

Case Report: A Rare Homozygous Missense Mutation of ADAT3 Gene in Intellectual Disability in a Saudi Patient

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Abstract

Intellectual disability (ID) is defined by significant limitations in intellectual functioning and adaptive behavior with an age of onset being less than 18 years.

The prevalence of intellectual disability/developmental delay is 1 – 3 % in the general population.

The definition of mental retardation/intellectual disability Shift from 'Mental retardation' to 'Intellectual disability' in the 2002 [1] suggested will "remain in effect for now and in the future," defines intellectual disability as: characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills. This disability originates before age 18.

The ADAT3 gene encodes one of two eukaryotic proteins that are necessary for the deamination of adenosine at position 34 to inosine in t-RNA. The first human mutation in the t-RNA editing machinery and expand the landscape of pathways involved in the pathogenesis of ID.

Keywords: Intellectual Disability; ADAT3 Gene, Adenosine Deaminase

Introduction

Intellectual disability (ID) is characterized by sub average intelligence and impaired adaptive functioning originating in the developmental period (< 18 y). Three domains are affected [1,2], Intellectual disability is a disability characterized by significant limitations in both intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills. Most individuals with Intellectual disability (ID) are identified early in childhood because of developmental delays, and a prominent feature of most developmental disorders.

The intellectual disability one of common disorder in Saudi Arabia, Although, Saudi Arabia has many tribal customs. Structurally, the family is considered one of the most important components of the cultural homogeneity in Saudi Arabia, from which stems the tribal affiliation (<http://countrystudies.us/saudi-arabia/22.htm>). The tribes may have a very high consanguinity rate, and may be considered "genetic isolates." Due to population stratification, a recessive founder or de novo mutation can thus quickly rise to a high frequency in a sub-community represented by tribes [3].

ADAT3-related intellectual disability is a newly recognized syndrome. And consider one of a common mutation cause intellectual disability in Saudi Arabia.

ADAT3-related intellectual disability syndrome has been recently described in 24 individuals from eight Saudi consanguineous families [4]. And was identified in 15 individuals from 11 families (10 Saudis and 1 Emirati) who are homozygous for the same founder mutation [5].

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Our patient carried Missense variant of (homozygous c.430G>A mutation of ADAT3 gene) with normal neuroimaging and eye examination.

Case Representation

One year-old boy referred to our hospital on the ninth month of his age for further evaluation as failure to thrive and developmental delay. He was born at full term after an uneventful pregnancy to healthy, consanguineous parents, no family history of abortion or still birth with. his birth weight was 3 kg and Apgar score 9/10. There was history of significant developmental delay, inability to roll over or sit even crawl noticed by parent, poor weight gain. No seizure, normal vision and hearing. Physical examination revealed facial dysmorphic with prominent forehead, spars up-slanted palpebral fissures, epicanthus fold, small nose, low set ear (Figure 1a, b, c). He was also noticed to have hypertonia. At nine months, he weighed 5.5 kg (at 3th centile), his length was 68cm (at 50th centile) whereas his head circumference was 46 (at 50th centile).



Figure 1

MRI and ultrasound abdomen were grossly unremarkable. The biochemical tests including liver transaminases, serum lactate as well as serum electrolyte and complete blood count were all in the normal range, Thyroid function test, random cortisol's were all normal. Eye examination and echocardiogram (ECHO) were completely normal.

Exome analysis was done and showed: A homozygous variant of ADAT3 (ADAT3: NM 138422: exon2: c.430G>A; P. V144M) that is likely pathogenic was identified and confirmed by Sanger sequencing.

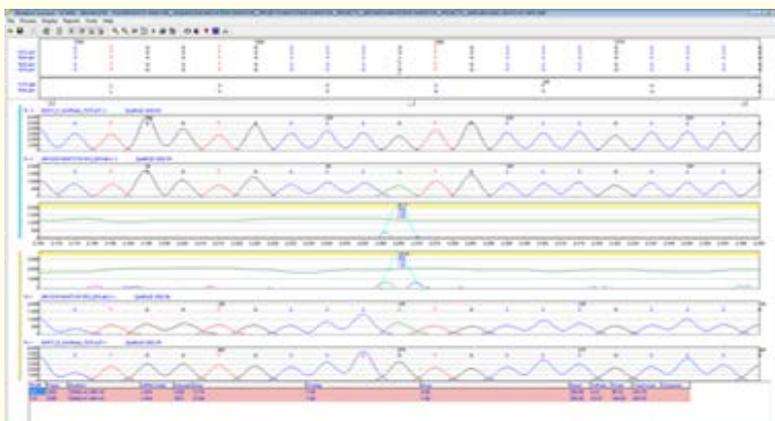


Figure 2: DNA chromatogram. Detected A missense mutation in ADAT3 segregates with the disease.

Blood sample in EDTA were obtained from the patient after informed written consent was given to the patients' parents. The sample was sent to SDL (SAUDI DIAGNOSTIC LABORATORY, for exome analysis. The genomic DNA used from the submitted sample for the coding, regions and splicing junctions of the 10 genes in this panel.

Discussion

Missense variants of ADAT3 are a common mechanism of Mental Retardation, Autosomal Recessive 36; MRT36: OMIM#615286. In this case, the data revealed a missense variant in ADAT3 (NM_138422), changing a valine residue to methionine (c.430G>A; P. V144M).

ADAT3 gene encodes tRNA-specific adenosine deaminase 3 (ADAT3). ADAT3 binds ADAT2 to form a heterodimer that functions as the tRNA-specific adenosine deaminase enzyme required for the conversion of adenosine to inosine at the first position (position 34) of the anticodon of tRNA.

It is believed that modified nucleosides can influence the stability and structure of tRNAs and improve the fidelity and efficiency of tRNAs in decoding the genetic message [4].

This is a highly specialized form of RNA editing which affects only t-RNA species that recognise the eight amino acids in eukaryotes (seven in yeast) that are encoded by four codons each. This so-called 'wobble' position was thought to increase the efficiency of translation by allowing the same t-RNA to recognise more than one codon [8].

Generally speaking, the study of the influence of anticodon modifications on the translation of specific codons has recently led to the realization that tRNA populations can act as a new layer of gene translation regulation through the modulation of their anticodon modification status, or through changes in the expression levels of different tRNA genes [7] is a newly recognized syndrome. And consider one of a common mutation cause intellectual disability in Saudi Arabia. this mutation would be traced back approximately 1600 years ago.

The paradox is that despite the difficulty in diagnosing ADAT3-related phenotype clinically, this appears to be the single most common mutation that causes intellectual disability in Arabia (Alkuraya, unpublished data).

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MRT36 is often associated with esotropia and failure to thrive. Other more variable features included microcephaly, hypotonia, and mild brain abnormalities on MRI, such as dilated ventricles or delayed myelination. [MIM:615286] this abnormality in brain, it appears that the brain is a particularly sensitive organ to abnormal tRNA editing as also speculated by others [6]. despite our patient had normal brain imagine, so we note that brain imaging is not helpful diagnostically, even when abnormal as the findings are largely non-specific [6].

ADAT3 plays roll in Intellectual disability in Saudi patient. with nonspecific phenotype.

The availability of next-generation sequencing has help in determined and diagnosis this single gene, however we know up to 50% of ID cases can be traced to de novo single-gene-dominant mutations [9,10].

Conclusion

A single homozygous founder mutation (c.430G>A; P. V144M) in the ADAT3 gene, which encodes a protein that functions in tRNA editing, was identified in intellectual disability individuals. With normal brain imagine and ophthalmology examination.

ADAT3 gene should be considered in individuals with the facial features, intellectual disability and growth failure.

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