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Novel *TEAD1* gene variant in a Serbian family with Sveinsson's chorioretinal atrophy

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ABSTRACT

Sveinsson's chorioretinal atrophy (SCRA) or helicoidal peripapillary chorioretinal degeneration (HPCD) as previously referred, is a rare ocular disease with autosomal dominant pattern of inheritance. The vast majority of reported cases were of Icelandic origin but the characteristic clinical picture of SCRA was also described in patients of non-Icelandic descent. Here, we report a novel disease-causing variant c.1261T>A, p.Tyr421Asn in *TEAD1*, detected in a Serbian family from Bosnia diagnosed with SCRA. The newly discovered change occurred at the same position as the "Icelandic mutation" (c.1261T>C, p.Tyr421His). According to our findings, this position in the exon 13 of the *TEAD1* gene, at base pair 94, should be considered as a mutation hotspot and a starting point for future genetic analyses of patients with SCRA diagnosis.

Sveinsson's chorioretinal atrophy (SCRA, OMIM#108985, ICD-10-CM Code H31.2, ORPHA:86813), also known as helicoidal peripapillary chorioretinal degeneration (HPCD), is a rare ocular degenerative disease that was first reported in 1939 in Iceland (Sveinsson, 1939). It is characterized by progressive bilateral, well-defined, tongue-shaped strips of atrophic retina and choroid that extend from the optic nerve into the peripheral ocular fundus (Jonasson et al., 2007) with no signs of inflammation (Franceschetti, 1962; Sveinsson, 1979). It is an autosomal dominant disease occurring at an early age, even at birth (Fossdal et al., 2004; Jonasson et al., 2007). HPCD has been described under different names, the first being chorioditis areata, given by Sveinsson who observed the condition in a mother and her son from Iceland (Sveinsson, 1939). Franceschetti (1962) reviewed peripapillary atrophies and classified this Icelandic form as peripapillary chorioretinal degeneration. Later, Sveinsson (1979) reported a four-generation family showing autosomal dominant mode of inheritance with age-related progression of lesions and gave again the old name to the disorder-chorioiditis areata. In 1981, Magnusson described another family with this eye disease from Iceland and called it atrophia areata (Magnusson, 1981). Fossdal et al. reviewed the nomenclature of the disorder and proposed a new name- Sveinsson chorioretinal atrophy (SCRA) (Fossdal et al., 2004).

In 1995, Fossdal and coworkers (Fossdal et al., 1995) mapped the responsible gene for HPCD to 11p15.3. In 2004 the same group reported a missense mutation- Y421H (c.1261T>C, p.Tyr421His) in the TEA domain transcriptional factor 1 (*TEAD1*) gene, carried by all examined patients but not detected in unaffected relatives and controls (Fossdal et al., 2004).

The disorder has mostly been observed in patients with Icelandic heritage (Sveinnsson, 1939, 1979; Franceschetti, 1962; Magnusson, 1981; Fossdal et al., 1995, 2004; Eysteinsson et al., 1998; Jonasson et al., 2007), although there have been isolated reports in other populations as well (Milenkovic et al., 2005; Kumar et al., 2017; Shen et al., 2018).

In 2005, our group reported SCRA in a father, daughter and son

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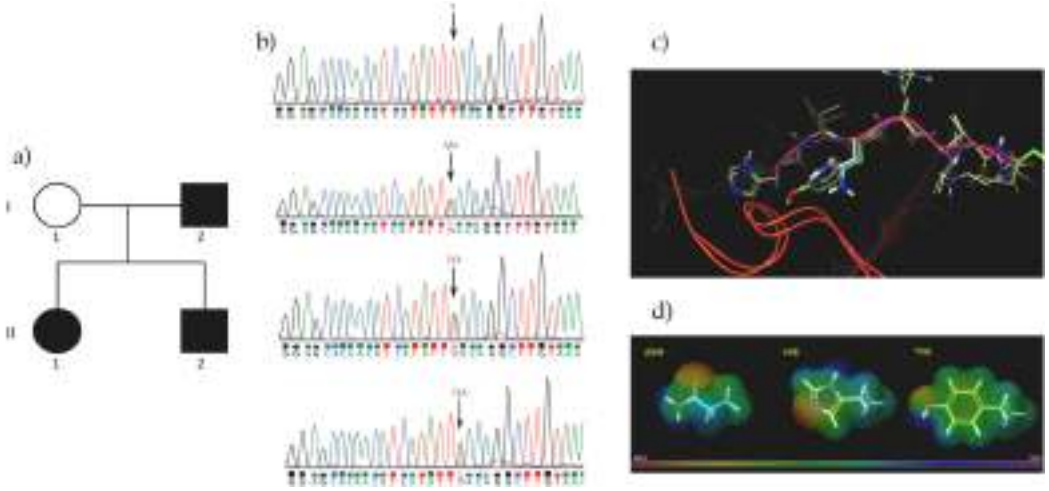

Fig. 1. Summarized findings on "Serbian" Sveinsson's chorioretinal atrophy: a) family pedigree; b) DNA sequences of the wild type and mutated *TEAD1* gene (all three patients with SCRA were heterozygous); c) superimposed C-terminal part of the crystal structures of human TEAD1 (PDB ID 4RE1, green carbons), TEAD1 Y421H mutant (PDB ID 6HIL, grey carbons) and TEAD1 Y421N mutant model (light blue carbons) at the YAP binding interface; d) size, shape and electrostatic potential mapped to electron density of Asparagine (in Serbian SCRA), Histidine (in Icelandic SCRA) and Tyrosine (in normal protein).

(Milenkovic et al., 2005). While the family was clinically examined and the disease was diagnosed by means of fundus fluorescein angiography, genetic testing has not been done at that time. Hence, the aim of the present study was to analyze the *TEAD1* gene in the affected individuals in this Serbian family from Bosnia and assess whether they were carrier of the "Icelandic mutation".

Three members of the same family (father, daughter and son) with helicoidal chorioretinal degeneration were analyzed. At the time when chorioretinal degeneration was diagnosed in this family, the father was 45, the daughter was 20 and the son was 15 years old. More detailed clinical findings have been previously described (Milenkovic et al., 2005). Signed informed consents for the study were obtained from the patients and all procedures were done in accordance with Helsinki Declaration of 1975.

Genomic DNA was isolated from peripheral blood by GeneJET WholeBlood Genomic DNA Purification Mini Kit (Thermo Fisher Scientific, Vilnius, Lithuania) according to manufacturer's recommendations. PCR was performed with forward 5′-TAACAGGTGGTAACAAACAGGGATA-3′ and reverse 5′-ATGGCAAATGCTCTGTCTCAA-3′ primers previously described (Fossdal et al., 2004) in 25 μL of PCR mixture containing PCR Master Mix (2X) (Thermo Fisher Scientific, Vilnius, Lithuania), 0.25 μM of each primer and 0.2 μg DNA. The presence of PCR products (size of 487bp) was verified on 3% agarose gel, stained with GreenSafe Premium (Nzytech, Lisbon, Portugal) and visualized under UV light. The PCR products were directly sequenced in forward and reverse directions using the ABI Big Dye Terminator chemistry on ABI 3500 instrument (Applied Biosystems, Foster City, CA, USA), with the same primers used for the generation of PCR amplicons (Fossdal et al., 2004). The sequences were analyzed using the Sequencher software (Gene Codes Corporation, Ann Arbor, MI). Sequence variants are numbered according to the reference sequence NM_021961.5/NP_068780.2. Identified sequence changes were confirmed by analyzing each sample in duplicate.

Sequencing of genomic DNA obtained from three cases of SCRA showed a substitution T to A at base pair 94 located in the exon 13 of *TEAD1* gene. This missense variant leads to the substitution of amino acid tyrosine with asparagine at position 421, in the C-terminal domain of TEAD1 transcription factor (ClinVar SCV001442517; NC_000011.10:g.129372002T>A, NM_021961.6:c.1261T>A/NP_068780.2:p.Tyr421Asn). This nucleotide change was in heterozygous state in all three patients.

In 2004, Fossdal and coworkers reported a single nucleotide T to C transition at base pair 94 in the exon 13 (NM_021961.5:c.1261T>C) of *TEAD1* gene that leads to the substitution of tyrosine with histidine at position 421, in the C-terminal domain of the TEA domain protein 1 (TEAD1) (NP_068780.2:p.Tyr421His). This missense mutation, responsible for SCRA was found in heterozygous state in all analyzed patients. All mutation-harboring subjects had Icelandic ancestors and all were members of the same extended pedigree (Fossdal et al., 2004).

Although Milenkovic previously reported a Serbian family from Bosnia with SCRA (Milenkovic et al., 2005), the report lacked genetic analysis. In the meanwhile, this analysis has been performed and it revealed a novel missense variant (NC_ 000011.10:g.12937202T>A, NM_021961.6:c.1261T>A/NP_068780.2:p.Tyr421Asn). Interestingly, the base substitution occurred at exactly the same position as the Icelandic one (Fig. 1). This newly identified allele variant was in heterozygous state too, and, unlike the c.1261T>C, p.Tyr421His, this one led to the replacement of tyrosine with asparagine (p.Tyr421Asn).

The TEA domain family member (TEAD) proteins, also called transcription enhancer factors (TEFs) comprise a conserved family of eukaryotic DNA-binding proteins that regulate the expression of multiple genes (Kaneko et al., 1998). TEAD1 belongs to the family of TEAD proteins (from 1 to 4) that are key transcription factors in the Hippo signaling pathway (Zhao et al., 2008). The Hippo signaling pathway is highly conserved from flies to mammals and has been identified as a critical molecular mechanism for organ size regulation, cellular proliferation, apoptosis and differentiation (Yu et al., 2013). Hippo pathway can be inhibited (hypo-Hippo) and can be hyper activated (hyper--Hippo). The hypo-Hippo has been implicated in some human cancers, pointing to a tumor suppressor function of this pathway (Johnson et al., 2014), while cells with hyper-Hippo have been shown to undergo apoptosis and are eliminated *in vivo*, a phenomenon related to neurodegenerative diseases, ischemia, autoimmune and metabolic diseases (Robertson et al., 2002). TEAD are transcriptional factors that are activated by cofactors YES associated protein (YAP) and Transcriptional coactivator with PDZ-binding motif (TAZ) in mammals. It has been shown that the interaction between YAP/TAZ and TEAD is essential for the maintenance and differentiation of retinal pigment in zebrafish (Miesfeld et al., 2015).

Both described genetic variants occur in the sequence encoding the C-terminal domain of TEAD1 protein, which is crucial for its interaction with co-factors YAP and TAZ (Kitagawa, 2007). Icelandic allele variant disrupts the interaction of TEAD1 and YAP/TAZ and blocks its transcriptional activity (Wu et al., 2008; Zhao et al., 2008). The histidine

residue adopts a different conformation at the binding surface compared to tyrosine residue (Bokhovchuk et al., 2019). The effect of the mutation found in the present study on protein function was assessed using the PredictSNP server (Bendl et al., 2014). It was shown that Tyr146Asn had a deleterious consequence on the TEAD1 protein activity with a confidence score of 0.87. The differences in size, shape, molecular properties and distribution of electrostatic potential of Tyr, His and Asn are evident (Fig. 1), *In silico* prediction of the TEAD1 protein structure using Jaguar from Schrödinger Suite Release (https://www.schrodinger.com/products/jaguar) point to altered interactions on binding interface in the mutated protein isoform compared to normal. In other words, the Serbian variant that introduces asparagine instead of tyrosine at position 421 in the protein also leads to YAP/TAZ:TEAD1 complex instability, corroborating the view that this position is a "hot spot" at the TEAD1 binding surface (Bokhovchuk et al., 2019). All genotyped individuals with SCRA diagnosis were heterozygous, i.e. the homozygous state for this change has never been detected. The variant in homozygous state could be lethal for humans, which would be in agreement with the importance of Hippo pathway in early development in mammals.

The *TEAD1* gene, according to Genome Aggregation Database v2.1.1., (https://gnomad.broadinstitute.org/gene/ENSG00000187079?dataset=gnomad_r2_1) (Jaguar, 2018), shows over 700 variants in the 5′ untranslated region (5′UTR), splice regions, introns, exomes and 3′UTR. Three variants were considered as benign/likely benign and 9 as with uncertain clinical significance. After excluding 3′UTR, introns and flagged variants, 184 were missense mutations, 103 were synonymous, 46 were in the 5′UTR, and 34 were in the splice region, and only one variant was loss of function, i.e. frameshift mutation.

Independently, Schrauwen and colleagues described a *de novo* nonsense mutation in *TEAD1* (Chr11: 12904591G>A; NM_021961.5: c.618G>A; NP_068780.2:p.Trp206Ter) that leads to TEAD1 protein truncation and its complete loss of function. This nonsense nucleotide substitution causes non-X-linked Aicardi Syndrome (AIC), a congenital neurodevelopmental disorder characterized by agenesis of the corpus callosum and chorioretinal lacunae (Schrauwen et al., 2015). It appears that nonsense (p.Trp206Ter) and missense nucleotide changes (Icelandic and Serbian) in *TEAD1* gene lead to different chorioretinal complications, with or without additional symptoms. These findings also point to the importance of TEAD1 in eye and vision function.

The present study strongly supports the view that Sveinsson's chorioretinal atrophy (SCRA) is not solely associated with Icelandic heritage. In addition, the base pair 94 located in the exon 13 of *TEAD1* gene should be considered as a mutation hotspot and a starting point for future genetic analyses of patients with clinical diagnosis of SCRA.

Declaration of competing interest

The authors declare no conflicts of interest.

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