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METAP1 Mutation Is a Novel Candidate for Autosomal Recessive Intellectual Disability

Ahmet Okay Caglayan, MD[1,*], **Fesih Aktar, MD**[2], **Kaya Bilguvar, MD**[3], **Jacob F. Baranoski, MD**[4], **Gozde Tugce Akgumus**[4], **Akdes Serin Harmanci, PhD**[4], **Emine Zeynep Erson-Omay, PhD**[4], **Katsuhito Yasuno, PhD**[4], **Huseyin Caksen, MD**[5], **Murat Gunel, MD**[4]

[1]Department of Medical Genetics, School of Medicine, Dokuz Eylul University, 35340, Izmir, Turkey

[2]Department of Pediatrics, School of Medicine, Dicle University, Diyarbakir, 21060, Turkey

[3]Department of Genetics, Yale Center for Genome Analysis, Yale School of Medicine, New Haven, 06510, CT, USA

[4]Departments of Neurosurgery, Neurobiology and Genetics. New Haven, CT 06520-8082, USA

[5]Divisions of Pediatric Neurology and Genetics, Department of Pediatrics, Meram Medical Faculty, Necmettin Erbakan University, Meram Medical Faculty, Konya, 42080, Turkey

Abstract

Intellectual disability (ID) is a genetic and clinically heterogenous common disease and underlying molecular pathogenesis can frequently not be identified by whole- exome/genome testing. Here, we report 4 siblings born to a consanguineous union who presented with intellectual disability and discuss the *METAP1* pathway as a novel etiology of ID. Genomic analyses demonstrated that patients harbor a novel homozygous nonsense mutation in the gene *METAP1*. *METAP1* codes for methionine aminopeptidase 1 (MetAP1) which oversees the co-translational excision of the first methionine remnants in eukaryotes. Loss of function mutations to this gene may result in a defect in the translation of many essential proteins within a cell. Improper neuronal function resulting from this loss of essential proteins could lead to neurologic impairment and ID.

Introduction

Intellectual disability (ID) is a common disease[1], and carry an often under-recognized burden to the individual, their family, and society[2]. Unfortunately, for most children with ID

[*]**Corresponding author:** Ahmet Okay Caglayan, M.D., Department of Medical Genetics, School of Medicine, Dokuz Eylul University, 35340, Izmir, Turkey, ahmetokay.caglayan@deu.edu.tr, **Tel**: +90-535-584-7978.

Author contributions AOC, KB and MG designed the study. AOC analyzed the exome data. AOC and KB performed linkage analysis. AOC, JFB and GTA performed sanger sequencing, AOC, FA, HC, and MG participated in ascertaining the patients and families and worked on the neurological and clinical investigation on the patients. KY wrote the in-house data analysis exome pipeline, EZEO run the pipeline. ASH analyzed the exome CNV data. AOC analyzed co-expression data. AOC wrote the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

the genetic etiology of their disorder remains unknown. This is primarily because of the tremendous locus heterogeneity which may include thousands of phenotypes that are often indistinguishable by neurologic examination[3]. However, recent studies employing new sequencing technologies have been successful in identifying a number of genes and molecular pathways responsible for various forms of ID[4–6].

Here, we report four Turkish siblings with ID. We performed an array of genomic analysis techniques including whole genome genotyping, linkage analysis, and whole exome sequencing (WES) and probable disease-causing mutation is detected in provisionally novel gene *METAP1*.

Clinical Report

The index patient (NG1338–2) is a 10-year-old boy who is the product of a consanguineous marriage (Figure 1A). He was born at term with normal birth measurements following an unremarkable pregnancy. He started sitting without support at 12 months and began walking at 24 months. He never developed fluent speech. At 10 years of age, he was admitted due to uncontrollable aggression with neurodevelopmental delay. Upon examination, he appeared normal for growth but was unable to speak, read, or write. He was able to follow simple commands. The Stanford-Binet Intelligence test revealed mild intellectual disability. Diagnostic workup including magnetic resonance imaging, electroencephalogram, TANDEM mass spectrometry, formal eye and ear examinations, and routine blood work were all within normal limits. The index case's 18-year-old sister showed similar symptoms and was also diagnosed with intellectual disability. She first walked when she was 18 months old and talked when she was 3 years old. She was brought to medical attention at the age of 5. At 18, she cannot read or write; she has bouts of uncontrollable aggression. While the other 3 affected siblings display no dysmorphic findings, she was found to have bilateral clinodactyly of her toes and her left 3rd finger. The other two siblings were similarly delayed with respect to attainment of developmental milestones. While they are reported not to possess any dysmorphic features, formal clinical work-up has not been performed.

Linkage Analysis

Inbreeding coefficient was calculated for the index case (NG1338–2) to be 0.07 by whole genome genotyping. After homozygosity mapping and multipoint parametric linkage analysis using genotyping results of six DNA samples, only one homozygous genomic interval with LOD scores above 2 (Figure 1B) was found. This region (LOD score of 2.5) was located on chromosome 4 between heterozygous SNP markers, rs776847 (70,892,919) and rs12510756 (111,132,892) (GRCH37/hg19). We therefore focused our subsequent analyses on the identification of potential disease-causing variants within this region (35.68 cM). Homozygosity analysis showed a single region shared only by the three affected individuals located at 4q13.3–4q25 between 75,718,547 and 109,296,917 bps (29.55cM) by PLINK software (Supplementary Table 1).

Whole Exome Sequencing

WES was carried out to the index patient (NG1338–2) as previously described[7]. A mean 20x coverage of all targeted bases was 87% (Supplementary Table 2 and Supplementary Table 3). Whole exome sequencing results were trimmed according to patient's homozygous segments and a homozygous nonsense mutation ENST00000296411.6:c.865C>T in *METAP1* (methionine aminopeptidase 1) was identified (Figure 1C). This mutation introduces a premature stop codon, which terminates the amino acid sequence at arginine 289. This truncated protein is predicted to undergo nonsense-mediated decay. Both parents were identified to be heterozygous for the variant via Sanger sequencing (Figure 1D). Finally, exome CNV analysis demonstrated no big events within the coding regions of the genome (Figure 1E and Figure 1F). This *METAP1* mutation has never been reported in publicly available databases such as dbSNP, 1000 Genomes or GnomAD. The number of rare (MAF < 0.1%) loss-of-function variants in *METAP1* gene found in ExAC (r0.3) is two. The probability of being intolerant of homozygous, but not heterozygous lof variants (pRec) value is 0,51 and the probability of being tolerant of both heterozygous and homozygous lof variants (pNull) value is 0.0048. The probability of being loss-of-function intolerant (pLI) score for *METAP1* gene is 0.49 which means that this gene cannot be categorized as a highly likely haploinsufficient gene aligning with the related disease inheritance[8]. *METAP1* gene observed / expected (oe) score is 0.27 which can be interpreted as a gene where only 27% of the expected loss-of-function variants were observed and therefore is likely under selection against LoF variants. Overall results suggested that the homozygous *METAP1* variant probably the disease-causing mutation in this family.

Discussion

During the regulation of gene expression translation step is evolutionarily critical and is strictly linked with several regulatory processes that, when disrupted, contribute to a number of human diseases[9, 10]. One of the translation regulatory mechanisms is N-terminal Met removal (NMR), which requires intact Met aminopeptidase (MetAP) activity[11–13]and between 55 and 70% of proteins undergo NMR[14, 15].

Since *METAP1* function is largely unknown but has a common role in essential cellular process[16, 17], it is unclear why reported patients display only intellectual deficits and not more widespread defects. Interestingly, other studies have found similar results when examining other genes that one would expect to have a systemic impact if altered. For example, Najmabadi et al. described a number of ubiquitously expressed genes with essential cellular functions, when mutated, tend to result in non-syndromic ID[18].

In our case, one possible explanation for this observation would be that eukaryotic cells express MetAP1 and MetAP2. Therefore, inactivation of MetAP1 may not result in complete loss of cellular MetAP activity and MetAP1 activity can largely compensate for MetAP2 in non-neuronal cells but not adequately compensate in neuronal cells. Using the Human Brain Transcriptome database, we found that both *METAP1* and *METAP2* are highly expressed in all brain regions; however, *METAP2* expression levels decline during fetal life. While overall *METAP1* global brain expression levels also decline during fetal life,

neocortical expression levels remain elevated during fetal life and persist into adulthood (Supplementary Figures 1 and 2). We also found that the developmental expression pattern of *METAP1* parallels that of other molecules important for neuronal proliferation like *CENPJ*[19]. This suggests that *METAP1* may play a role in the proliferation step of neurogenesis (Supplementary Table 4, Supplementary Table 5).

This study has a few limitations. Major limitation of the study is only single large consanguineous pedigree was analyzed and replication studies are needed. Another one is considering some variant types would have been missed due to nature of the technique we cannot rule out additional disease-causing variants that can modify the patients' phenotypes and cause intrafamilial phenotypic variations.

Although genetic heterogeneity is a rule for ID and new genomic technologies found number of new ID genes day by day, known genes explain only small fraction of the ID patients and more ID-related genes yet to be identified. For the first time in the literature, this report describes cases of non-syndromic ID that are probably the result of initiator methionine retention. Further studies are needed to investigate functional effects of initiator methionine retention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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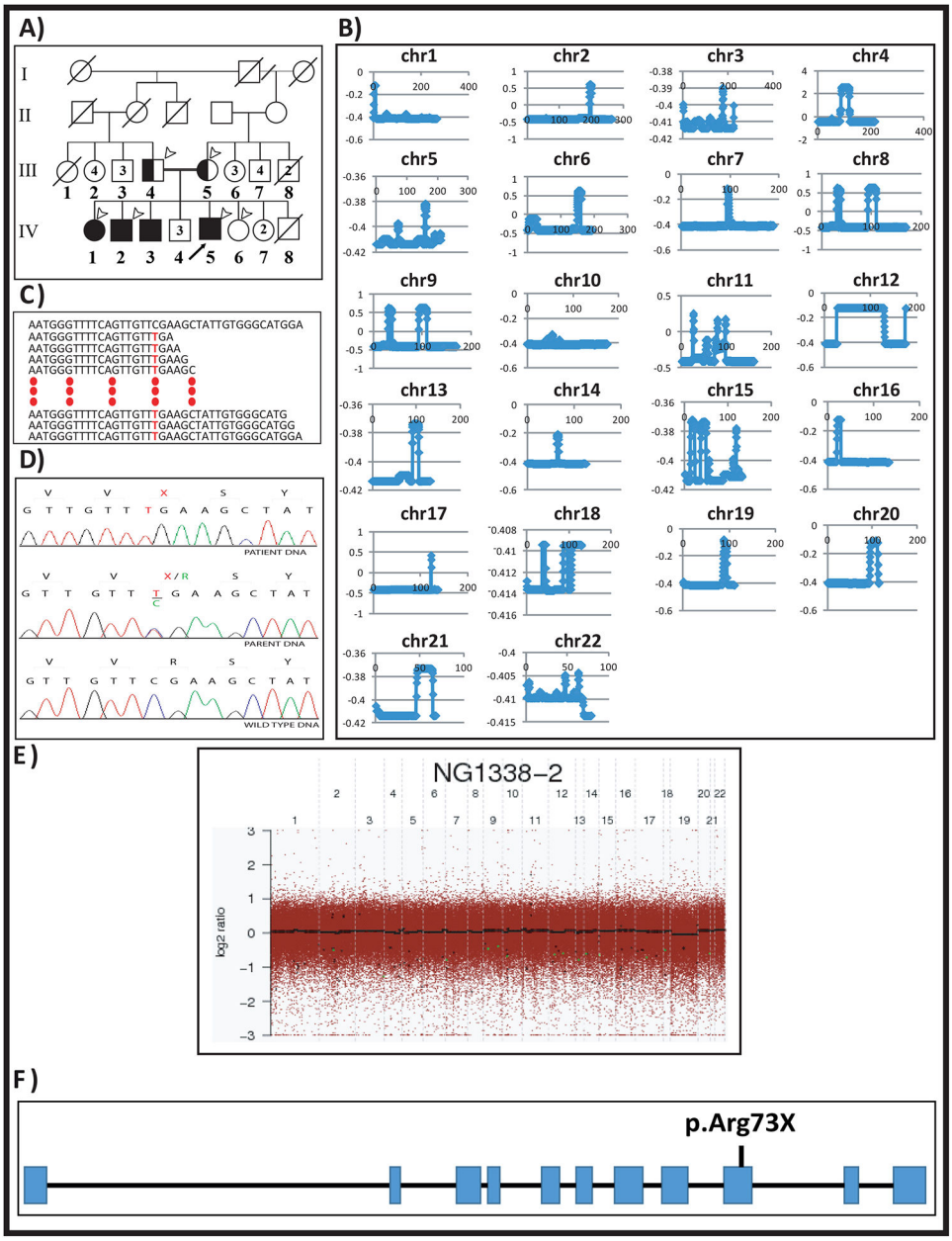

Figure 1. A) NG1338:

A) NG1338: Simplified pedigree shows *METAP1* variant which aligning with the phenotype. Individual III.4 and III.5, father and mother of the index case, respectively, are mandatory heterozygotes demonstrated with half-filled symbol. Individuals IV.1, IV.2 and IV.5 were homozygous and affected, sibling IV.3 is affected but not tested with Sanger due to no available DNA. Individual IV.6 is a wild type and unaffected sibling. Arrow heads depict individuals who are being analyzed in the linkage analysis and sanger sequencing.

B) Linkage Analysis: The y axis corresponds to lod score and the x axis represents distance in cM for each chromosome. The locus on chromosome 4 was the only one to give the theoretical maximum for this pedigree.

C) Sequence Alignment: Whole-exome sequencing results for patient NG1338–2 revealing the homozygous nonsense mutation in *METAP1*. The top line is the wild-type reference sequence and subsequent lines represents a different coverage read (for this region was 77x) from whole exome sequencing data.

D) Sanger Sequencing Results: Chromatographs confirm the mutation found with whole-exome sequencing and show segregation as being homozygous versus heterozygous, in the affected siblings versus their parents, respectively. Mutated base pairs outlined with red in the wild-type genotype.

E) Exome CNV Analysis of NG1338–2: The log ratio comparing NG1338–2 and control sequence depths of coverage for each exon are depicted as gray dots. The black lines demonstrate regions of segmented copy neutral events, green lines are segmented deletion events and red lines are amplification events.

F) Exon view of the *METAP1*, nonsense mutation is shown on top of the exon.