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Authorship

Contribution: E.T. designed and performed research, analyzed data, and wrote the manuscript; I.P.T. and M.A.D. contributed vital new reagents or analytical tools, performed research, analyzed data, and reviewed all drafts of the manuscript and approved the final version; and I.P., A.D.S., I.N.-S., E.-D.P., D.F., M.G., and E.K. performed research, analyzed data, reviewed all drafts of the manuscript and approved the final version.

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Footnote

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TO THE EDITOR:

Novel somatic mutations in UBA1 as a cause of VEXAS syndrome

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Systemic autoinflammatory disorders encompass a heterogeneous group of monogenic disorders that are characterized by recurrent episodes of systemic and organ-specific inflammation.[1]

Using a genotype-first approach, Beck et al recently described VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome, a new late-onset treatment-refractory inflammatory syndrome with associated hematological abnormalities.[2] VEXAS is caused by acquired somatic mutations at methionine 41 (p.Met41) of UBA1, the major E1 enzyme responsible for initiating ubiquitylation. The mutations were predominantly found in myeloid lineages and were absent in lymphoid lineages. Functional analysis identified loss of the cytoplasmic isoform UBA1b, initiated from p.Met41, and the subsequent gain of a new

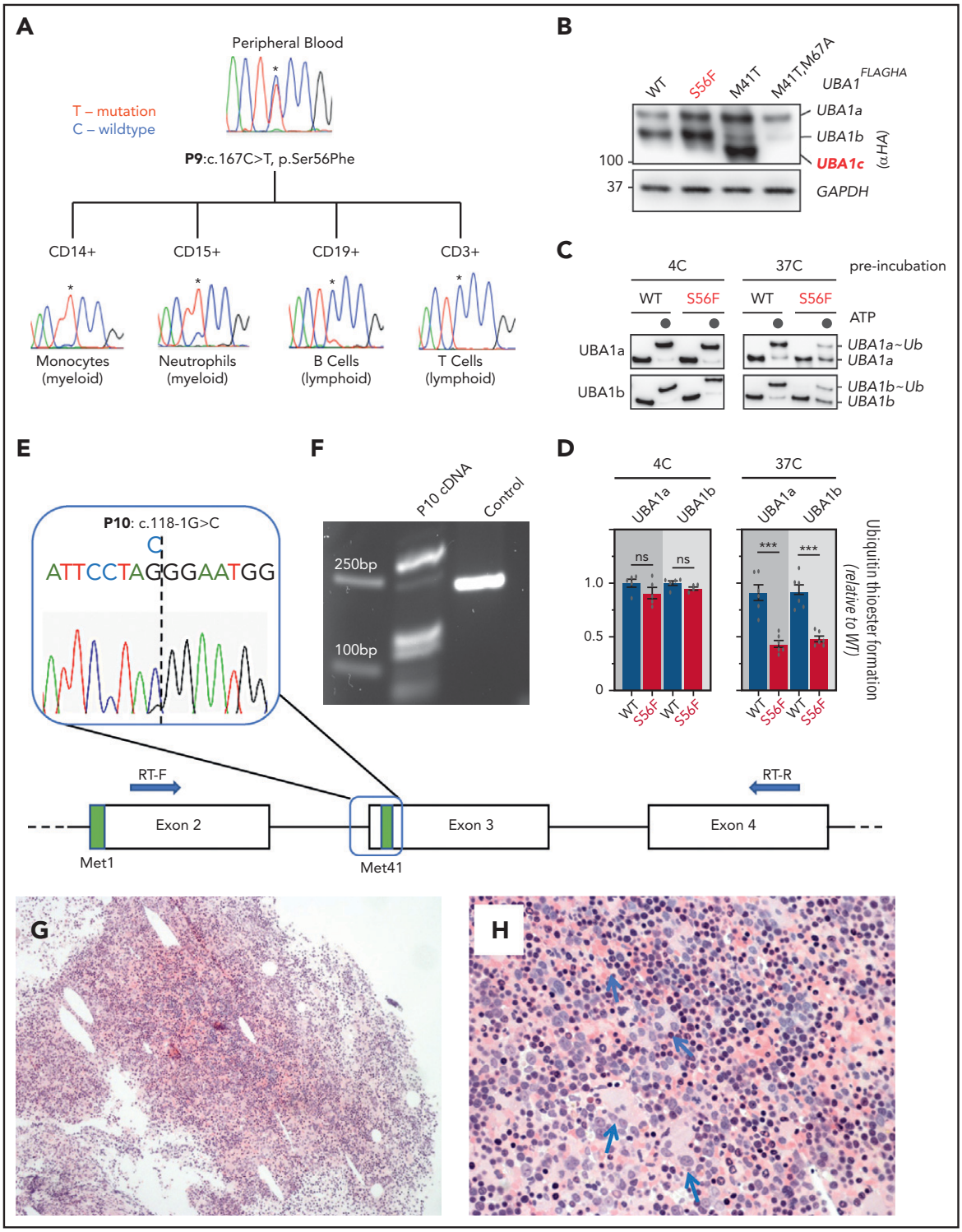

Figure 1. Somatic mutations in UBA1 cause VEXAS. (A) Electropherograms showing that the c.167C>T, p.Ser56Phe variant (denoted by an asterisk) is present in peripheral blood and is specifically enriched in sorted myeloid, but not lymphoid, cells. (B) In contrast to the p.Met41 variants, the p.Ser56Phe patient variant does not result in loss of UBA1b or gain of UBA1c, as revealed by immunoblot analysis of HEK293T cells transfected with the indicated UBA1^{FLAGHA} patient variants. WT, wild-type. (C) The p.Ser56Phe mutation reduces catalytic activity of nuclear UBA1a and cytoplasmic UBA1b in a temperature-dependent manner. Ubiquitin thioester formation assays were performed by preincubating denoted recombinantly purified UBA1 variants at 4°C or 37°C for 30 minutes, followed by incubation with ubiquitin and adenosine triphosphate (ATP) for 30 minutes on ice and immunoblot analysis. (D) Quantification of relative ubiquitin thioester formation of UBA1 proteins shown in (C). Ubiquitin thioester formation was calculated as a normalized fraction of modified protein [Ub~UBA1/(Ub~UBA1+UBA1)], and wild-type (WT) protein was set to 1 (n = 6 independent experiments using 2 independently purified protein preparations). ***$P < .001$, standard Student t test. (E) Electropherogram of the c.118-1G>A mutation in peripheral blood of P10 showing the mutant allele, present at the intron 2 acceptor, to be the predominant allele. (F) Reverse transcriptase polymerase chain reaction of patient-derived RNA revealed that the c.118-1G>C variant results in a reduction in correctly spliced UBA1 and the formation of multiple incorrectly spliced products (expected band size = 250 bp). Because the patient is deceased, no fresh tissue was available; therefore, RNA was extracted from paraffin-embedded fixed tissue. (G-H) Representative bone marrow morphology from patient P9 with p.Ser56Phe mutation, stained with haematoxylin and eosin. Hypercellular trephine morphology shows erythroid expansion, reduced granulopoiesis, and scattered atypical megakaryocytes (blue arrows). ns, not significant.

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Table 1. Clinical features of 18 patients tested for the pathogenic *UBA1* variants

Feature	Beck et al[2],* (N = 25)	P1-8	P9	P10	P11-18
Mutations, n/N	p.Met41Thr (c.122T>C) (15/25) p.Met41Val (c.121A>G) (5/25) p.Met41Leu (c121A>C) (5/25)	p.Met41Thr (c.122 T>C) (5/8) p.Met41Val (c.121A>G) (3/8)	p.Ser56Phe (c.167C>T)	p.(splice) (c.118-1G>C)	*UBA1* negative
Demographics					
Males, n/N (%)	25/25 (100)	8/8	Male	Male	8/8
Age of onset, mean (range)	64 (45-80)	67 (60-74)	76	67	60 (40-71)
Deceased, n/N (%)	10/25 (40)	4/8 (50)	No (current age 81 y)	Yes (age of death 72 y)	1/8
Laboratory findings CRP, median (IQR), mg/L Paraprotein, n/N	73 (18-128)	100 (19-268) No (8/8)	48 (7-204) No	48 (13-84) IgGκ	98 (25-263) Yes 2/8 IgAκ ×1 IgAλ ×1
Key Features					
Fever, n (%)	23 (92)	8/8 (100)	Yes	Yes	8/8
Skin involvement, n (%)	22 (88)	7/8 (88)	Painful nodular rash	Painful nodular rash	5/8
		Painful nodular rash (4/8)		Eczematous rash	Painful nodular rash (2/8)
		Panniculitis (1/8)			Erythema nodosum (1/1)
		Urticarial vasculitis (1/8)			PG (1/1)
		Bullous vasculitis (1/8)			Sweets (1/1)
		Eczematous rash (1/8)			Nonspecific (1/1)
		Periorbital angioedema/cellulitis (1/8)			Cellulitis like (1/1)
Pulmonary infiltrate, n (%)	18 (72)	2/8 (25)	No	No	No
Ear/nose chondritis, n (%)	16 (64)	4/8 (50)	No	No	3/8
Venous thromboembolism, n (%)	11 (44)	1/8 (12.5)	No	No	No
Macrocytic anemia, n (%)	24 (96)	8/8 (100)	Yes	Yes	4/4, 4/4 Normocytic anemia
Other, n/N	N/A	Weight loss (8/8) Arthritis (1/8)	Myalgia, generalized stiffness, weight loss, fleeting arthralgia	Orchitis, generalized arthritis	Arthritis (2/8) Myalgia (3/8)
		Liver microabscesses (1/8)			Myofasciitis (1/1)
		Interstitial nephritis (1/8)			Splenomegaly (1/1)
		Ischemic colitis (1/8)			
Principal diagnosis	For details, see Beck et al	AOSD (1/8)	PMR/MDS	Unclassified	AOSD (1/8)
		Unclassified (6/8)			MDS (3/8)
		RP (1/8)			GCA/PMR (3/8)
					PG/sweets (1/)

↑, above normal range; ↓, below normal range; AML, acute myeloid leukaemia; AOSD, adult onset stills disease; AZA, azathioprine; CRP, C reactive protein; CyS, cyclosporin; CyC, cyclophosphamide; DMARDs, disease-modifying antirheumatic drugs; GCA, giant cell arteritis; MDS, myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance; MMF, mycophenolate; MTX, methotrexate; N/A, not applicable; NR, nonresponder; PG, pyoderma gangrenous; PMR, polymyalgia rheumatica; PR, partial response; R, response; RP, relapsing polychondritis.
*Shown as median and interquartile range (IQR).
†Summary of bone marrow features of 4 confirmed VEXAS cases which were included in Beck et al.[2]
‡Good response to steroids, but now steroid dependent for control of inflammatory symptoms.

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Table 1. (continued)

Feature	Beck et al[2],* (N = 25)	P1-8	P9	P10	P11-18
Bone marrow features†					
Cellularity, n/N	↑ (4/4)	↑ (2/2)	↑	↑	↑ (2/6)
Erythropoiesis, n/N	↓ (4/4)	↓ (2/2)	↑ with dysplastic change, nuclear inclusions	↓ with dysplastic change	↓ (2/6)
Granulopoiesis, n/N	Expanded with dysplasia (4/4)	Expanded with dysplasia (2/2)	↓	↑ with minor dysplasia (<10%), vacuoles in promyelocytes	Expanded with dysplasia (3/6)
Megakaryocytes, n/N	↑ with dysplastic change (4/4)	↑ with dysplastic change (1/2) Normal number with atypical forms (1/2)	↑ with dysplastic change	Normal number with dysplastic change	↑ with dysplastic change (3/6)
Bone marrow vacuoles, n/N	(2/4)	(2/2)	Undetermined	Yes	Undetermined (not commented)
Bone marrow diagnosis, n/N	Nondiagnostic (3/4) MDS (1/4)	Nondiagnostic (1/2) MDS with excess blasts	MDS with multilineage dysplasia	MDS with multilineage dysplasia	MDS (2/6) MDS-AML (1/6) MGUS (2/6) Normal (1/6)
Treatment history					
Glucocorticoids, n,N (%)	25/25 (100)	8/8 (100)	Yes PR‡	Yes PR	8/8
Synthetic DMARDs, n/N	For details, see Beck et al	CyS (1/8) NR AZA (2/8) NR MTX (2/8) NR CyC (2/8) NR MMF (2/8) NR Dapsone (1/8) NR	None	None	CyS (1/8) NR AZA (2/8) NR MTX (2/8) PR (1/1) MMF (2/8) NR Dapsone (1/8) NR Leflunomide (1/8) NR
Biological DMARDs, n/N	For details, see Beck et al	Tocilizumab (3/4) 2 NR, 1 PR Anakinra (1/4) NR Rituximab (1/4) NR	None	None	Infliximab (1/1) R Anakinra (1/1) R Tocilizumab (1/1) R

↑, above normal range; ↓, below normal range; AML, acute myeloid leukaemia; AOSD, adult onset stills disease; AZA, azathioprine; CRP, C reactive protein; CyS, cyclosporin; CyC, cyclophosphamide; DMARDs, disease-modifying antirheumatic drugs; GCA, giant cell arteritis; MDS, myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance; MMF, mycophenolate; MTX, methotrexate; N/A, not applicable; NR, nonresponder; PG, pyoderma gangrenous; PMR, polymyalgia rheumatica; PR, partial response; R, response; RP, relapsing polychondritis.

* Shown as median and interquartile range (IQR).

† Summary of bone marrow features of 4 confirmed VEXAS cases which were included in Beck et al.[2]

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isoform, UBA1c, as the underlying disease mechanisms. No additional variants, other than those at p.Met41, were identified, suggesting that mutation of this residue alone causes VEXAS.

Here, we report 10 additional cases of VEXAS and describe 2 new mutations as a cause of this disease.

We investigated 18 patients for a severe systemic inflammatory disorder, cytopenias, and with bone marrow dysplastic features; all were men older than 40 years of age. Four of these patients, who were already deceased, were identified from a database based on their phenotype. Sanger sequencing was undertaken, resulting in the identification of pathogenic or likely pathogenic variants in 10 of 18 patients (P1-P10). Of the 10 patients with a mutation, 8 (P1-P8) had mutations at p.Met41, and 2 had novel variants. To determine whether samples negative for mutations following Sanger sequencing harbor somatic mutations at a low allele frequency, we performed deep amplicon sequencing of exon 3 to an average depth of 2900 reads per sample. No variant was identified in any of the sequenced samples. Clinical features of all patients are shown in Table 1.

The first novel variant identified was a somatic variant, NM_153280:c.167C>T, p.Ser56Phe in P9, with an approximately equal ratio of reference and variant alleles in peripheral blood. This variant is not present in the Genome Aggregation Database (gnomAD)[3] and is predicted to be deleterious by all tested bioinformatics predictions (supplemental Table 1, available on the *Blood* Web site). To determine whether the c.167C>T variant was preferentially expressed in myeloid cell lineages, we used magnetic-activated cell sorting to sort peripheral blood into myeloid ($CD14^+/CD15^+$) and lymphoid ($CD3^+/CD19^+$) lineages. Sanger sequencing of the variant in extracted genomic DNA revealed that the myeloid lineage populations had predominantly mutant alleles, whereas B- and T-cell lymphoid lineages were predominantly wild-type (Figure 1A). Similar to canonical VEXAS mutations, the p.Ser56Phe variant did not affect the cellular localization of UBA1 (supplemental Figure 1). Surprisingly, however, it did not result in the cytoplasmic isoform swap from UBA1b to UBA1c observed in p.Met41 variants (Figure 1B). Rather, this variant resulted in a temperature-dependent impairment in UBA1 catalytic activity compared with wild-type enzyme (Figure 1C-D). The second novel variant identified was at the splice acceptor site (NM_153280:c.118-1G>C) of exon 3 (Figure 1E) in P10. This variant is not present in gnomAD and is predicted to alter splicing by SpliceAI (supplemental Table 1). Analysis of patient-derived RNA revealed a reduction in properly spliced transcript and the creation of multiple incorrectly spliced products (Figure 1F).

The remaining 8 patients (P1-8) had a somatic variant that substituted the Met41 residue. Five of the patients had c.122T>C; p.Met41Thr substitution, whereas the remaining 3 patients had the c.121A>G; p.Met41Val substitution (Table 1). Bone marrow histopathology was consistent with previously reported patients, with vacuolated promyelocytes, increased cellularity and granulopoiesis, and decreased erythropoiesis (supplemental Figure 2). P9 (p.Ser56Phe) also showed increased cellularity; however, in contrast with the other VEXAS cases, he had increased erythropoiesis and reduced granulopoiesis (Figure 1F-G). Eight patients who tested negative for the pathogenic *UBA1* variant had many clinical features similar to VEXAS patients. All presented with fever, a high degree of skin involvement, and chondritis. Although all had anemia, the macrocytic type was only seen in 50% of the *UBA1*$^-$ individuals (Table 1).

Because VEXAS mutations are acquired and the disease is progressive, we hypothesized that its progressive nature could be due to the mutant clone expanding over time. Therefore, we identified a case from the original study[2] and 1 from this study (P6) with the p.Met41Thr substitution for whom bone marrow biopsies spanning 5 years were available. Sequencing of genomic DNA extracted from each biopsy did not reveal any difference in the proportion of mutant/wild-type alleles, with the predominant allele in each biopsy being the mutant T allele (supplemental Figure 3).

By sequencing a cohort of patients suspected of having VEXAS, we identified 10 patients with *UBA1* mutations. Although 8 of these substituted p.Met41, the remaining 2 patients harbored novel mutations that provide new insights into the disease mechanism of VEXAS. First, the c.118-1G>C variant altered splicing in vitro. We hypothesize that this mutation results in aberrant UBA1 messenger RNAs that lack regions around p.Met41 required for translation of the cytoplasmic UBA1b isoform. Second, analysis of the p.Ser56Phe variant led to the identification of a distinct disease mechanism whereby a temperature-dependent impairment in catalytic activity of UBA1, and not loss of the UBA1b isoform, results in VEXAS. Although we do not see a differential impact on UBA1 isoforms at the chosen conditions of our in vitro assays, we hypothesize that the p.Ser56Phe variant might lead to a preferential inactivation of cytoplasmic UBA1b isoform in cells (eg, through binding of activity-stabilizing proteins to the N terminus of nuclear UBA1a that is not present in cytoplasmic UBA1b); alternatively, cells may be more sensitive to reductions in activity to UBA1b. This novel disease mechanism may account for the difference in hematological pathology observed for P9 (ie, increased erythropoiesis and reduced granulopoiesis) compared with the rest of the cohort. Thus, our study suggests that a phenotypic spectrum may exist for VEXAS that is governed by the underlying mutation, the disease mechanism, and proportion of mutation-containing cells.

Previous analyses of sorted blood from patients harboring p.Met41 variants showed that the variant is predominant in myeloid cell lineages but not in lymphoid cell lineages.[2] We observed the same restriction of mutations to myeloid lineages for the p.Ser56Phe patient, suggesting that this restriction is not specific to Met41 mutations. This may imply that loss-of-function mutations in cytoplasmic UBA1 invokes a survival advantage in myeloid lineages that does not exist in lymphoid lineages or, simply, that myeloid cells can survive the loss of cytoplasmic UBA1, which other cell types cannot. Interestingly we did not find any difference in the proportion of mutant/wild-type alleles in bone marrow over a 5-year period during which the disease progressed. Further studies will be required to better understand the clonal nature of this disease and how this associates with disease severity; however, the predominance of the mutant allele from the first biopsy onward suggests that, even at the initial presentation of symptoms, the mutation is already the prevalent allele.

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Several studies have linked myelodysplastic syndrome (MDS) with an increased incidence of autoimmune and autoinflammatory complications.[4] Previous studies have identified particular autoimmune manifestations associated with distinct karyotypes in MDS.[5] A more recent study found that somatic mutation of transcription factor pathways and abnormal karyotypes are associated with autoinflammatory complications.[6] The identification of somatic UBA1 mutations in VEXAS, in particular, helps to explain why some MDS patients also have autoinflammatory complications.[7] Future studies of VEXAS-like *UBA1*-negative cases using the cell lineage–specific whole-exome sequencing approach might lead to the discovery of additional somatic mutations that link inflammatory and hematological abnormalities. This will also result in a better understanding of the underlying genetic causes of MDS and facilitate stratification and development of targeted treatments. Although VEXAS patients do not appear to have additional somatic mutations that are typically associated with high-risk MDS, the condition is associated with poor outcome and is refractory to standard therapies. A more radical treatment approach, such as bone marrow transplant, might need to be considered early in the disease course.

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Authorship

Contribution: J.A.P. performed genetic and splicing analyses; C.C. analyzed bone marrow biopsies; A.W., J.C.C., and D.O.C. performed functional analysis of the Ser56Phe variant and edited the manuscript; J.R.C., E.B., D.T.B., M.Q., M.G., and D.M. provided clinical cases and collected the data; R.M.D.T. performed cell sorting of peripheral blood; P.E. assisted with genetic analyses; D.B.B. analyzed data; S.S. conceived the study, was responsible for the clinical care of patients, and obtained funding; and J.A.P., C.C., D.B.B., and S.S. wrote the manuscript.

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