.0 (Affymetrix) microarray was used to determine regions of homozygosity-by-descent and whole exome sequencing (WES) was performed in one affected individual using Extended Nextera Rapid-Capture Exome and Illumina HiSeq2500.

Results We found two regions with an logarithm of the odds (LOD) score of 3.234: a region spanning 4.0 Mb in 19q13.32-q13.33 and a pericentromeric 20 Mb area in chromosome 2 (2p12-q11.2). WES disclosed in the critical region of chromosome 19 a homozygous variant (c.418C>T, p.Arg140Trp) in Mediator complex subunit 25 (*MED25*), predicted as deleterious by PolyPhen-2, Provean, Mutation Taster and Sorting Intolerant From Tolerant (SIFT). MED25 is a component of the Mediator complex, involved in regulation of transcription of nearly all RNA polymerase II-dependent genes. Deleterious mutations in *MED12*, *MED17* and *MED23* have already been associated with ID.

Conclusions These findings demonstrate that the combination of field investigation of families in highly inbred regions with modern technologies is an effective way for identifying new genes associated with ID.

INTRODUCTION

Intellectual disability (ID) is a highly heterogeneous condition affecting 2% of the population worldwide. It is the most common motive for referral to clinical genetic centres and one of the most important unsolved problems in healthcare.[1 2] The genetic basis of autosomal recessive ID (ARID) is extremely heterogeneous and the number of underlying gene defects may well go beyond a thousand.[3] Currently, fewer than 100 loci and genes have been identified associated with ARID (OMIM), which is particularly prevalent in highly consanguineous populations and genetic isolates.[4 5] In Brazil, the frequency of consanguineous marriages is about 15 times higher in the Northeast region (9%) than in the Southern part of the country (0.62%).[6–8] A study conducted in small communities in Northeastern Brazil identified rates of consanguineous unions ranging from 6% to 41.1%.[9] As part of a research project on consanguinity and disability aiming the identification of new disease genes, which is being performed in the backlands of Northeastern Brazil, we ascertained several families with multiple individuals with disabilities and selected some of them for additional investigation. Subjects of the current investigation belonged to a large inbred family in which three consanguineous unions generated seven individuals with moderate to severe ID associated with a distinct facial phenotype.

METHODS

Clinical analysis and family material

After obtaining a written consent from the legal guardians of subjects of this study, a detailed clinical and neurological evaluation was performed. A pedigree was constructed based on the family information (figure 1) and blood samples from affected and unaffected family members were collected for DNA extraction (Autopure LS device, Gentra Systems). The protocol of data sampling and the consent procedure were reviewed and approved by the National Committee for Ethics in Research—CONEP (Process 0359.0.133.000-11).

Linkage study

Linkage study was performed using DNA samples from three affected (V-8, V-12 and V-13) and three healthy individuals (IV-4, V-6 and V-10) from the same family. Genotyping was done with the Genome-Wide Human SNP Array 6.0 (Affymetrix, Santa Clara, California, USA), and the data were analysed using HomozygosityMapper for homozygosity mapping.[10] The Alohomora software was used to convert the obtained data into files for linkage analysis, Pedcheck for checking Mendelian segregation and Merlin software to obtain multipoint LOD scores.[11 12] The disease was analysed as an autosomal recessive mode of inheritance with complete penetrance and the disease allele frequency was estimated as 0.001.

Exome and Sanger sequencing

Whole exome sequencing (WES) was performed in a DNA sample from one affected individual (V-12) using Extended Nextera Rapid-Capture Exome and

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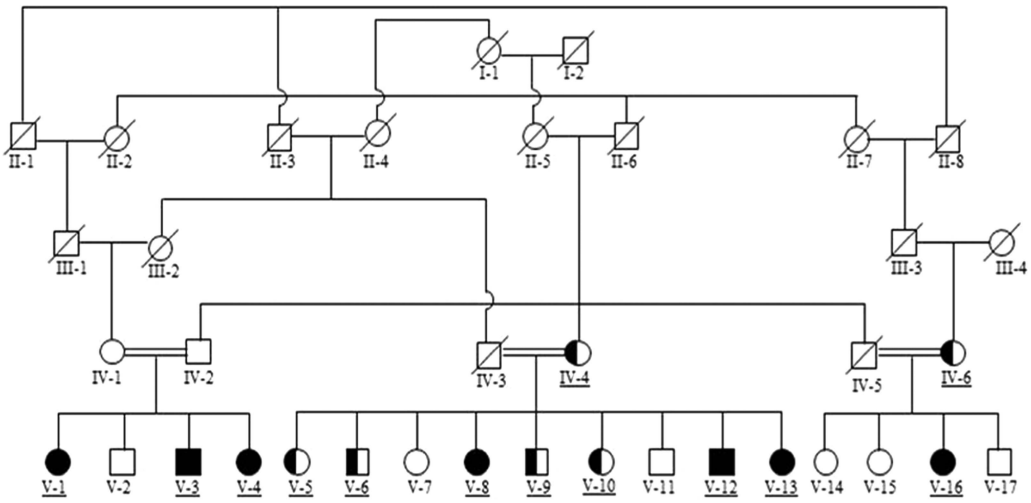

Figure 1 Family pedigree: individuals with intellectual disability are represented in filled symbols and half-filled symbols indicate heterozygous individuals. Genotyped individuals are underlined.

sequenced in Illumina HiSeq2500 (Illumina, San Diego, California, USA). Exome reads were analysed in a standard Bioinformatics pipeline based on Burrows-Wheeler Aligner (BWA) for sequence alignment on GRCh37 reference, Broad Institute GATK for genotyping, SnpEff for variant annotation and ExomeDepth for CNV detection.[13–16] Potentially deleterious variants detected in regions of homozygosity-by-descent and not present in 61 486 exomes from the Exome Aggregation Consortium (ExAC) and in Brazilian population controls (608 healthy individuals) were selected for further scrutiny and segregation analysis by Sanger sequencing. PCR products were amplified using the following primers: forward: 5′-GGCGTTGC TTCTGATTCCAT-3′; reverse: 5′- GAGTCCTCACCTCCCCAA TC-3′; and the reaction products were analysed in the ABI 3730 DNA Analyzer equipment (Applied Biosystems, Carlsbad, California, USA). The results were analysed using the Sequencher 5.0 and MEGA 5.

RESULTS

We evaluated seven individuals (two men, ages 33–51) belonging to three related consanguineous families. Variable degree of ID was present in all seven individuals: moderate in two (V-3 and V-4) and severe in the remaining five. They all are illiterate and never attended regular school. One individual (V-3) was able to work supervised, and the severe patients were totally dependent for basic care and able to speak a few words and most of the time utter incomprehensible sounds and need constant vigilance. Behaviour problems, as aggressiveness and sexual arousal, were occasionally present. The facial characteristics were very similar in all affected individuals: tall forehead, prognatism, prominent chin, very large and overhanging nose tip (figure 2). This facial phenotype was not present among parents and the five clinically evaluated unaffected siblings. The legal guardians of patients have provided consent for publication of these photographs.

Figure 2 Facial features of affected individuals: tall forehead, prognatism, prominent chin and very large and overhanging nose tip. (A, B) V-1 age 43 years; (C, D) V-3 age 37 years; (E, F) V-4 age 33 years; (G, H) V-8 age 51 years; (I, J) V-12 age 43 years; (K, L) V-13 age 38 years; (M, N) V-16 age 42 years.

Autozygosity mapping and parametric linkage analysis led to the identification of two linkage regions which get the same maximum LOD score of 3.234 on chr19: 47 658 320–51 657 650 (19q13.32-q13.33) and on chr2: 76 245 774–102 080 926 (2p12-q11.2). Sequences of 167 genes are located on candidate region of chromosome 2 and 214 genes on candidate region of chromosome 19. Those regions are devoid of genes associated with ARID, with the exception of the recently described autosomal recessive mental retardation-41 (MRT41; OMIM 615637), caused by truncating homozygous mutation on *KPTN* gene, located on chromosome 19.[17] MRT41 was recognised in four individuals with non-syndromic ARID from consanguineous Amish families.

The coverage of WES with at least 10 reads was 99.18%, every base was independently read on average 158 times and a total of 95 313 806 sequences were generated. We selected for further evaluation homozygous coding variants present in a consensus coding transcript not present in controls. The only remaining coding variant in the linkage regions which fulfil these criteria of possible disease-causing variant was the missense change c.418C>T (p.Arg140Trp; chr19:50 332 240; NM_030973) in *MED25* gene (OMIM 610197) (figure 3). It encodes one of the subunits from Mediator's tail region that are required for regulating expression of most RNA polymerase II (polII) transcripts.[18] This variant cosegregated with the disease and was not present in Brazilian population controls (608 healthy individuals) as well as in 61 486 exomes from the ExAC (Cambridge, Massachusetts, USA; http://exac.broadinstitute.org) (18 November 2014 accessed date). Moreover, p.R140W is conserved across *MED25* orthologues and predicted as deleterious by PolyPhen-2, Provean, Mutation Taster and SIFT.[19–22]

DISCUSSION

ID is a highly heterogeneous disorder, and identification of autosomal genes associated with this condition, in particular in families with few affected members, only recently became more feasible, mostly because of more efficient technologies for linkage analysis and identification of the responsible gene. On the other hand, the search for large consanguineous families with multiple affected individuals once more proved to be an effective way for identifying new genetically determined autosomal recessive forms of ID. Indeed, the number of X linked ID associated genes currently surpasses the frequency of ARID related genes, because most studies of the genetic causes of ID were concentrated on X-chromosome-linked ID. However, it is estimated that X linked forms represents only 10% of ID, which suggests that a large number of autosomal genes associated with ID remain to be recognised.[4 23]

The Mediator complex (MED) is a multi-protein complex composed of more than 20 subunits that form four distinct modules evolutionarily conserved in eukaryotes required for regulating expression of most RNA polII transcripts, which include protein-coding and most non-coding RNA genes, performing its function by interacting directly with RNA Pol II activators bound at regulatory elements and also elongation factors of target genes.[18 24 25] Several studies using experimental models (*Danio rerio*, *Drosophila*, *Caenorhabditis elegans* and mouse models) indicated that some components of the MED may interact with specific transcription factors, thus regulating the expression of distinct groups of genes during development and/or cell differentiation.[26]

In recent years, functional studies showed the importance of MED25 in the activation of transcription by several transcription factors, including the retinoic acid receptor (RARα),[27] orphan receptor (HNF4α),[28] chondrogenic factor (Sox9),[29] PEA3 group members,[30] activating transcription factor 6 (ATF6α)[31] and estrogen receptor α.[32] These factors are involved in different developmental processes and they control multiple metabolic pathways,[28 32] development of motor and sensory neurons,[33] response of human cells to endoplasmic reticulum stress, which are critical for cell survival and defects can cause neurodegeneration[34] and chondrogenesis.[29]

Morpholino-mediated knockdown of *med25* induced palatal malformation in zebrafish, which is comparable with that observed in zebrafish *sox9* mutants.[29] Furthermore, expression analysis of *MED25* in wild-type rats tissues detected ubiquitous expression and highest expression levels were found in dorsal root ganglia, cerebellum, cortex and optic nerve indicating an important involvement of *MED25* in the nervous system.[35]

A single report of a large family associates the homozygous variant p.Ala335Val in *MED25* with Charcot–Marie–Tooth

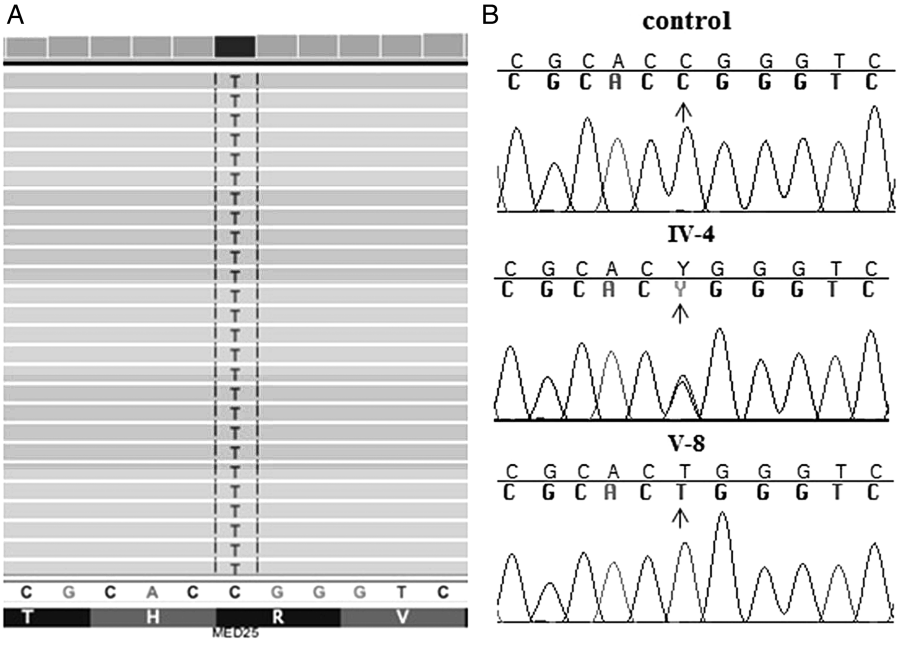

Figure 3 Mutation in *MED25*: (A) Whole exome sequencing (WES) image of the *MED25* BAM file base counts, highlighting the c.418C>T variant. (B) Sanger sequencing electropherograms showing homozygous control (arrow), heterozygous (arrow) at position c.418 of *MED25* gene in a carrier (III-2) and homozygosity (arrow) in an affected individual (IV-1).

disease type 2B2 (CMT2B2, OMIM #605589).[35] The variant attributed to CMT2 on MED25 (c.1004C>T) has a population frequency among Europeans (non-Finnish) of 1/160 (0.006042), which is quite large for a rare disease. Additionally, no other family with CMT2B2 was reported since the original publication of 2009 and no other gene belonging to MED was associated with CMT. Additionally, no other gene coding for proteins belonging to MED was ever associated with CMT. Finally, since there is no evidence for CMT-like features in the presented Brazilian family, it appears that the p.Ala335Val variant identified in CMT2B2 patients might be a rare benign variant rather than the causative mutation. Mutations in other members of MED have been already assigned to other syndromes. Deleterious missense variants in *MED12* have been previously associated with Ohdo, Lujan and Opitz–Kaveggia syndromes, all X linked syndromic forms of ID.[36–38] A homozygous missense mutation (p.L371P) in *MED17* has been associated with syndromic severe ID with infantile cerebral and cerebellar atrophy.[39] Finally, a homozygous disease-causing coding variant (p.R617Q) within the *MED23* gene was identified in an Algerian consanguineous family with five affected individuals with non-syndromic ID. This mutation modified the response of *JUN* and *FOS* immediate early genes to serum mitogens by altering the interaction between enhancer-bound transcription factors and Mediator. Dysregulation of these genes have been also observed in cells from patients with other neurological disorders, including Opitz–Kaveggia, caused by *MED12* mutation.[40]

These findings emphasise the critical role of Mediator in brain functioning and development and highlight the importance of a combined strategy of field evaluation in remote areas in which large inbred families are common and state-of-art technologies for identification of novel deleterious variants in genes currently not associated with a distinct phenotype.

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Contributors TF: field evaluation of families, linkage analysis, family genotyping, manuscript concept. USM: family genotyping, manuscript revision. ALSP and PRN: clinical evaluation. JPK: NGS bioinformatics and exome data analysis. IC: NGS bioinformatics. MZ: manuscript concept and revision. FK: clinical evaluation, exome data analysis, manuscript concept and revision. SS: health agents training, patients field evaluation, manuscript concept and revision.

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