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Basic science

Description of a novel splice site variant in *UBA1* gene causing VEXAS syndrome

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Abstract

Objective: Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a complex immune disorder consequence of somatic *UBA1* variants. Most reported pathogenic *UBA1* variants are missense or splice site mutations directly impairing the translational start site at p.Met41, with recent studies showing that these variants are frequent causes of recurrent inflammation in older individuals. Here we aimed to characterize a novel *UBA1* variant found in two patients clinically presenting with VEXAS syndrome.

Methods: Patients' data were collected from direct assessments and from their medical charts. Genomics analyses were undertaken by both Sanger and amplicon-based deep sequencing, and mRNA studies were undertaken by both cDNA subcloning and mRNA sequencing.

Results: We report a novel, somatic variant in a canonical splice site of the *UBA1* gene (c.346-2A>G), which was identified in two unrelated adult male patients with late-onset, unexplained inflammatory manifestations including recurrent fever, Sweet syndrome-like neutrophilic dermatosis, and lung inflammation responsive only to glucocorticoids. RNA analysis of the patients' samples indicated aberrant mRNA splicing leading to multiple in-frame transcripts, including a transcript retaining the full sequence of intron 4 and a different transcript with the deletion of the first 15 nucleotides of exon 5.

Conclusion: Here we describe abnormal *UBA1* transcription as a consequence of the novel c.346-2A>G variant, identified in two patients with clinical features compatible with VEXAS syndrome. Overall, these results further demonstrate the expanding spectrum of variants in *UBA1* leading to pathology and provide support for a complete gene evaluation in those patients considered candidates for VEXAS syndrome.

Keywords: autoinflammatory diseases, myelodysplasia, *UBA1* gene, mosaicism, VEXAS syndrome.

Rheumatology key messages

- The characterization of a novel intronic *UBA1* variant has expanded the landscape of VEXAS syndrome–associated variants.
- The refractive and progressive nature of VEXAS syndrome highlights the necessity for further *UBA1* variant elucidation.

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Introduction

Autoinflammatory diseases include monogenic and polygenic immune disorders characterized by recurrent episodes of sterile inflammation. Currently, >50 different monogenic autoinflammatory diseases have been molecularly elucidated, and these are categorized by their underlying inflammatory pathway in inflammasomopathies, type I interferonopathies, NF-kB disorders, actinopathies, and ubiquitinopathies [1].

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is a monogenic ubiquitinopathy, since it is a consequence of somatic, hypomorphic *UBA1* variants [2–8]. The *UBA1* gene encodes for the E1 ubiquitin-activating enzyme that starts ubiquitylation, a post-translational modification that attaches ubiquitin to target proteins in cellular processes such as proteosome-mediated protein degradation or intracellular signalling [9]. From a clinical perspective, VEXAS syndrome is characterized by concurrent inflammatory and haematological features [2, 10, 11]. The inflammatory manifestations include neutrophilic dermatosis, relapsing polychondritis, pulmonary manifestations, recurrent fever, arthritis, and ocular inflammation [2, 10, 11]. The haematologic features are relatively homogeneous among patients and include anaemias that often require blood transfusions, macrocytosis, peripheral cytopenias, bone marrow vacuolization, and venous thromboembolism [2, 10, 11]. From a genetic perspective, the spectrum of pathogenic *UBA1* variants causing VEXAS syndrome is limited, with <15 reported to date and the majority clustering in or around exon 3, specifically at the p.Met41 residue [2–8].

In this study, we identified two unrelated male adult patients, clinically resembling VEXAS syndrome, in whom we detected an unreported c.346-2A>G transition at the splice acceptor site of intron 4 of *UBA1*, distal to the p.Met41 residue. We hypothesized this novel variant could be disease-causing and herein we show the results of experiments performed to characterize its molecular consequences, which confirm its pathogenic behaviour.

Methods

Patients

The patients' data were collected at the time of clinical diagnosis or genetic testing, from direct assessments and from their medical charts. Written informed consent was obtained from patients at their respective medical centres. The Ethical Review Boards of New York University, USA, (NCT06004349) and Hospital Clínic, Barcelona, Spain, (HCB/2022/0855) approved the study. All investigations were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

DNA analyses

Genomic DNA samples were prepared from blood or tissues using the QIAmp DNA Blood Mini Kit or the QIAamp DNA Investigator Kit (QIAgen, Hilden, Germany) according to the manufacturer's instructions. *UBA1* genotyping was performed by both Sanger sequencing and amplicon-based deep sequencing (ADS). For Sanger sequencing, all exons of *UBA1* (RefSeq NM_003334.4) were PCR-amplified using in-house designed primers (Supplementary Table S1, available at *Rheumatology* online), purified with Illustra ExoProStar 1-Step (Cytiva, Little Chalfont, UK), bidirectionally fluorescence sequenced using an ABI BigDye® Terminator v3.1 Cycle Sequencing Kit and run on an automated ABI 3730XL DNA analyzer (Applied Biosystems, Thermo Fisher Scientific, Austin, TX, USA). Sequence reads were analyzed using the SeqPilot software (JSI Medical Systems, Ettenheim, Germany), and detected variants were classified according to the previously published recommendations [12].

ADS studies were performed by means of amplifying the target exon and intronic boundaries of the *UBA1* gene by in-house-designed PCR, and subsequent deep sequencing (>×1000) on a S5XL platform (Ion Torrent, Life Technologies, Waltham, MA, USA). Reads were mapped against the GRCh38 using the Burrows–Wheeler Alignment algorithm, and variants were subsequently analyzed using the Integrative Genomics Viewer [13]. The mutant allele fraction (MAF) was calculated as the proportion of variant reads from the total reads and expressed as a percentage.

RNA analyses

RNA samples were prepared from blood samples collected in Tempus™ tubes (Applied Biosystems, Thermo Fisher Scientific, Woolston, UK) and purified with a Qiagen RNeasy kit (Qiagen). gDNA digestion was performed using Qiagen DNase I (Qiagen). For subcloning, cDNA libraries were produced using the reverse transcriptase SuperScript™ IV (Thermo Fisher). cDNA was then amplified with TaqRed (Azura Genomics, Raynham, MA, USA) using primer set 5′ATGAAGCGGCTCCAGACATC3′ and 3′GACAGAACT CACCCACTCGC5′. The PCR products were ligated into the TOPO-TA plasmid (Thermo Fisher), transformed into *E. coli*, purified, and Sanger sequenced to identify the mRNA transcripts.

To evaluate the sequence of the various transcripts directly, RNA libraries were prepared from total mRNA using the NEBNext Ultra II Directional RNA Library Prep Kit (New England Biolabs, Ipswich, MA, USA) with the rRNA depletion configuration. RNA libraries were validated using TapeStation (Agilent Technologies, Santa Clara, CA, USA), pooled and quantified by qPCR, and sequenced on a NextSeq platform using a NextSeq 500 High-Output 150-paired-end 2 × 75 cycles kit (Illumina, San Diego, CA, USA). Sequence reads were aligned to the GRCh38 using the Ensembl annotation version 109 with STAR (version 2.7.0d). Gene expression quantification at the exon level and differential exon usage analysis were performed using the DEXSeq package in R. To identify novel transcripts, the sequence reads were aligned to the same reference using Bowtie2 (version 2.3.4.1) and Tophat (version 2.1.1). Subsequently, we employed specific applications from Cufflinks (v2.2.1) for further analysis. Initially, BAM files obtained from the previous steps were filtered based on our region of interest. Cuffcompare was used to predict the transcripts for each group, and gffread was utilized to generate FASTA files of the predicted transcripts.

Sequences alignment

The sequence of the human *UBA1* gene was obtained from Ensembl genome bowser (https://www.ensembl.org), and the sequence alignments were performed using the CLUSTALW Omega software (https://www.ebi.ac.uk/Tools/msa/clustalo/).

Results

Patient presentations

Patient 1 is a 67-year-old Spanish man who had onset of symptoms at age 50. During the course of the disease, he experienced recurrent fevers and inflammatory cutaneous manifestations, including Sweet syndrome–like neutrophilic dermatosis, livedo reticularis, purpuric papules, plaques, and pulmonary manifestations. He also had anaemia, macrocytosis and thrombocytopenia (See Table 1 and Supplementary Table S2, available at *Rheumatology* online for detailed features). A bone marrow biopsy revealed multiple cytosolic vacuoles in both myeloid and erythroid progenitor cells.

Patient 2 is a 60-year-old man from the USA who had onset of symptoms at age 58. Like patient 1, he experienced recurrent erythematous skin lesions, but also had urticarial-like eruptions (Fig. 1A). He also experienced intermittent arthralgias and acute asymmetric arthritis involving various joints in his hands and feet. He had anaemia and thrombocytopenia, with classic cytosolic vacuoles in erythroid and myeloid progenitor cells in the bone marrow (Supplementary Table S2, available at *Rheumatology* online). These manifestations responded only to glucocorticoids, after failing to respond to multiple DMARDs and biologics (Table 1). Both patients had an otherwise unremarkable laboratory work-up.

Table 1. Clinical features of enrolled patients

	Patient 1	Patient 2
Clinical manifestations		
Recurrent fever	Yes	No
Recurrent skin manifestations	Yes	Yes
Erythematous papules/ plaques/nodules	Yes	Yes
Purpuric papules/plaques	Yes	No
Urticaria-like lesions	No	Yes
Livedo reticularis	Yes	No
Others	Sweet syndrome-like	Sweet syndrome-like
Recurrent chondritis	No	No
Musculoskeletal manifestations	No	Yes
Arthralgias/arthritis	No	Yes
Myalgias/myositis	No	No
Ocular inflammatory manifestations	No	No
Papiledema	No	No
Headache	No	Yes
Gastrointestinal manifestations	No	Yes
Pulmonary manifestations	Yes	No
Lung infiltrates	No	No
Venous thromboembolism	No	No
Lymphadenopathies	No	No
Splenomegaly	No	No
Treatments | Outcome		
Colchicine	Yes | Negative	Yes | Negative
NSAIDs	No	Yes | Negative
Glucocorticoids	Yes | Positive	Yes | Positive
MTX	Yes | Negative	No
MMF	No	Yes | Negative
AZA	No	No
HCQ	No	Yes | Negative
CYC	No	No
CSA	No	Yes | Negative
Dapsone	No	Yes | Negative
Anti-histamines	No	Yes | Negative
IVIGs	Yes | Partial	Yes | Partial
Omalizumab	No	Yes | Negative
anti-TNF	No	Yes | Negative
anti-IL-6	No	No
anti-IL-1	No	No
anti-CD20	No	No
Jak-inhibitors	No	Yes | Partial

MAS, macrophage activation syndrome.

DNA analyses

Both patients share key features generally seen in VEXAS syndrome, caused by the variants at p.Met41 (p.Met41Leu/Thr/Val), including sex, age at onset, skin manifestations, and cytoplasmic vacuoles in progenitor cells in the bone marrow. Although these individuals did not display frequently observed VEXAS manifestations, such as chondritis, unprovoked venous thrombosis, and inflammatory eye disease, we hypothesized that a *UBA1* variant may have been causative. To evaluate this, all exons of the *UBA1* gene were first Sanger DNA sequenced, which detected the c.346-2A>G transition at the splice acceptor site of intron 4 in both patients (Fig. 1B). This variant has not been reported in patients with VEXAS, nor registered in population or disease databases (Supplementary Table S3, available at *Rheumatology* online). To confirm its post-zygotic nature, we quantified the mutant allele in peripheral blood, with the results showing a MAF in both patients (78.1% in patient 1 and 21.5% in patient 2) compatible with that expected for a post-zygotic variant (Supplementary Table S4, available at *Rheumatology* online), thus confirming the presence of *UBA1* mosaicism. Furthermore, we also investigated for the presence of the post-zygotic *UBA1* variant in non-haematopoietic tissues (nails) in patient 1, with results confirming its presence at lower frequencies than in peripheral blood (Supplementary Table S4, available at *Rheumatology* online).

mRNA analyses

Bioinformatics analyses predicted that the c.346-2A>G *UBA1* variant may impair the normal mRNA splicing by destroying one of the canonical splice sites of the gene (Supplementary Table S3, available at *Rheumatology* online). To investigate its consequences at the molecular level, we performed direct mRNA *UBA1* sequencing from peripheral blood (patient 1), and cDNA subcloning and clone Sanger sequencing (patient 2). Both experimental approaches for mRNA analyses gave identical results, with the detection of three *UBA1* mRNA transcripts, two of which were novel. Among them, the largest transcript was 3674 bp (compared with 3572 bp of the wild-type transcript), due to the retention of intron 4, and it was predicted to generate an in-frame mRNA transcript with the insertion of 34 extra amino acid residues (Fig. 1C–E and Supplementary Fig. S1, available at *Rheumatology* online). By contrast, the shortest transcript was 3557 bp, predicted to generate an in-frame mRNA transcript with the loss of the first 15 bp of exon 5, resulting in the deletion of five amino acid residues (p.116Phe_120Glu) (Fig. 1C, D and F).

Discussion

VEXAS syndrome is a late-onset autoinflammatory disease resulting from somatic variants at the *UBA1* gene [2]. Since its first description, hundreds of patients have been genetically confirmed around the world. These studies suggest that VEXAS syndrome is one the most common conditions among

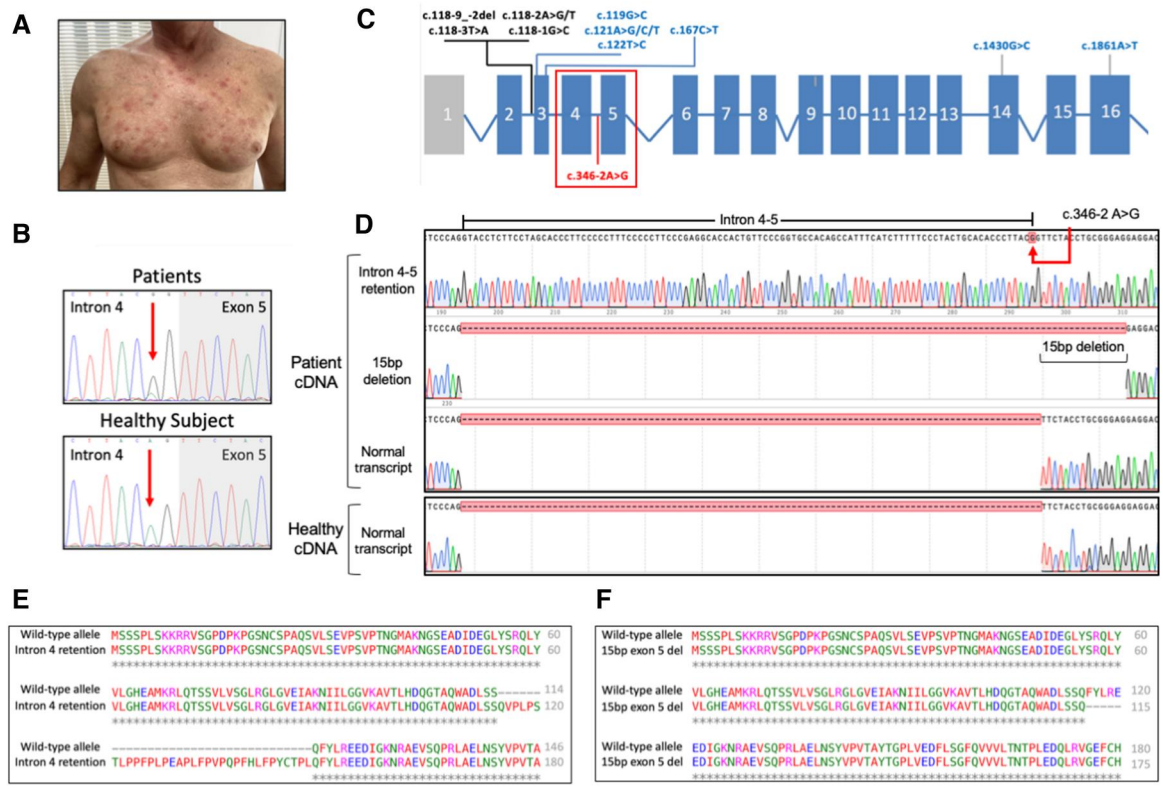

Figure 1. Results of DNA and mRNA analyses. (A) Cutaneous inflammatory lesions detected in patient 2. (B) Sense Sanger chromatograms from patients carrying the c.346-2A>G *UBA1* variant (upper panel) and from a healthy subject (bottom panel). The red arrow indicates the position where the nucleotide variant is located. (C) Genomic organization of the human *UBA1* gene. The blue rectangles indicate exons, the grey rectangle an untranslated 5′ and 3′ region, and the blue lines introns. Pathogenic variants previously reported are shown in the upper part of the gene, with the intronic variants displayed in black letters and the exonic variants in blue letters. The novel variant here described is shown in red letters. (D) Schemes of mRNA transcripts of the wild-type allele from a healthy subject (bottom panel) and from the enrolled patients (upper panels). The three upper panels represent the *UBA1* mRNA transcripts identified in enrolled patients by both cDNA subcloning and mRNAseq. (E) Sequence alignment of predicted proteins encoded by the wild-type *UBA1* mRNA allele and the novel mRNA transcript retaining the full sequence of the intron 4–5. (F) Sequence alignment of predicted proteins encoded by the wild-type *UBA1* mRNA allele and the novel mRNA transcript with the deletion of the first 15 nucleotides of exon 5

the genetically determined autoinflammatory diseases, especially in men older than 50 years, in which its prevalence is similar to or higher than that of other well-known rheumatic diseases such as PAN or Behçet's disease [8]. Interestingly, despite the high number of genetically confirmed patients, the landscape of pathogenic *UBA1* variants causing VEXAS is unusually scarce, with variants at p.Met41 (Leu/Val/Thr) accounting for >95% of reported patients [2–8, 10, 11]. This marked homogeneity in the genetics of VEXAS syndrome clearly differs from the genetics of other autoinflammatory diseases with mosaicism, such as cryopyrin-associated periodic syndromes, in which it is relatively common that each patient carries a different, often novel, somatic variant [14, 15]. There is no clear explanation for these differences in the diversity of pathogenic variants, although this may be due to the small range of *UBA1* variants, allowing for clonal expansion.

Herein we detected a novel somatic variant at a canonical splice site in the *UBA1* gene in two unrelated, male patients with symptoms with strong similarities to VEXAS syndrome [2]. Similarities included late-onset of the disease (in their 50s), recurrent and diverse cutaneous inflammatory lesions as a consequence of a neutrophilic dermatosis, increased acute-phase reactants, macrocytic anaemia, cytosolic vacuoles in myeloid and erythroid precursor cells in the bone marrow, a positive response to glucocorticoids, and refractoriness to other anti-inflammatory treatments, including biologics. Additional VEXAS syndrome features had been also detected in one of the two enrolled patients, including recurrent fever, pulmonary manifestations, arthritis, and thrombocytopenia [2, 10, 11].

We also evaluated the consequences of the novel *UBA1* variant in the normal transcription of the gene. As expected for a variant located in a canonical splice site, we identified two novel mRNA transcripts of the gene resulting from intron retention and cryptic splice site activation. These novel transcripts are predicted to affect the *UBA1* protein product by creating two isoforms (either with an additional 34 amino acids, or with 5 amino acids removed) that are estimated to have decreased E1 enzyme activity, resulting in VEXAS syndrome clinical manifestations. We suspect this splice mutation has a similar enzymatic defect to that of other reported variants, with loss of enzymatic activity rather than an isoform swap that results in VEXAS syndrome [3, 16].

Overall, these clinical, genetic and molecular data support the diagnosis of VEXAS syndrome in both patients, thus increasing the landscape of genetic diversity of this syndrome. However, the patients described here lack some of the frequent features reported in VEXAS syndrome, such as relapsing polychondritis, ocular inflammatory manifestations, venous thromboembolism, and severe cytopenias [2, 10, 11]. The absence of these does not rule out the diagnosis of

VEXAS syndrome, as recent investigations have reported that the landscape of inflammatory manifestations is broader than initially thought, with some patients carrying known disease-causing variants lacking some features initially considered as hallmarks of the syndrome [8]. Moreover, despite the similar clinical presentation seen in both patients, there were additional manifestations observed in patient 1, such as recurrent fevers, pulmonary manifestations and a higher ESR. Potential explanations for the differences in presentation between the two patients may include earlier age at disease onset (50 years in patient 1 *vs* 58 years in patient 2), leading to differences in the course of the disease (17 years in patient 1 *vs* 2 years in patient 2), and marked differences in the frequency of the *UBA1* mutant allele in the peripheral blood (variant allele frequency of 78.5% in patient 1 *vs* 21.5% in patient 2). Finally, it seems that the course of the disease in the patients described here is slightly milder than that of patients carrying variants at p.Met41 residue, this conclusion being based on the longer course of disease in one patient (17 years), and the tendency to normal or slightly decreased values in ferritin levels, leucocyte and platelet counts. To explain this observation, we hypothesize that the clinical differences observed between these two groups (p.Met41 variants *vs* the novel splice site variant) may reflect their different outcomes in terms of the functioning of *UBA1*-encoded protein. However, there may exist alternative explanations for these observations, which further studies with additional patients will have to address to establish accurate genotype–phenotype correlations.

In summary, we report a novel *UBA1* splice site mutation producing two non-canonical mRNA transcripts predicted to result in reduced-function isoforms and manifest clinically as VEXAS syndrome. The novel splice mutation expands the scope of somatic *UBA1* variants causing VEXAS syndrome and potentially expands the genotype–phenotype correlations within this disease. While the mechanism of the pathogenicity remains unclear, the refractive and progressive nature of this mosaic syndrome highlights the necessity for further understanding of additional pathogenic variants in this disease.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data included in the present work are, by definition, de-identified, and are available upon reasonable request to the corresponding author. Data shall only be made available after a submitted research proposal has been approved by the authors, with investigator support and after a signed data access agreement.

Contribution statement

Study Conception and Design was undertaken by J.I.A. and D.B.B. Methodology for the data and sample collection was contributed by I.R.-P., D.O.C., M.K.W. and G.H. Methodology for the genomics studies was contributed by D. O.C., A.M.-V., J.Y. and J.I.A. Methodology for the mRNA seq studies was contributed by N.B., M.T., F.C. and J.I.A.. Formal analysis was undertaken by all authors. Writing of the original draft was undertaken by S.I., J.I.A. and D.B.B. All authors contributed to revising, reviewing and editing of the manuscript and read and approved the final version. J.I. A. and D.B.B. act as guarantors for the study, have had access to all the data and controlled the decision to publish.

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