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Whole Exome Sequencing Reveals A Mutation in *ELP2* Gene in Iranian Family Suffering from Autosomal Recessive Mental Retardation

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Abstract

Variety of genes has been reported for intellectual disability in different ethnic group and whole exome sequencing facilitate the way of gene discovery in such heterogeneous diseases. Here, we reported a novel mutation in *ELP2* gene (c.2429 G>A) in Iranian case of mental retardation. The gene *ELP2* encodes acetyl transferase subunit of RNA polymerase II playing an important role in transcription elongation and chromatin remodeling. The c.2429 G>A mutation predicted as pathogenic and resulted in substitution of amino acid cysteine with tyrosine at position 811 of polypeptide chain. The proband was homozygous of the mutation and received one copy of affected allele from each parent. Although, the association of elongator proteins with neurological diseases is well established, there is only one study reported two missense mutations of *ELP2* in the world which was observed in Iranian mental retarded patients. In fact, c.2429 A>G is the third report of *ELP2* mutations in Iranian families suffering from mental retardation showing the importance of this gene in Iranian cases although phenotype-genotype correlation is needed.

Keywords: Whole exome sequencing; Intellectual disability; Autosomal recessive mental retardation; *ELP2* gene; Iranian population

Abbreviations: ELP2: Elangator Complex; ID: Intellectual Disabilities; CNVs: Copy Number Variations; MR: Mental Retardation; WES: Whole Exome Sequencing; dbSNP: The Single Nucleotide Polymorphism; MRT-58: Mental Retardation-58

Introduction

The genetic counseling of intellectual disabilities (ID) is very complicated as variety of genetics and environmental factors can be involved in etiology of the disease. Chromosomal aneuploidies, copy number variations (CNVs), unbalanced translocations, single gene defects, microdeletion and microduplication syndromes are the well-known genetic causes of ID9 while pregnancy's teratogens including infections, ray and chemical exposure can resulted in mental retarded babies [1,2]. These indicated that precise genetic counseling is urgent in such cases. Variety of genes has been reported for non-syndromic MR which is mostly connected to neural cell differentiation, proliferation and attachment [3,4]. Meanwhile, development of next generation sequencing facilitates the discovery of novel candidate genes in heterogeneous conditions like mental retardation [5,6]. Recently, Glissen et al. reported 528 confirmed- and 628 candidate-genes for intellectual disability using deep genome sequencing [7].

In this study, an Iranian non-syndromic mental retarded case who was excluded for syndromic ID was subjected for whole exome sequencing and pathogenic variant was found in *ELP2* gene. The candidate variation is a third report of *ELP2* mutations in MR cases.

Material and Methods

Here, we report a consanguineous Iranian family having 2-year-old boy who presented progressive postneonatal growth failure, small head, hypotonia and low-set ears (Figures 1 and 2). MR examination of the brain was performed, utilizing axial T1, T2 and FLAIR sequenced. The examination was supplemented with sagittal T1 and coronal T2 weight sequence. The periventricular T2 high signal intensity is seen can be myelination process considering patient age follow up imaging is recommended. Mild supratentorial ventriculomegaly was observed. The 4th ventricle is medline. There is no evidence of midline shift or mass effect.

There is no evidence of acute intraparanchymal hemorrhage no significant extra-axial collections are noted flow voids are maintained within the internal carotid arteries bilaterally as well as within the vertebrobasilar system. The cortex and white matter show normal signal intensity. No abnormalities are seen ganglia or thalamus. The brain stem and cerebellum show no abnormal signal intensity. The sella, pituitary gland and grossly were normal. The CPA areas appear normal. The visualized paranasal sinuses and mastoid air cells are well developed, and orbital contents are unremarkable. There were findings compatible with generalized poly neuropathy. These included with all CMAPS are mildly low amplitude. All SNAPs were uncontainable. Waves were normal. Needle exam was unremarkable. Motor Nerve Conduction assay has been illustrated in Table 1.

Metabolic disorders were excluded by specialist physician and the proband was referred to our lab for genetic counseling. The karyotype was normal, and no history of MR was previously observed in the family, so the case was subjected for whole exome sequencing. 5 mL of peripheral blood was collected from index patient and all the informative family members in EDTA-containing tube. Genomic DNA was extracted using salting out methods. The index genomic DNA was sent to Macrogen (Macrogen, South Korea) for whole

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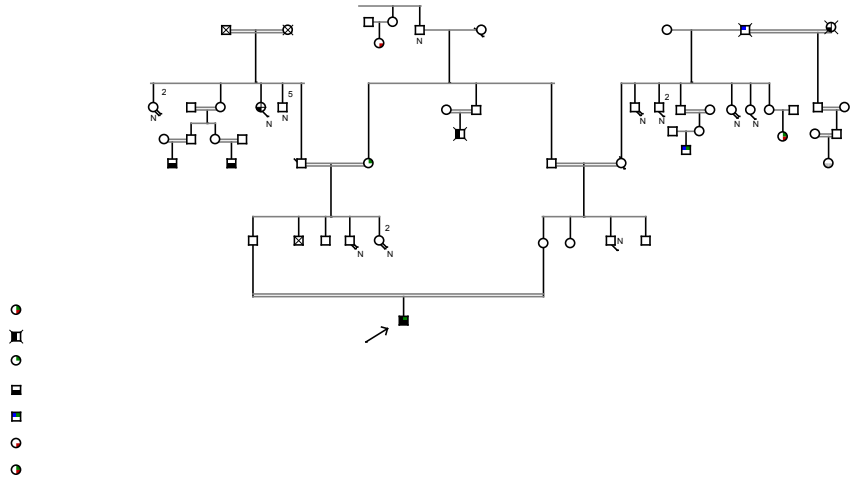

Figure 1: Molecular analysis of a consanguinity pedigree with symptom of mental retardation. Proband was homozygous of ELP2 c.2429 G>A. Father and mother were carrier of this mutation).

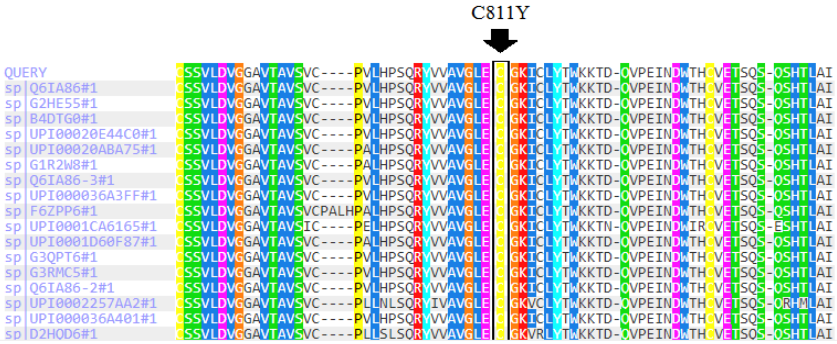

Figure 2: Protein sequence alignment of ELP2 protein from different organisms confirmed that the Cysteine 811 is a conserved amino acid. Shown are 75 amino acids surrounding the mutation position (marked with a black box). Data has been recruited from PolyPhen-2 analysis of the mutation.

Site	Lat.	Dur.	AMP	Area	Segment	Distance	interval	NCV
Tibial Right								
Ankle	2.2 ms	4.2 ms	4.2 mV	9.6 mV	*Ankle		2.2 ms	44.6 m/s
Popliteal	5.0 ms	4.7 ms	3.2 mV	8.9 mV	Ankle-popliteal	125 mm	2.8 ms	
Peroneal Right								
Ankle	1.8 ms	3.5 ms	1.5 ms	2.9 mV	*Ankle		1.8 ms	48.0 m/s
Head of fibula	4.3 ms	3.7 ms	1.3 mV	2.9 mV	Ankle –head of fibula	120 mm	2.5 ms	
					Head of fibula- popliteal			
Median					**Right**			
Wrist	1.7 ms	3.9 ms	1.1 mV	2.1 mV	*Wrist		1.7 ms	47.9 m/s
Elbow	3.6 ms	4.6 ms	1.2 mV	2.8 mV	Wrist-elbow	90 mm	1.9 ms	
					Elbow -axilla			
Ulnar Right								
Wrist	1.7 ms	2.6 ms	2.0 mV	2.0 mV	*Wrist		1.7 ms	42.2 m/s
Elbow	3.2 ms	2.7 ms	2.0 mV	2.0 mV	Wrist-elbow	65 mm	1.5 ms	
					Elbow-axilla			

Table 1: Motor nerve conduction study.

exome sequencing (WES). The reported nucleotide changes were then filtered, and candidate variant pathogenicity was considered by *in silico* softwares including mutation taster and PolyPhen. The candidate variant was then confirmed through PCR-sequencing using the specific primers (Table 1). The inheritance of the mutation was traced among other family members.

Results

The WES reveals 96252 variants in coverage of 95X. After filtering the data, we found that the proband is a homozygous for *ELP2* c.2429G>A (C811Y) on chromosome 18. The change was a missense mutation in which a codon sequence of Cysteine 811(TGT) replaced with codon sequence of amino acid Tyrosine (TAT).

Primer	Sequence	PCR product
ELP2- Forward primer	5´-AGGAATGGGGCTCAAAGATT -3´	582 bp
ELP2- Reverse primer	5´-CAAAGTGGTAGACACGACGAA -3´	

Table 2: Primer sequence and amplicon size of *ELP2* candidate variants.

Software	Prediction
Mutation Taster	Disease causing
PolyPhen-2	Probably damaging

Table 3: *In silico* analysis of *ELP2* c.2429 G>A.

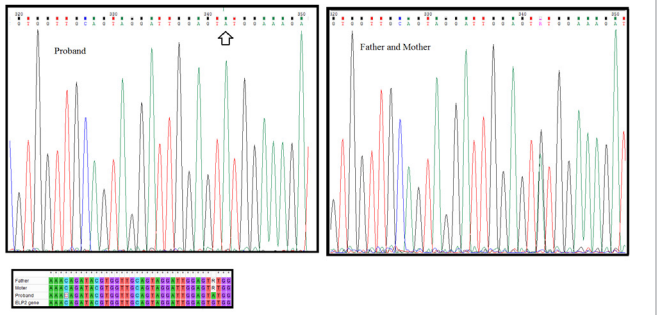

Figure 3: Sanger sequencing confirmed the c.2429 A>G in the pedigree.

In silico analysis confirmed the mutation is pathogenic and occurred in conserved domain of *ELP2* protein of different species (Tables 2 and 3). In addition, the mutation was novel and was not previously reported in 1000G, dbSNP or literatures before. We also found the parents were carrier of the mutation showing the autosomal recessive form of the MR in this pedigree (Figure 3).

Discussion and Conclusion

Here, we present a novel mutation of *ELP2* in Iranian child suffering from non-syndromic mental retardation using WES analysis. The mutation was predicted as pathogenic and resulted in substitution of amino acid cysteine 811 with amino acid tyrosine (*ELP2*: CD 811: TGT>TAT). The parents were the obligate carriers of the mutation which was consistent with autosomal recessive form of MR. The *ELP2* gene (also known as *MRT-58*) was located on 18q12.2 and encodes the core subunit of histone acetyltransferase complex that associates with RNA polymerase II [8]. It has also found that the *ELP2* can modulate the transcription elongation and chromatin remodeling through acetylation of H3 and H4 [8,9]. Mutations in subunits of elongator complex (*ELp1-ELp6*) resulted in a series of neurodevelopmental disorders [10]. Apart from *ELP1* and *ELP4* which are responsible for familiar dysautonomia and rolandic epilepsy, respectively [11,12], *ELP2* reported as a novel cause of autosomal recessive mental retardation-58 (*MRT58*; OMIM: 617270) [9]. In 2011, by means of deep sequencing, Najmabadi et al. introduced 50 novel genes connected to autosomal recessive intellectual disability among which *ELP2: R462L* and *T555P* was reported as two pathogenic variants in Iranian and Lebanese ID cases [9]. Although there are only two studies showing the involvement of *ELP2* in intellectual disability, our study has reported the third one (CD811: TGT>TAT) in the world. Of note, all of these mutations were reported in Iranian family showing the probable role of *ELP2* variants in this population.

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Conflict of Interest

The authors declare no conflict of interest for this manuscript.

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