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Two male patients from an extended seven generation Turkish family diagnosed with Renpenning syndrome: identifying the causative mutation and review of the literature

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ABSTRACT

Intellectual disability (ID) is a lifelong condition that begins during the developmental period, and characterized by significant limitations in intellectual functioning and adaptive behavior including social, conceptual and practical skills. In these case series, we aimed to identify the genetic etiopathogenesis of two male patients with ID from a seven-generation large-Turkish family. Two affected boys with syndromic ID were evaluated. Genome-wide auto zygosity mapping was performed on affected individuals and other available healthy family members for identifying shared chromosomal segments between affected individuals. Critical region co-segregating with the disease was confirmed and narrowed down by short tandem repeat polymorphism markers. Whole exome sequencing was performed to identify the responsible genes and mutations. Sanger sequencing was performed for segregation analysis. We performed a comprehensive genetic analysis to reveal the underlying genetic aetiology of the patients and identified a mutation on *PQBP1* gene (NM_005710.2:c.459-462delAGAG) that is associated with Renpenning syndrome. Considering the clinical findings and genetic data of the affected probands, the patients were diagnosed with Renpenning syndrome and this is the first report for Renpenning syndrome with attention deficit and hyperactivity disorder comorbidity.

Keywords: Renpenning syndrome, PQBP1, intellectual disability, microcephaly

Intellectual disability (ID) is a lifelong condition beginning during the developmental period, and characterized by significant limitations in intellectual functioning and adaptive behavior (DSM-V). There are tremendous genetic heterogeneity for ID caused by single-gene mutations [1]. It is estimated that approximately more than 2 000 genes of the genome can be associated with ID [2]. IDs are more frequent in males than females and that X-linked gene defects have major roles in the aetiology of X-linked IDs (XLID) [3].

Renpenning syndrome (OMIM #309500) is an XLID syndrome characterized by ID ranging from mild to severe. These patients have a variety of phenotypic abnormalities including microcephaly, short stature, small testes and facial dysmorphisms includ-

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ing tall narrow facies, nasal anomalies, short philtrum and cupped ears [4-6]. Almost all of the patients are male but recently a female proband has been reported by Raymond *et al*. [7] due to complete skewing of the X chromosome inactivation.

In these case series, we aimed to identify the genetic etiopathogenesis of two male patients that belong to a seven-generation extended Turkish family. The probands had syndromic ID (S-ID) with mild dysmorphic findings. Since S-ID is a very heterogeneous syndrome in terms of both phenotype and genotype we aimed to perform genome-wide autozygosity mapping to map and identify all shared chromosomal segments. Then, in order to identify the causative mutant gene that shared between affected probands we performed whole exome sequencing (WES). We herein review and discuss the findings in view of the literature.

CASES PRESENTATION

Patients

Two affected individuals of a large Turkish family with S-ID were evaluated (Fig. 1). The study protocol was approved by the Ethics Committee of Karadeniz Technical University, Faculty of Medicine (approval

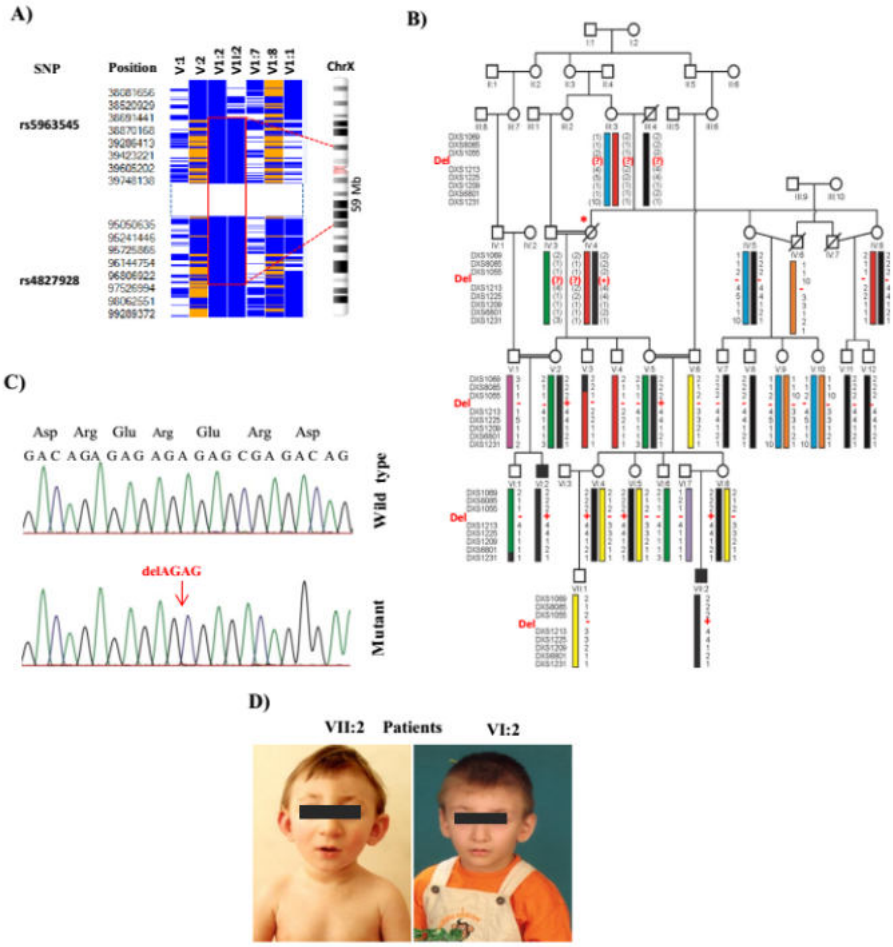

Fig. 1. Genome-wide autozygosity mapping and haplotype analysis. (A) Schematic representation of the genome-wide homozygosity mapping data. Homozygous genotypes identical to the genotype data obtained from the affected individuals VI:2 and VII:2 are shown in blue, non-homozygous genotypes are shown in white and heterozygous genotypes appear in orange. A single homozygote segment, which is marked as a vertical rectangle, is approximately 55 Mb in size. SNPs correspond to borders of a hemizygous segment, are marked as horizontal rectangle and shown on the left side of the image. The location of the homozygote segment on the X chromosome ideogram is shown on the right side of the image. (B) Pedigree and haplotype analysis of critical chromosomal region with selected STR markers on X chromosome shown at the left side of the pedigree. The mutation segregation is shown in red. The mutant delAGAG allele was originated from the IV:4 female subject as de novo and inherited to her descents (red star). (C) Wild type and mutant allele Sanger sequencing chromatogram. The mutation region is shown in red. (D) Two patients' photographs.

number: 2013/73). An informed consent was obtained from the guardians of the patients for publication.

DNA Isolation, PCR Reactions and Sanger Sequencing

Genomic DNA isolation was performed from peripheral blood of patients and controls by using standard protocol (salting-out). All PCR primers were designated by primer3 program [8]. Sanger sequencing was performed on ABI 3130 platform by using

Table 1. Clinical findings of both patients in the family

General	Features	Patient VII:2	Patient VI:2
Age	Year of birth	2010	2003
	Age at diagnosis	1	8
Physical	Height	73 cm (10p)	120 cm (10p)
	Head circumference	41.5 cm (<3p) -3.81SD	47.4 cm (<3p) -4SD
Dysmorphic findings	Long face	+	-
	Triangular face	+	+
	Micrognathia / Mandibular prognathia	≠	+ / -
	Large cupped ears	+	+
	Prominent nasal bridge	-	-
	Wide nasal bridge	+	+
	Cleft Palate / Lip	- / -	- / -
	High Palate	+	+
	Thin upper lip	-	+
	Thin hair	*	+
	Laterally sparse eyebrows	+	+
Genital anomalies	Small testis	-	Unspecified
Skeletal system findings	Clinodactyly of the 5th fingers	-	-
	Camptodactyly	-	-
	Scoliosis	-	-
	Talipes equinovarus (TEV)	-	+ (Orthosis treatment)
Neurological findings	Global developmental delay	+	+
	Intellectual disability / IQ	? / Unspecified	+ / Mild (IQ=50)
	Hyperreflexia	-	Unspecified
	Spasticity	-	Unspecified
	MRI	-	The third, fourth and lateral ventricular enlargement
	EEG	-	+ (normal)
	Seizures	-	-
Psychiatric findings	Autistic features	?	-
	Attention deficit hyperactivity disorder (ADHD)	-	+
	Emotional lability	-	+

≠Lower jaw growth continues until the age of 4.

*Permanent terminal hair occurs after 2 years of age.

?These diagnoses cannot be done at this age.

BigDye™ Terminator v3.1 Cycle Sequencing Kit according to manufacturer's protocol.

Genome-Wide Autozygosity Mapping and Whole Exome Sequencing

Genome-wide autozygosity mapping was carried out by using Illumina HumanCytoSNP-12 v2.1® platform. To identify the disease segregating genomic segments between affected families, raw data of the Illumina Iscan® platform was transferred to the VIGENOS (Visual Genome Studio, Hemosoft, Ankara) program which facilitates visualization of the large quantity of genomic data in comprehensible visual screens. WES performed by the Illumina HiSeq® platform. Reads were aligned to human genome reference consortium build 37 (GRCh37/hg19) and subsequently, the WES analysis pipeline was performed according to Genome Analysis Toolkit (GATK) best practices [9]. Sanger sequencing was used to confirm the presence of the identified mutation in affected individuals and to perform segregation analysis.

Clinical Findings

We studied a seven-generation Turkish family in which two affected males (VI:2 and VII:2) were born with S-ID from consanguineous parents (Figs. 1A and 1B). Common shared clinical findings in both patients include microcephaly, triangular face, highly arched palate, beaked nose, cupped ears, laterally sparse eyebrows and developmental delay (Table 1).

Case 1 (VII)

He was first evaluated by child neurology due to developmental delay and dysmorphic findings. Because the age of the proband is under of two psychiatric evaluations was not conducted.

Case 2 (VI)

He was first evaluated by child psychiatry and child neurology with speech delay at the age of 3 and referred to special education due to developmental delay. During the follow-up, the patient had complaints of restlessness, not paying attention to the course and irritability and diagnosed with attention deficit and hyperactivity disorder (ADHD), comorbid oppositional and defiant disorder based on DSM-IV-based disruptive behavioral disorders screening and evaluation scale [10]. The form was completed by the patient's caregivers and teachers. The clinical interview was completed by a child-adolescent psychiatrist.

Genome-Wide Autozygosity Mapping

Critical region co-segregating with the disease was confirmed and narrowed down by short tandem repeat polymorphism markers genotyping on the X chromosome of two affected individuals and their family members because the pedigree of the family was consistent with the X-chromosomal inheritance pattern of the disease (Figs. 1A and 1B), and narrowed the disease co-segregating region to a 55 Mb region. But, unexpectedly we saw that the critical region on X-chromosome was shared with unaffected male family members (Fig. 1B). Thus, we decided to perform WES as trio (VI:7, VI:8, and VII:2).

Whole Exome Sequencing

We found a four base-pair deletion mutation on polyglutamine-binding protein 1 (PQBP1) (NM_005710.2:c.459-462delAGAG;p.(Arg153SerfsX41)) gene (generally known as delAGAG). This gene and mentioned mutation were associated with Renpenning syndrome, before [11].

Confirming Mutation and Performing Mutant Allele Segregation Analysis

This finding was verified by Sanger sequencing and it was shown that this particular mutation was present exclusively in affected individuals and in their obligate carrier mothers (V:2, VI:8) and sisters (V1:4, V1:5, and V:5). We also performed mutant PQBP1 allele segregation analysis on all available family members by Sanger sequencing (Figs. 1B and 1C). When we analyzed the pedigree, shared haplotypes and mutation segregation we saw that the mutant delAGAG allele was originated from the IV:4 female subject as de novo and inherited to her descents. The sisters of the female subject of the IV:4 (those are IV:5 and IV:8) and their progeny did not have the mutant delAGAG allele (Fig. 1B).

DISCUSSION

Renpenning syndrome is an ultra-rare (estimated incidence < 1:1 000 000) [12] subgroup of XLID and is characterized by a variety of phenotypic findings in-

Table 2. Comparison of clinical findings in reported families with Renpenning syndrome

Findings	Renpenning *et al.* [11]	Golabi *et al.* [24]	Sutherland *et al.* [25]	Porteous *et al.* [4]	Hamel *et al.* [26]	Lenski *et al.* [27]	MRX55 [4]	Family N9 [4]	Family N45 [4]	Stevenson et al.[4]	Present study	Total
Ancestry	Dutch	?	English	Scottish	Dutch?	?	Moroccan	Dutch	Dutch	?	Turkish	
Affected males	20	3	8	6	4	2	3	3	3	4	2	58
Short stature < 3rd centile	6/10	3/3	5/8	1/2	1/1	1/1	1/1	2/3	1/3	0/4	0/2	21/38 (55%)
Head circumference < 3rd centile	13/14	3/3	7/8	0/2	4/4	2/2	0/1	3/3	3/3	3/4	2/2	40/46 **(86%)**
Long/Triangular face	0/6	3/3	2/8	2/2	2/2	1/1	1/1	2/2	3/3	3/4	2/2	21/34 (61%)
Mandibular prognathia	2/4	-	2/8	1/2	1/2	0/2	-	1/3	2/3	0/4	0/2	9/30 (30%)
Large ears	1/10	-	1/8	1/2	-	-	-	0/3	0/3	1/4	2/2	6/30 (20%)
Cupped ears	0/5	3/3	-	1/2	3/3	-	-	1/3	1/3	4/4	2/2	15/25 (60%)
Dystopia canthorum / Wide nasal bridge	0/5	2/3	-	0/2	-	-	-	-	-	0/4	2/2	4/16 (25%)
Cleft Palate	0/20	0/3	0/8	0/2	2/4	0/2	-	2/3	0/3	1/4	0/2	5/51 (9 %)
High Palate	0/5	-	0/8	0/2	1/4	-	-	3/3	3/3	0/4	2/2	9/31 (29%)
Thin upper lip/Short philtrum	5/5	-	-	1/2	2/2	1/1	1/1	2/2	2/3	0/4	1/2	15/22 **(68%)**
Thin/ brittle hair	0/5	2/3	-	0/2	0/2	-	-	0/3	0/3	0/4	1/2	3/24 (12%)
Small testis	4/9	0/2	4/5	0/2	0/1	-	-	0/3	0/3	2/3	-	10/28 (35%)
Clinodactyly of the 5th fingers	-	-	0/8	0/2	2/2	-	-	0/3	0/3	0/4	0/2	2/24 / (8%)
Global developmental delay	20/20	3/3	5/8	6/6	3/3	2/2	3/3	3/3	3/3	4/4	2/2	54/57 **(94%)**
Intellectual disability / Mild (IQ 50-70)	1/14	0/1	1/8	6/6	0/3	0/2	-	0/2	0/3	0/2	1/2	9/43 (20%)
Spasticity	0/5	3/3	6/8	0/6	3/3	1/1	-	0/3	0/3	0/4	-	13/33 (36%)
Seizures	3/20	1/2	0/8	0/2	-	1/2	-	0/3	0/3	0/4	0/2	5/46 (10%)
Attention deficit hyperactivity disorder (ADHD)	-	-	-	-	-	-	-	-	-	-	1/2	-

cluding microcephaly, short stature, dysmorphic facies, lean body, small testes, and a varying degree of ID [4, 11-14]. It is stated that in this syndrome, as being for most genetic syndromes, phenotypic variability is the rule rather than the exception [4]. Thus, in accordance with this already reported phenotypic variability, our patients with Renpenning syndrome shared some common findings as microcephaly, triangular face, large cupped ears and IDs while some of their clinical findings were discordant (Tables 1 and 2). Our literature reviews about clinical findings of reported patients with Renpenning syndrome are summarized in Table 2. Accordingly the most common clinical findings are global developmental delay (94%), microcephaly (86%) and thin upper lip/short philtrum (68%), respectively.

The *PQBP1* gene contains nine transcripts and two conserved coding sequences (CCDS) (Fig. 2A). The delAGAG mutation leads to a premature stop codon, resulting in a truncated version of the protein that partially lacks proline rich domain (PRD) and completely lacks nuclear localization sequence (NLS) and carboxy terminal domain (CTD) domains of the *PQBP1* protein (Figs. 2B and 2C).

Musante *et al*. [15] showed that in their patient-derived cells, the mRNAs carrying indel mutations

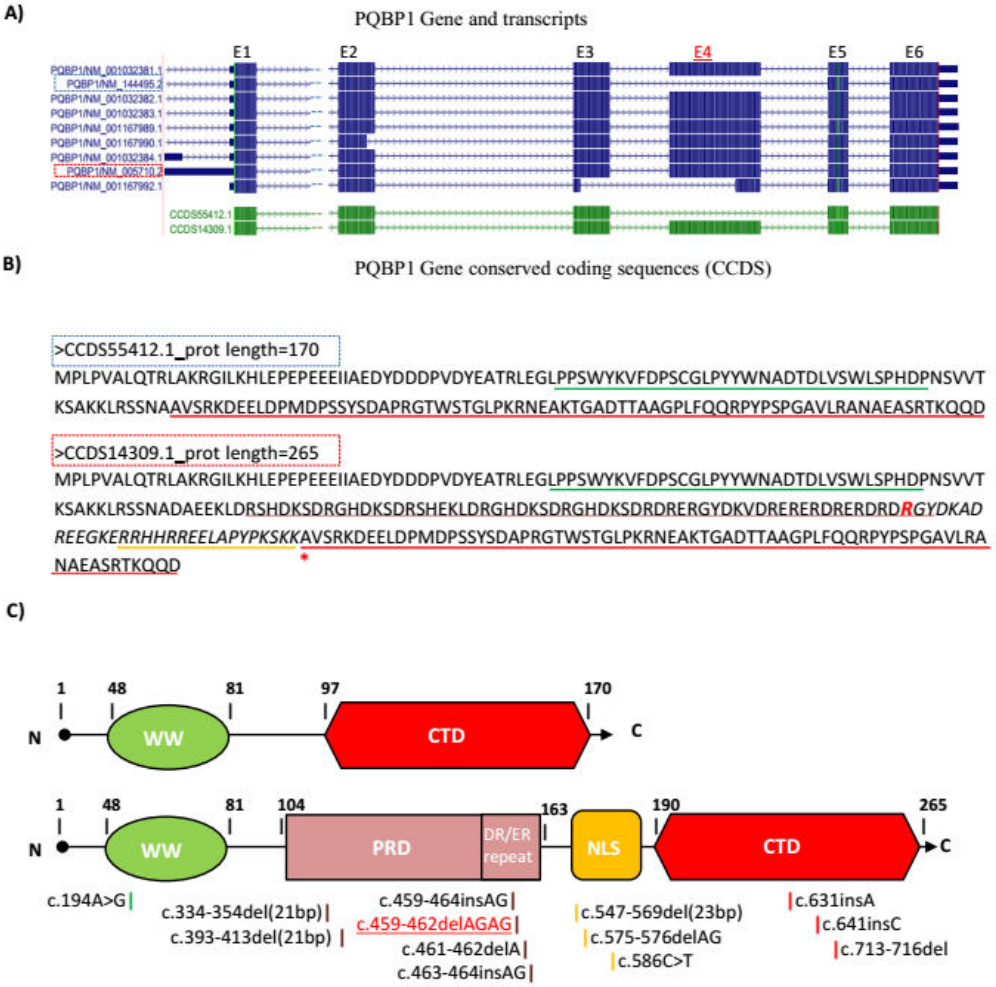

Fig. 2. The gene model, transcripts, reported mutations, and protein products of the PQBP1 gene. (A) A UCSC genome browser screenshot of the PQBP1gene and transcripts. Horizontal blue rectangles and the E symbol upside of the rectangles show exons and exon numbers, respectively. Horizontal green rectangles show conserved coding sequences. The delAGAG mutation localized exon (E4) is depicted as red. The blue and red dotted rectangles show the 19 kDa and 37 kDa protein-coding transcripts of the PQBP1gene, respectively. (B) Protein amino acid sequences of the two conserved coding sequences. Corresponding amino acid sequences to PQBP1 protein domains are underlined with colors as depicted in C, and the effect of delAGAG mutation on amino acid sequences depicted as italic. The star symbol at the bottom of Alanine (A) depicts the stop codon position. (C) Schematic drawing of domains of the PQBP1 protein. All available reported mutations causing Renpenning syndrome is shown at the bottom of the corresponding domains. Our mutation was shown as red. PRD = Proline rich domain, NLS = Nuclear localization sequence, CTD = Carboxy terminal domain, WW: WW domain.

that cause premature stop codon on the PRD domain including delAGAG, incur nonsense mediated decay (NMD) and result in decreased expressions of the mutant mRNAs and associated protein truncated variants. Further, they showed the existence of the 19 kDa protein isoform (Figs. 2B and 2C), which is an unaffected product from delAGAG and other indel mutations located on PRD/NLS domains, in control and in patient-derived cells. Many functional studies were done in relation to microcephaly and ID causes of these mutations on *PQBP1* to date. One of these showed that indel mutant forms of the protein (delAG and delAGAG) binds to Fragile X-mental retardation protein (FMRP) by a gain-of-function pathogenic mechanism and promotes its degradation [16]. Because FMRP is an important regulator of homeostatic synaptic scaling, dysregulated FMRP degradation might cause disruption of neuronal development that leads to intellectual disability. In addition, *PQBP1* regulates nuclear events such as splicing and gene transcription [17, 18].

To our knowledge present study is the second report for Renpenning syndrome from Turkey. Kurt Colak *et al*. [19] reported recently a patient they suspected of having Renpenning syndrome, but in addition, they also suspected from the *PACS1* related Schuurs-Hoeijmakers syndrome for their reported patient. Their reported second de novo mutation on the PACS1 gene (c.640C>T; p.(Arg214Trp)) is a well-known and published disease-causing mutation in medical literature for Schuurs-Hoeijmakers syndrome [20-23]. De novo *PACS1* pathogenic variant and phenotypic findings were thought to be compatible with Schuurs-Hoeijmakers. There was no phenotype in favor of blended phenotype and/or dual diagnosis, and can be regarded genotypically as pathogenic variant *PACS1*.

CONCLUSION

In this study, we have performed a comprehensive genetic analysis to reveal the underlying genetic etiology of two male patients from a large extended Turkish family and identified that the responsible mutation is a known delAGAG on the *PQBP1* gene and patients are affected from Renpenning syndrome. It is clear from the functional studies mentioned above that the delAGAG mutation results in truncated protein and causes Renpenning syndrome. In addition, it is worth analyzing further the cellular function of the 19 kDa protein isoform of the *PQBP1* gene and its effect on heterogeneity and clinical severity of the Renpenning syndrome.

Authors' Contribution

Study Conception: BT; Study Design: HK, EK; Supervision: HK, EK; Funding: EK; Materials: SÇB, HK, EK; Data Collection and/or Processing: BT, HK, EK; Statistical Analysis and/or Data Interpretation: BT, TD, GYB; Literature Review: BT; Manuscript Preparation: BT and Critical Review: TD, HK, EK.

Informed Consent

Written informed consent was obtained from the families of the patients for publication of these cases and any accompanying images or data.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Accession number: This variant was submitted to LOVD database; variant ID: 0000712203

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