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Original Article

UV-sensitive syndrome: Whole exome sequencing identified a nonsense mutation in the gene *UVSSA* in two consanguineous pedigrees from Pakistan

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ABSTRACT

Background: UV-sensitive syndrome (UV^{S}S) is a rare autosomal recessive genodermatosis characterised by photosensitivity, and hyperpigmentation, freckling, and dryness of sun exposed areas. In contrast to other photosensitivity disorders, affected patients show no predisposition to cutaneous melanoma or neurological dysfunction. UV^{S}S results from a defect in the transcription-coupled nucleotide excision repair (TC-NER) mechanism. UV^{S}S can be caused by mutations in the genes *ERCC8*, *ERCC6*, and *UVSSA*.
Objective: To determine the underlying genetic cause of UV^{S}S and its functional consequences in nine members of two large, unrelated consanguineous pedigrees from Pakistan.
Methods: Genomic DNA from one affected member of each family was subjected to whole exome sequencing. The identified mutation was then validated via Sanger sequencing using samples from all available family members. Molecular cloning and mammalian cell cultures were used for the translation and localisation of wild type (WT) and mutant constructs.
Results: A novel homozygous nonsense mutation, (c.1040 G > A [p.(Trp347*)]), was detected in exon 6 of the *UVSSA* gene in both families. Sanger sequencing revealed co-segregation of the nonsense mutation with the UV^{S}S phenotype. Immunoblotting revealed the anticipated 81 kDa band for the WT construct, and a truncated protein of around 39 kDa for the mutant. In mutant samples, immunofluorescence revealed mislocalisation of UVSSA from the nucleus to the cytoplasm.
Conclusions: This is the first report of UV^{S}S in the Pakistani population and the fourth report of a disease-causing mutation in *UVSSA*. The study broadens the *UVSSA* mutational spectrum, and contributes to functional understanding of truncated UVSSA proteins.

1. Introduction

UV-sensitive syndrome (UV^{S}S) is a rare disorder resulting from defects in the nucleotide excision repair (NER) system. UV^{S}S is characterised by photosensitivity, pigmentation anomalies in sun exposed areas, and the absence of tumors in the skin and internal organs. Affected patients display normal growth, and intellectual development, and life-span. Cutaneous expression in UV^{S}S resembles that of a mild xeroderma pigmentosum (XP) phenotype [1]. At the cellular level, cultured fibroblasts from UV^{S}S patients show similarities to Cockayne syndrome (CS) cells in terms of response to UV irradiation, including increased sensitivity, normal UV-induced DNA repair synthesis, and reduced recovery of RNA synthesis (RRS) [2,3]. Both CS and UV^{S}S patients display normal global genome NER (GG-NER) and deficient transcription-coupled NER (TC-NER) [4].

UV^{S}S is subclassified into the three complementation groups: UV^{S}S/CS-A, UV^{S}S/CS-B, and UV^{S}S. These are caused respectively by mutations in the excision repair cross complementation 8 (*ERCC8*) gene; the excision repair cross complementation 6 (*ERCC6*) gene; and the UV-stimulated scaffold protein A (*UVSSA*) gene [5–8]. To

Abbreviation: UVSSA, UV-stimulated scaffold protein A.

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date, research has reported a total of nine UV^{S}S cases from Japan, France, Iran and Israel (Table 1) [5–8]. Reported mutations in *UVSSA* comprise a nonsense mutation (p.Leu123*) in three patients from Japan; a deletion mutation (p.Ile31Phefs*9) in two patients from Iran and Israel; and a missense mutation (p.Cys32Arg) in one patient from Japan [7,8].

The present report describes the identification via whole exome sequencing (WES) of a novel homozygous nonsense mutation (c.1040 G > A [p.(Try347*)]) in *UVSSA* in nine UV^{S}S cases from Pakistan. To our knowledge, this is the first report of UV^{S}S in the Pakistani population, and only the fourth report of a causal UV^{S}S mutation in *UVSSA*.

2. Materials and methods

2.1. Human subjects

The study cohort comprises a total of nine UV^{S}S cases and five unaffected individuals from two large consanguineous families (A and B) from Pakistan (Fig. 1a, b). The two families are not known to be related. However, both are members of the Baloch tribe. The affected individuals from both families (n = 4, Family A; n = 5, Family B) are siblings, thus suggesting an autosomal recessive mode of inheritance. To confirm the diagnosis of UV^{S}S, all affected individuals underwent a detailed clinical examination by a consultant dermatologist at the Department of Dermatology, Sandeman Provincial Hospital Quetta, Pakistan. For each family, data were collected concerning consanguinity, number of affected individuals, and disease history in previous generations. The study protocol was approved by the Institutional Review Board of BUITEMS in adherence with the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants, or from legal guardians in the case of minors.

2.2. Genomic DNA extraction and whole exome sequencing

Genomic DNA was extracted from the blood samples of all 14 participants (indicated by "DNA" in Fig. 1a, b) using standard procedures. For the purposes of WES, genomic DNA (2 μg) from two affected individuals (IV-1 from family A and IV-3 from family B) was fragmented. The samples were then prepared in accordance with the Agilent Sure select V6 target enrichment kit preparation guide. Sequencing was carried out on an Illumina HiSeq4000 sequencer, which generates 100 base pairs (bp) paired end reads. Fastq files were aligned to the reference human genome (hg19) using the Burrows-Wheel Alignment (BWA) tool (v0.7.12). Duplicates were detected and discarded using the Picard Mark Duplicate tool (v1.130). Identification of SNPs and indels was performed using the Genome Analysis Toolkit (GATK v3.4.0). The exome data were filtered for high-quality novel variants in data bases like dbSNP142, the 1000 Genome data base (phase 3), Clinvar (05/2015) and ESP6500SI_V2. The potential functional effects of missense variants were investigated using the protein prediction tools SIFT, Polyphen2, and mutation taster.

2.3. Variant prioritisation

Variants detected via WES were filtered in order to identify those located within the following 11 candidate genes: *XPA, ERCC3, XPC, ERCC2, DDB2, ERCC4, ERCC5, ERCC6, ERCC8, POLH* and *UVSSA*. These genes are implicated in a range of photosensitivity disorders (XP, CS, trichothiodystrophy, and UV^{S}S). Variants of prime importance were non-synonymous variants, splice site variants, nonsense variants, and frameshift variants. Variants with a reported frequency of > 1%, and missense variants that lacked pathogenicity according to the three applied prediction tools, were excluded from the subsequent analyses.

2.4. Mutation validation via Sanger sequencing

To validate the *UVSSA* mutation identified via WES, all available samples from both families were subjected to Sanger sequencing. Polymerase chain reaction (PCR) was used to amplify the genomic region flanking exon 6 of the *UVSSA* gene (NM_020894.2). This was performed using forward primer 5′-ATGGGCGTCTGGCAGGTTC and reverse primer 3′-AAGGGCCATTCAGTCACCGG. PCR generated 341 bp fragments. Purified PCR products were sequenced directly using an AB1373 automated DNA sequencer (Applied Biosystems CA).

2.5. Molecular cloning and mammalian cell cultures

For this purpose, a pcDNA3.1+N-DYK vector containing the sequence for *UVSSA* transcript variant 1 was used (GenScript, Piscataway, NJ). The mutant constructs (c.1040 G > A [p.(Trp347*)]) were generated via targeted mutagenesis using the QuickChange II XL Site-Directed Mutagenesis Kit (Agilent Technologies), in accordance with the manufacturer's instructions. To verify the constructs, Sanger sequencing was performed. The primer sequences used for cloning and mutagenesis are available upon request.

The HEK293 T human embryonic kidney cell line with large T antigen (kind gift from Thomas Zillinger [Institute of Clinical Chemistry and Clinical Pharmacology, University of Bonn]) was maintained at 37 °C (5% CO_2) in Dulbecco's modified eagle medium (Lonza). The medium was supplemented with 10% fetal calf serum (Life Technologies); 1% penicillin-streptomycin (10,000 U ml^{-1}, Life Technologies); and 1% Amphotericin B (250 μg ml^{-1}, Life Technologies). Cells were cultured in Petri dishes for western blotting, and on coverslips in 12-well plates for immunofluorescence analysis. Transfections were carried out using the Lipofectamine 2000 Transfection Kit (Thermo Fisher Scientific), in accordance with the manufacturer's instructions. For each petri plate, the following amounts of reagents were used: 8 μg plasmid; 800 μl Opti-MEM (Life Technologies); and 20 μl Lipofectamine 2000. For each well in a 12-well plate, 0.5 μg of plasmid, 50 μl Opti-MEM, and 1 μl

Table 1
Reported mutations in UV^{S}S patients.

No. of patients	Complementation group	Gene	Mutation	Reference
3	UV^{S}S-A	*UVSSA*	p.Lys123*	[7,8]
2	UV^{S}S-A	*UVSSA*	p.Ile31Phefs*9u	[7,8]
1	UV^{S}S-A	*UVSSA*	p.Cys32Arg	[7]
9	**UV^{S}S-A**	***UVSSA***	**p.(Trp347*)**	**Present study**
2	UV^{S}S/CS-B	*ERCC6*	p.Arg77*	[6,7]
1	UV^{S}S/CS-A	*ERCC8*	p.Trp361Cys	[5]

UV^{S}S-A, UV-sensitive syndrome-A; CS-B, Cockayne syndrome-B; CS-A, Cockayne syndrome-A; *UVSSA*, UV-stimulated scaffold protein A; *ERCC6*, excision repair cross complementation 6; *ERCC8*, excision repair cross complementation 8.

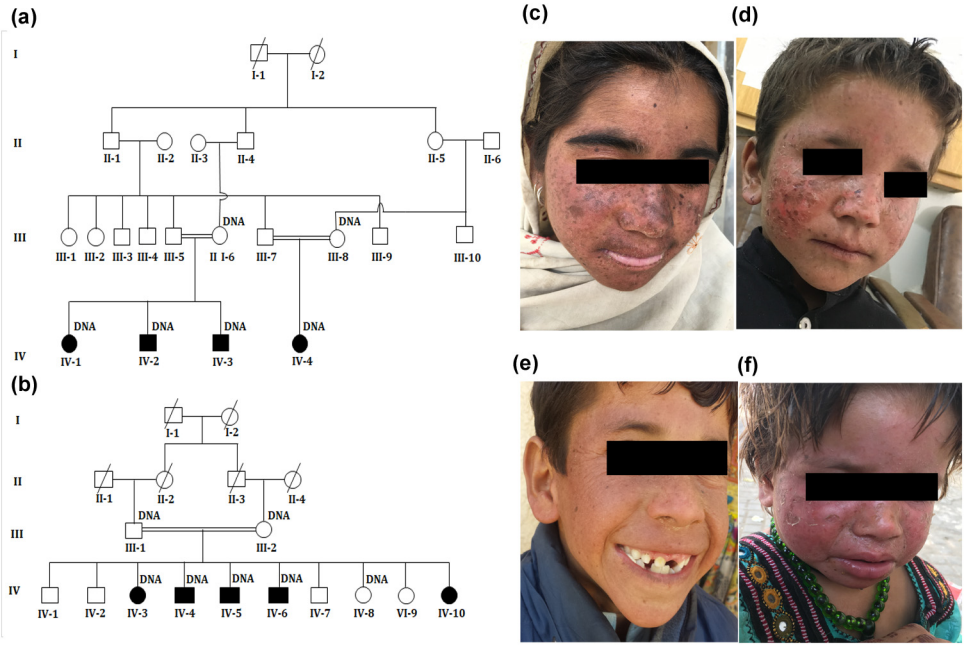

Fig. 1. Pedigrees and clinical features of the two UV^{S}S families. The pedigrees of (a) family A and (b) family B indicate autosomal recessive segregation of the UV^{S}S phenotype. Filled circles and squares indicate affected females and males, respectively. Double lines indicate consanguinity. DNA indicates individuals available for the present study. Clinical phenotype of affected individuals (c) IV-1 and (d) IV-2 from family A and (e) IV-5 and (f) IV-10 from family B. Erythema, dryness, and hyperpigmentation of exposed skin is evident. None of the nine affected individuals had any history of cutaneous melanoma.

Lipofectamine 2000 were used. Cells were harvested at 48 h and 24 h post-transfection for the purposes of western blotting and immunofluorescence, respectively.

2.6. Immunoblotting of HEK293 T cell extracts

For immunoblotting analyses, cells were collected in ice-cold PBS and centrifuged at 150 x g at 4 °C for 10 min. The cell pellets were re-suspended in 40 μl of 10× RIPA buffer (Cell Signaling Technology) and 360 μl of protease inhibitor cocktail (Roche). The mixture was incubated on ice for 15 min. Ten cycles of 10 s sonication were then performed. The mixture was re-incubated on ice for 10 min, followed by centrifugation at 10,500×*g* for 10 min at 4 °C. The supernatant was then transferred to clean tubes. Purified lysates were mixed with 4x Laemmli sample buffer (Bio-Rad Laboratories), which was diluted in β-Mercaptoethanol. Protein separation was performed on 4–15% TGX stain-free gels (Bio-Rad Laboratories), and transferred to a PVDF membrane (Amersham Biosciences). Western blotting was carried out using the WesternBreeze chemiluminescent Kit (Invitrogen), in accordance with the manufacturer's instructions. Monoclonal mouse anti-flag M2 antibody (Sigma) was used as a primary antibody. Membranes were developed for a maximum of 20 min using the ChemiDoc MP imager (Bio-Rad). All experiments were performed in triplicate.

2.7. Immunofluorescence analysis in HEK293 T cells

For immunofluorescence analyses, transiently transfected HEK293 T cells were grown on coverslips. The cells were then washed with 1x PBS, fixed with 1 × 4% PFA at room temperature for 10 min, washed three times with 1x PBS for 5 min, permeabilized for 10 min with 0.1% PBS-Tween20, and blocked for 1 h in PBS containing 1% bovine serum albumin, 10% normal goat serum, and 10% PBS-T. The cells were incubated with monoclonal anti-flag M2 antibody (Sigma Aldrich) for 1 h at room temperature. The cells were then washed: (i) three times with 1x PBS for 10 min; (ii) with goat anti-mouse-cy3 secondary antibody (5 μg/ml A10521, Life Technologies) for 40 min; and (iii) three times with 1x PBS for 10 min. The cells were then mounted using Mowiol 4–88 (Roth). Images were captured using 63x or 10x oil immersion objectives, a Zeiss Axioplan 2 imaging microscope, and the Cytovision 7.4 software.

3. Results

3.1. Clinical history and presentation of index cases

Families A and B resided in the city of Quetta in Balochistan Province and were of Baloch ethnicity. Affected individuals from family A comprised four siblings aged between 4 and 9 years (IV:1, IV:2, IV:3, IV:4). All four individuals presented with hyperpigmented facial spots, resembling the mild xeroderma pigmentosa (XP) phenotype. Scaling of the skin was reported to occur in summer and in direct sunlight. Individuals with a history of greater sun exposure displayed facial freckling and more severe xerosis and erythema (Fig. 1c, d). Photosensitivity was reported to be more severe in summer and in direct sunlight.

Affected individuals from family B comprised five affected siblings aged between 3 and 17 years (IV:3, IV:4, IV:5, IV:6, IV:10). All five individuals presented with hyperpigmentation of sun-exposed skin, resembling the mild XP phenotype. The five individuals also displayed erythema and photophobia. As in family A, hypersensitivity and xerosis were reported to become more severe in summer and in direct sunlight (Fig. 1e, f). Neither family had any known history of inherited photosensitivity or other genetic disorder in previous generations.

Concerning additional symptoms, all nine affected individuals had a history of normal growth as well as unremarkable neurological and psychomotor development. No history of cutaneous melanoma or ectodermal dysplasia was reported. The affected individuals also did not show any sign of non-melanoma skin cancer, skin atrophy, hair abnormalities or vision loss.

3.2. Variant identification by exome sequencing

WES generated ~6 GB of sequence data per sample. For patients IV-1 and IV-3, a coverage depth of 20X was achieved for around 90.2% and 86.4% of targeted exons, respectively. In patient IV-1, a total of 90,458 variants were identified. These included 10,564 non-synonymous variants, 136 nonsense mutations, 188 in-frame deletions, 160 in-frame insertions, and 280 frameshift variants. In patient IV-3, a total of 89,136 variants were identified. These included 10,833 non-synonymous variants, 126 nonsense mutations, 189 in-frame deletions, 152 in-frame insertions, and 274 frame shift variants. In both patients, exome data analysis identified the homozygous nonsense mutation (c.1040 G > A [p.(Trp347*)]) in the *UVSSA* gene.

3.3. Validation of the identified mutation via Sanger sequencing

The homozygous nonsense variant identified by WES is located in exon 6 of *UVSSA*. This region was PCR amplified in all available samples from both families, and then sequenced using the Sanger sequencing approach. Alignment of sequencing data with the reference sequence (NM_020894.2) confirmed the homozygous mutation (c.1040 G > A [p.(Trp347*)]) in all 9 affected individuals from both families. In the respective parents and in one unaffected sibling (IV-8 from family B), the mutation was present in a heterozygous state (Fig. 2). The identified mutation therefore co-segregated with the UV^{S}S phenotype in both families. This mutation resulted in the conversion of tryptophan (UGG) to a stop codon (UGA) at amino acid position 347. Exome data analysis of variants in one affected individual of each family revealed a shared block of 8.9 kb of genomic DNA across the site of the mutation. The identified mutation is not reported in the exome variant server (EVS); or the human genome mutation database (HGMD). However, the mutation is reported in a heterozygous state, and with a minor allele frequency of 8.15e-6 in the genome aggregation database (gnomAD).

3.4. Nonsense mutation in UVSSA leads to a smaller protein

To determine the size of the WT and the mutant protein, immunoblotting analyses were performed. Immunoblotting revealed that the WT UVSSA construct led to the translation of a protein of around 80 kDa, while the nonsense mutation p.(Trp347*) resulted in a protein of around 39 kDa (Fig. 3a).

3.5. Truncated protein leads to a mislocalisation

To determine the subcellular locations of the WT and mutated proteins, immunofluorescence analyses were performed. For WT UVSSA, imaging revealed a diffuse homogeneous distribution in the cell nucleus and to a lesser extent in the cytoplasm (Fig. 3b–d). For mutant constructs, the protein was present in the cytoplasm only (Fig. 3e–g).

4. Discussion

In the present study, clinical and genetic evaluation was performed in nine individuals with a UV^{S}S phenotype from two families of Pakistani origin. WES identified a novel homozygous nonsense mutation in the *UVSSA* gene, which was validated by Sanger sequencing. Previous research has identified a total of three *UVSSA* mutations in UV^{S}S families from Japan, Iran, and Israel [7,8]. The present mutation is thus the fourth *UVSSA* mutation reported to date for UV^{S}S, and the first causal UV^{S}S mutation reported in subjects from Pakistan. This mutation most probably indicates a founder mutation due to the fact that individuals from both families belong to the same ethnic tribe; this assumption was supported by variants around the

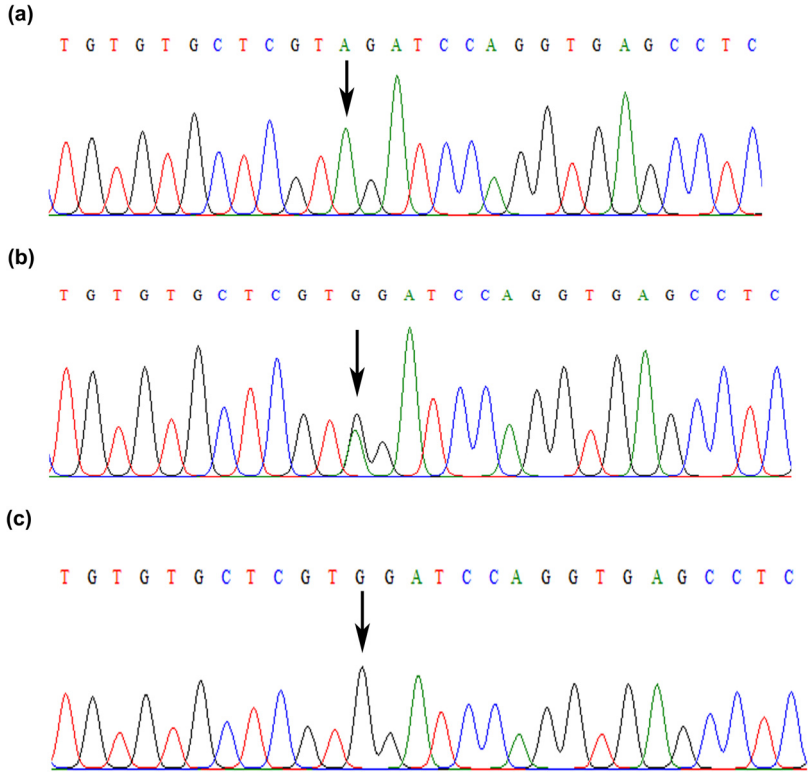

Fig. 2. Sequencing analysis of *UVSSA*. A homozygous nonsense mutation (c.1040 G > A) was detected in the affected individuals of families A and B. The DNA sequences of exon 6 from (a) an affected individual; (b) a heterozygous carrier; and (c) a control individual. Arrows indicate the position of the mutation.

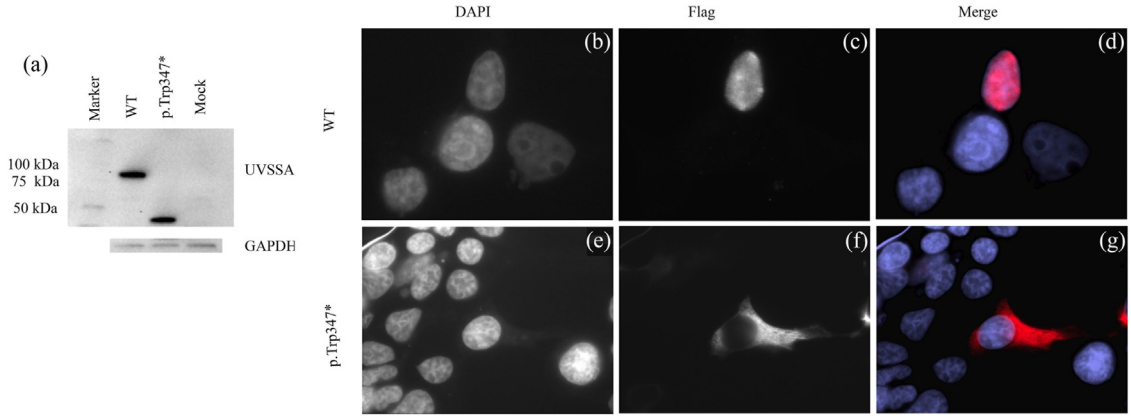

Fig. 3. (a) Immunoblotting of cell lysates following transient transfection with UVSSA-WT and -mutant constructs. A band of the anticipated 81 kDa size was detected for the WT. The p.(Trp347*) mutation resulted in a protein with a band of around 39 kDa. All experiments were carried out in triplicate. (b–g) Immunofluorescence analyses in HEK293 T cells transiently transfected with WT and mutant UVSSA encoding plasmids show for the WT a diffuse homogeneous distribution in the cell nucleus and to a lesser extent in the cytoplasm (b–d). For mutant constructs, the protein was present in the cytoplasm only (e–g).

mutation (c.1040 G > A) in *UVSSA* that showed an identical block of genomic DNA in both affected individuals.

Recent research identified the *UVSSA* gene, formerly known as *KIAA1530*, as a causal gene for UV^{S}S [7,8]. *UVSSA* is located on chromosome 4p16.3, comprises 14 exons, and encodes a 709 amino acid protein with a molecular weight of 81 kDa [9,10]. It is implicated in regulating TC-NER activity [11].

Amino acid sequences have demonstrated that the UVSSA protein shows no obvious similarity to any other protein family [7]. Three dimensional structure predictions have revealed a motif of 143–163 amino acids near the N-terminus that is homologous to the Hrs, Vps-27, and STAM (VHS) domains. The ENTH domain and the DUF domain are positioned at the C-terminal region. The STAM and ENTH domains interact with RNA polymerase II in the NER pathway, and facilitate its ubiquitination and dephosphorylation [12,13]. To investigate the role of the DUF- and the VHS domain in the NER pathway, previous authors transduced UVSSA truncation mutants into UV^{S}S-A cells, and assayed their ability to complement the RRS defect. Mutants lacking either the VHS domain or the DUF domain failed to restore RRS activity in these cells [7]. Crystallographic analyses have revealed that the two previously reported mutations p.Cys32Arg and p.Lys123* in *UVSSA* are located in the VHS domain of STAM 1, and that the mutated UVSSA protein causes a loss of NER activity due to absence of RNA pol II ubiquitination [7]. The mutation p.Ile31Phefs*9 is also positioned at the N-terminal region of the UVSSA protein that is crucial in terms of its function in the NER pathway. The present immunoblotting experiments in cell cultures demonstrated that the nonsense mutation p.(Tyr347*) led to a truncated UVSSA protein of around 39 kDa. In the study by Nakazawa et al. (2012), no proteins were demonstrated for the truncating mutations (p.Ile31Phefs*9, p. Lys123*) [7]. This may have been attributable to the fact that the mutations were localised much closer to the N-terminus and/or to possible nonsense-mediated RNA decay. The nonsense mutation (c.1040 G > A), identified in this study, produced a truncated protein of 39 kDa. The resulting truncated mRNA appears to have escaped the NMD pathway. This might be due to the fact that the activation of the NMD pathway depends on the position of the resp. nonsense mutation. Nonsense mutations that are located more than 50–55 nucleotides upstream of 3` exon-exon junctions cause mRNA decay [14]. However, the mutation detected in this study resides only 8 nucleotides upstream of the 3` exon-exon junction and is therefore most probably not affected. As a consequence of p.(Tyr347*), both putative nuclear-localisation signals (NLS1 and NLS2), as well as the purely understood DUF2043 domain, will be abolished. The mutation therefore appears to result in a substantial disruption of normal UVSSA function. Disturbed protein function was also suggested by the results of the present immunofluorescence analyses, since these demonstrated that the protein was present in the cytoplasm and was not present in the cell nucleus.

In conclusion, the present study is the first to report UV^{S}S patients from Pakistan, and identified the fourth pathogenic mutation in the *UVSSA* gene to date. Identification of the (c.1040 G > A [p.(Trp347*)]) mutation broadens the mutational spectrum of *UVSSA* as a cause of UV^{S}S, while demonstration of the mislocalisation of the mutant protein may facilitate future functional insights into UV^{S}S.

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Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jdermsci.2019.08.003.

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