Original Article

A Homozygous Nonsense Variant in *UVSSA* Causes UV-sensitive Syndrome from Very Large Kindred: The First Report from Iran

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Abstract

Background: Recessive disruptive mutations in nucleotide excision repair genes are responsible for a wide range of cutaneous photosensitivity and, in some cases, are associated with multi-system involvement. The heterogeneous nature of these conditions makes next-generation sequencing the method of choice to detect disease-causing variants.

Materials and Methods: A patient from a large multiplex inbred Iranian kindred with several individuals suffering from skin sun-sensitive manifestations underwent complete clinical and molecular evaluations. Whole exome sequencing (WES) was performed on the genomic sample of the proband, followed by bioinformatics analysis. Subsequently, co-segregation of the candidate variant with the condition was performed by Sanger sequencing.

Results: A rare homozygous nonsense variant, c.1040G>A (p. Trp347*), was identified in the *UVSSA* gene, resulting in UV-sensitive syndrome (UV^{S}S) complementation group A. The global minor allele frequency of the variant is < 0.001 in population databases. Tryptophan 347 residue is conserved among mammalians and vertebrates, and the null variant is believed to lead to a truncated protein with cellular mislocalization.

Conclusions: Here, we report the first genetic diagnosis of UV^{S}S-A in Iran via the successful application of Next-generation sequencing, which expands our understanding of the molecular pathogenesis of this condition.

Keywords: Human UVSSA protein, Iran, nonsense codon, nucleotide excision repair, UV-sensitive syndrome, whole exome sequencing

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Introduction

Nucleotide excision repair (NER) is a DNA repair mechanism that removes bulky DNA lesions resulting from thymine dimers or chemical adducts. NER operates via two pathways: global genome repair that repairs DNA lesions throughout the genome and transcription-coupled repair (TC-NER) in actively transcribed genes. Recessive loss-of-function mutations in the genes involved in these repair pathways cause a broad spectrum of cutaneous solar photosensitivity, a common symptom in all patients. It is often associated with multiple developmental anomalies.[1]

Cutaneous photosensitivity is a rare pathologic condition encompassing clinically and genetically heterogeneous disorders with or without the involvement of other body organs, including Xeroderma pigmentosum (XP), Cockayne syndrome (CS), and trichothiodystrophy. Autosomal recessive UV-sensitive syndrome (UV^{S}S) is the only subtype of the CS spectrum in which

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patients experience only sun exposure phenotypes, including freckles, sunburn, and telangiectasia, without an increased risk of skin tumors and developmental delay.[2] There are three complementation groups for UV^{S}S named UV^{S}S/CS-A, UV^{S}S/CS-B, and UV^{S}S-A (also known as UVSS3) which are caused by mutations in excision repair cross complementation 8 (*ERCC8,* also known as *CSA*), excision repair cross complementation 6 (*ERCC6,* also known as *CSB*), and UV-stimulated scaffold protein A (*UVSSA*) genes respectively.[3] Mutations in the first two genes could cause CS and UV^{S}S, whereas *UVSSA* gene mutations are only responsible for UV^{S}S complementation group A.[1,3,4]

Next-generation sequencing (NGS) as a high-throughput sequencing method provides the opportunity to uncover known and novel disease-associated genes in genetically heterogeneous disorders.[5] Here we report the successful application of whole-exome sequencing (WES) to identify a rare pathogenic nonsense variant in large inbred kindred with several individuals affected by cutaneous photosensitivity from the northeast of Iran.

Materials and Methods

Subjects and clinical examinations

A ten-year-old boy with UV-sensitivity and skin lesions from a large multiplex inbred pedigree with several affected individuals with the same condition from Makhunik, an isolated far-reaching small village from northeast Iran in the South Khorasan province, was referred to us for genetic testing and diagnosis [Figure 1]. Following informed written consent, family history, pedigree analysis, and clinical evaluations were performed. Subsequently, 5 ml of venous blood was obtained in EDTA-containing tubes from the patient.

WES, bioinformatics analysis, and validation

Genomic DNA was extracted from peripheral lymphocytes using the standard phenol-chloroform procedure. Qualitative and quantitative assessment of DNA was performed by 1% agarose gel and a NanoSpece Cube biophotometer (Nanolytik®, Dusseldorf, Germany), respectively.

The genomic DNA of the proband was subjected to WES with a mean depth of coverage of 100X for more than 92% of sequenced regions. In summary, 1.0 µg of genomic DNA was fragmented by the hydrodynamic shearing system (Covaris, Massachusetts, USA), and sequencing libraries were generated in a solution-phase using Agilent SureSelect Human All Exon kit (Agilent Technologies, CA, USA) according to manufacturer's instruction. Products were purified using the AMPure XP system (Beckman Coulter, Beverly, USA) and quantified using the Agilent high-sensitivity DNA assay on the

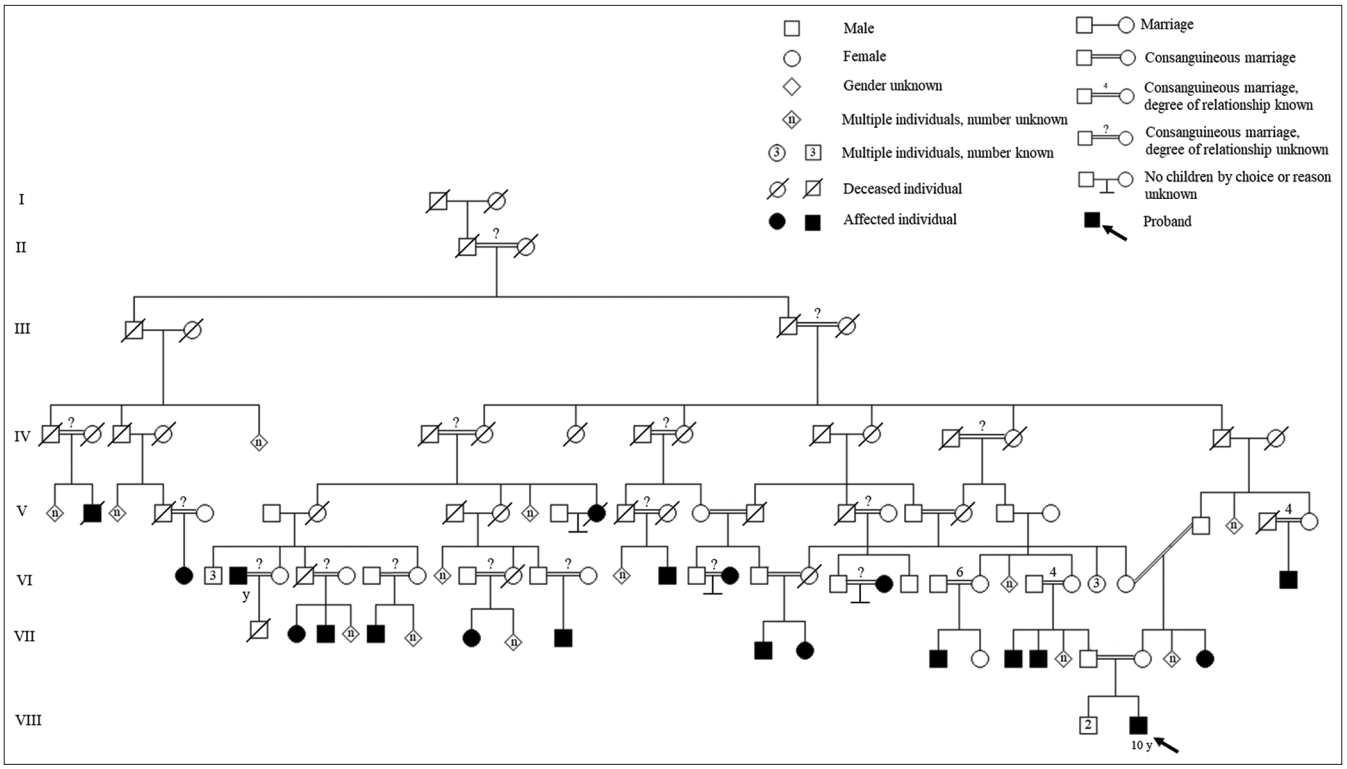

Figure 1: The pedigree of the studied ten-year-old proband from large multiplex inbred Iranian kindred with several individuals suffering from skin sun-sensitive manifestations. Most marriages are consanguineous; however, the degree of relationship was not clear for most marriages for couples who were distant relatives. The degree of relationship is stated above the relationship line if it is not obvious from the pedigree. If couples were distant relatives and the degree of the relationship was unknown, it is stated as "?". The condition affected males and females from 6 to 55 years old. The skin abnormalities were manifested as erythema, face freckles, telangiectasia, dried skin in sun-exposed areas, and no cutaneous tumors. Affected individuals did not have hearing loss, mental and developmental delay, eye abnormalities, and neurological disorders. Pedigree analysis suggests an autosomal recessive pattern of inheritance. The proband with UV-sensitive syndrome (UV^{S}S) complementation group A is marked

Agilent Bioanalyzer 2100 system. High-throughput sequencing was performed on IlluminaHiseq 2000 to generate 101 bp pair-end reads.

Short reads were mapped to the reference genome (hg19, NCBI Build 38) using Burrows-Wheeler Aligner (BWA).[6] Samtools v1.12 and Picard v2.25.6 (https://broadinstitute.github.io/picard) were applied to sort the Binary Alignment Map (BAM) files and mark duplicates, respectively.[7] Variant calling was performed by Genome Analysis Toolkit (GATK) v4.2,[8-10] and variant annotation was accomplished by ANNOVAR.[11] Variant prioritization was based on missense, start codon loss, nonsense, stop loss, splice site, frameshift, and in-frame variants with global minor allele frequency (MAF) of <1% in NCBI dbSNP human build 147,[12] 1000 genomes project phase 3,[13] NHLBI GO exome sequencing project (ESP),[14] Genome Aggregation Database (gnomAD) version 2.1.1,[15] Iranome project (http://www.iranome.ir),[16] and a local database called GTaC. Variants with a Combined Annotation Dependent Depletion (CADD) score of >20 were retained based on Combined Annotation Dependent Depletion v1.6.[17] MutationTaster2[18] and Functional Analysis through Hidden Markov Models–Multi-kernel learning (FATHMM-MKL) Coding Prediction online tool v2.3[19] were applied to determine the alteration effect. ConSurf was used to evaluate the conservation of the amino acid residues of UV-stimulated scaffold protein through evolution.[20]

Confirmation of the causative variant was performed through Sanger sequencing [Figure 2a] using 5'TAGAGCAGCCTTCCTTGCAT3' and 5'TTAAGGGCCATTCAGTCACC3' oligonucleotides as forward and reverse primers, respectively, in addition to 2X Master Mix (Ampliqon®, Denmark) in a 25 µl PCR reaction among available healthy and affected members of the pedigree. PCR products were sequenced on an automated sequencer, ABI 3130XL (Applied Biosystems, Foster City, California, USA), using Big Dye Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, California, USA). Sequence chromatograms were compared with the reference sequence NM_020894 by SeqMan software version 5.00© (DNASTAR, Madison, WI, USA). Variant nomenclature was based on the human genome variation society (HGVS).[21] Co-segregation of the candidate variant with the condition was analyzed by Sanger sequencing.

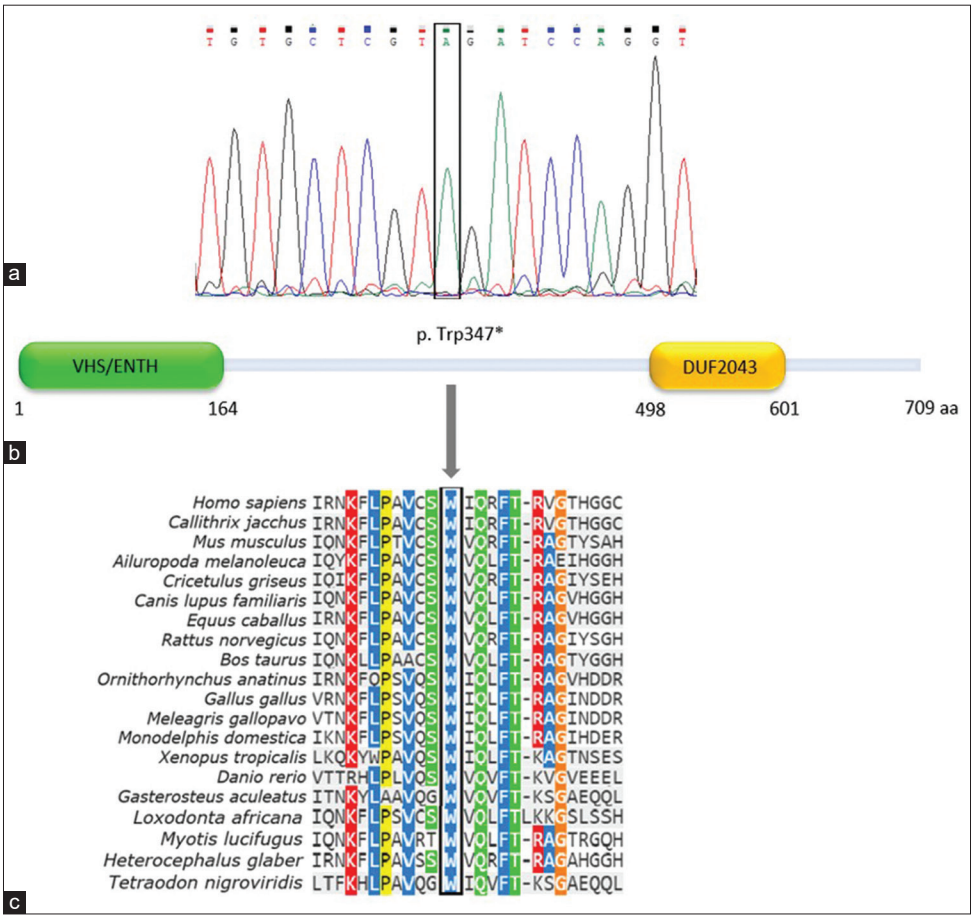

Figure 2: Sanger sequencing, protein location, and c.1040G>A variant conservation. (a) The electropherogram of the variant resulted from Sanger sequencing in the *UVSSA* gene from a patient with UV-sensitive syndrome (UV^{S}S) complementation group A. The c.1040G>A variant in a homozygous state is placed in a box. (b) Schematic illustration of UVSSA domains and location of p. Trp347* mutation (c) Multiple sequence alignment of UVSSA shows the high conservation of Trp347 residue among mammalians and vertebras. VHS/ENTH: Vps27-Hrs-STAM-like domain/epsin NH2-terminal homology domain

Results

Clinical findings

The proband was the third child, born after a full-term, uneventful pregnancy. His parents were second cousins. The parents and siblings of this ten-year-old boy were healthy, but one aunt, two uncles, and multiple distant relatives presented the same phenotype. He belongs to a large pedigree with skin abnormalities from an isolated far-reaching small village. Most marriages in this village were consanguineous; however, the degree of relationship was not clear for most marriages as the kindred was so inbred, and even the informant consultees could not explain the complex relationships between couples who were distant relatives. The condition affected males and females from 6 to 55 years old. The skin abnormalities were manifested as erythema, face freckles, telangiectasia, and dried skin in sun-exposed areas, but no cutaneous tumors. Affected individuals did not have hearing loss, mental and developmental delay, eye abnormalities, and neurological disorders.

Molecular findings

A homozygous transition nonsense variant, c.1040G>A (p. Trp347*), known as rs748398748 in the dbSNP database, was identified in the exon 6 of the *UVSSA* gene. The variant is available in heterozygous statues in gnomAD and Iranome with global MAF of 0.000008148 and 0.00125, respectively. Allele frequency among Persian Gulf Islanders is much more common, with a 0.01 MAF score. The variant was predicted to be pathogenic using online software tools, MutationTaster2 and FATHMM MKL Prediction [Table 1]. In addition, multiple sequence alignment of the human protein compared to other orthologues by ConSurf revealed that the amino acid Tryptophan 347 is highly conserved among mammalians and vertebrates [Figure 2c].

Discussion

UV-sensitive syndrome (UV^{S}S) is a form of cutaneous photosensitivity with no increased risk of skin tumors and developmental delay.[2] Mutation in *UVSSA* causes UVSS complementation group A, a rare condition with only five reported pathogenic variants worldwide. In this study, we have performed clinical and genetic evaluation in a patient from a large multiplex inbred Iranian kindred with several individuals suffering from skin sun-sensitive manifestations. The successful application of WES led to the identification of a homozygous variant in the UVSSA gene.

Table 1: Summary of molecular and bioinformatics findings

Variant	c. 1040G >A (p. Trp347*)
dbSNP ID	rs748398748
Zygosity	Homozygous
Iranome global MAF	0.00125
Iranome Persian Gulf Islander MAF	0.01
MutationTaster2	Disease-causing
FATHMM-MKL Coding Prediction	0.93817 (Damaging)
CAAD score (Phred scale)	37
ConSurf score (prediction)	8 (Conserved)
ACMG variant category	Pathogenic

Trp=Tryptophan, dbSNP=Single Nucleotide Polymorphism Database, MAF=Minor Allele Frequency, FATHMM-MKL=Analysis through Hidden Markov Models- Multi-kernel learning, CAAD=Combined Annotation Dependent Depletion, ACMG=American College of Medical Genetics

Although several patients belonging to the UV^{S}S complementation group A were initially assigned to mild XP-E by mistake,[22,23] Cleaver *et al.*[24] uncovered the subtle differences between the characteristics of those patients and CS or XP, which led to the hypothesis that they might belong to an unknown complementation group. In this context, the UV^{S}S-A complementation group was first described by Itoh *et al.*[25] as a new class of NER deficiency which showed biochemical characteristics of CS, including normal unscheduled DNA synthesis (UDS) without the typical clinical features of this syndrome. They observed normal post-replication repair in the fibroblasts of patients, which ruled out XP. Additionally, UV light irradiation caused an increased UV sensitivity and suppressed RNA synthesis (RRS) recovery. In contrast, neither microinjection nor transfection with the DNA repair gene (*ERCC1*) corrected the defects of the cells. On the other hand, the cell fusion assay revealed that patients did not belong to any known group of CS or XP.[25] Later, the UVSSA protein was found to be causative for UV^{S}S, and different causative mutations were identified in this gene [Table 2].[26]

The UV-stimulated scaffold protein A gene, previously known as *KIAA1530*, located on 4p16.3 which contains 14 exons encoding a 4773 nucleotides long mRNA and a highly conserved 709 amino acid protein with a molecular weight of 81 kDa.[3] As shown in Figure 2b, the protein contains a ubiquitin-binding VHS-like domain (Vps27-Hrs-STAM) and an epsin NH2-terminal homology (ENTH) in the N-terminal (residue 1-164) in addition to a highly conserved DUF2043 domain (residue 498- 601) in the C-terminal.[4,28] Both VHS and DUF2043 domains are vital for normal RRS activity, and any mutation that disrupts these domains or leads to a truncated protein could cause an interruption in TC-NER.[28]

The UVSSA protein interacts with RNA polymerase II as well as ubiquitin carboxyl-terminal hydrolase 7 (USP7), a deubiquitinating protease that identifies and eliminates ubiquitin from proteins, at UV-induced lesions in DNA via VHS/ENTH domain.[3,4,26] UV-stimulated scaffold protein A operates in TC-NER by recruiting deubiquitinating enzyme USP7 in which the UVSSA-USP7 complex stabilizes ERCC6 through deubiquitination.[26] It also plays a role in the ubiquitination and phosphorylation of stalled RNA polymerase II and the restoration of RNA synthesis after UV irradiation.[3,4,26]

Five reports of more than ten cases with UV^{S}S have been documented in the literature so far [Table 2], and herein we

Table 2: Summary of all mutations of autosomal recessive UV-sensitive syndrome (UVSS) reported so far

Mutation	Gene	Complementation group	Origin	No. of reported patients	References
p. Lys123*	*UVSSA*	UV^{S}S-A	Japan	3	[22,25,27]
p. Cys32Arg	*UVSSA*	UV^{S}S-A	Japan	1	[23]
p. Ile31Phefs*9	*UVSSA*	UV^{S}S-A	Israel	1	[3,4,24]
p. Trp347*	*UVSSA*	UV^{S}S-A	Pakistan, Iran	29	[28] and present study
p. Trp361Cys	*ERCC8*	UV^{S}S/CS-A	France	1	[29]
p. Arg77*	*ERCC6*	UV^{S}S/CS-B	Japan	2	[30-32]

UV^{S}S-A=UV-sensitive syndrome complementation group A, UV^{S}S/CS-A=UV-sensitive syndrome/Cockayne syndrome complementation group A, UV^{S}S/CS-A=UV-sensitive syndrome/Cockayne syndrome complementation group B, Lys=Lysine, Cys=Cysteine, Arg=Arginine, Ile=Isoleucine, Trp=Tryptophan, Phefs*=frameshift alteration, *=Stop codon

report the first cases with c.1040G>A mutation in the *UVSSA* gene in Iran.[3,4,28-30] Applying WES in two cell lines derived from unrelated UV-sensitive patients led to the identification of a homozygous nonsense mutation, Lys123X.[22,25,27] Direct sequencing of other affected individuals revealed a homozygous frameshift mutation, c. 87delG (p. Ile31Phefs9*) in an Israeli patient affected by UV-sensitive syndrome, and a missense mutation, c.94T>C (p. Cys94Arg) in a patient with mild XP phenotype.[3,4,23,24] Patients with truncating mutations did not express the protein in derived cell lines. However, a patient's cell line with missense mutation expressed the protein.[3] As our patients had a nonsense variant, it is likely to believe that the RNA is expected to be degraded through the nonsense-mediated mRNA decay (NMD) process and manifest with severe cutaneous symptoms.

Herein, using WES in a large inbred pedigree with several patients affected by UV-sensitive syndrome (UV^{S}S), a nonsense variant was identified in the *UVSSA* gene that co-segregates with skin abnormality in the pedigree. The first report of *UVSSA*: c.1040G>A (p. Trp347*) in UV^{S}S patients was performed by Ijaz *et al*. in a pedigree from Pakistan in 2019. Molecular cloning of the mutant *UVSSA* and immunofluorescence study depicted a 39 kDa truncated protein with mislocalization at the cytoplasm instead of the nucleus, which interferes with its vital function in the TC-NER. Due to the geographical proximity of our cases and the Ijaz *et al*.[28] study, it is likely to believe that this variant has a common origin in both populations.

According to the American College of Medical Genetics (ACMG) and genomics for interpretation of the variants, it is concluded that *UVSSA*: c.1040G>A (p.Trp347*) is **pathogenic** through one very strong, one strong, one moderate, and three supporting lines of evidence: **PVS1** (null variant), **s**,[27] **PM2** (extremely low frequency or absent from controls in the population databases), **PP1** (co-segregation of the variant with the phenotype in the pedigree), **PP3** (several lines of *in silico* analysis showed deleterious effects of the variant), **PP4** (specific genotype-phenotype correlation),[33] **PP5** (Reputable source has recently reported the variant as pathogenic).[28]

Conclusion

This is the first study to report a mutation (c.1040G>A) in *UVSSA* led to UV^{S}S from Iran. The results are helpful for cascade screening and genetic counseling and are applicable to preventing disease recurrence via preimplantation or prenatal genetic diagnosis. Further investigations with more families are needed to extend our knowledge of the role of genes and mutations in the molecular pathogenesis of the disease in Iran.

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Conflicts of interest

There are no conflicts of interest.

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