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Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease

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Abstract

BACKGROUND—Adult-onset inflammatory syndromes often manifest with overlapping clinical features. Variants in ubiquitin-related genes, previously implicated in autoinflammatory disease, may define new disorders.

METHODS—We analyzed peripheral-blood exome sequence data independent of clinical phenotype and inheritance pattern to identify deleterious mutations in ubiquitin-related genes. Sanger sequencing, immunoblotting, immunohistochemical testing, flow cytometry, and transcriptome and cytokine profiling were performed. CRISPR-Cas9–edited zebrafish were used as an in vivo model to assess gene function.

RESULTS—We identified 25 men with somatic mutations affecting methionine-41 (p.Met41) in UBA1, the major E1 enzyme that initiates ubiquitylation. (The gene *UBA1* lies on the X chromosome.) In such patients, an often fatal, treatment-refractory inflammatory syndrome develops in late adulthood, with fevers, cytopenias, characteristic vacuoles in myeloid and erythroid precursor cells, dysplastic bone marrow, neutrophilic cutaneous and pulmonary inflammation, chondritis, and vasculitis. Most of these 25 patients met clinical criteria for an inflammatory syndrome (relapsing polychondritis, Sweet's syndrome, polyarteritis nodosa, or giant-cell arteritis) or a hematologic condition (myelodysplastic syndrome or multiple myeloma) or both. Mutations were found in more than half the hematopoietic stem cells, including peripheral-blood myeloid cells but not lymphocytes or fibroblasts. Mutations affecting p.Met41 resulted in loss of the canonical cytoplasmic isoform of UBA1 and in expression of a novel, catalytically impaired isoform initiated at p.Met67. Mutant peripheral-blood cells showed decreased ubiquitylation and activated innate immune pathways. Knockout of the cytoplasmic UBA1 isoform homologue in zebrafish caused systemic inflammation.

CONCLUSIONS—Using a genotype-driven approach, we identified a disorder that connects seemingly unrelated adult-onset inflammatory syndromes. We named this disorder the VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome. (Funded by the NIH Intramural Research Programs and the EU Horizon 2020 Research and Innovation Program.)

IDENTIFYING THE CAUSES OF SYSTEMIC INflammatory diseases, particularly in adult populations, remains a challenge that limits our understanding of the pathophysiology, prognosis, and

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treatment. Genetic approaches have provided important insights into pathogenic mechanisms in both mendelian autoimmune[1] and autoinflammatory[2,3] diseases and in genetically complex disorders.[4] Somatic mutations, acquired and then clonally selected, have long been implicated in benign and neoplastic hematologic diseases[5] but remain a poorly understood contributor to autoinflammatory and rheumatologic diseases; these mutations have been identified largely with the use of targeted sequencing approaches.[6]

The widespread availability of genomic DNA sequencing has led to genotype-driven approaches to delineate human disease.[7-9] The starting point of this approach typically involves bringing together a group of persons who have undergone genomic sequencing and who do not necessarily have similar phenotypes. The objective is to find damaging variants in a common gene that underlie a previously unrecognized grouping of patients with particular clinical characteristics. These studies take advantage of shared genetic commonalities, rather than clinical similarities, to overcome the limitations of recognizing discrete phenotypes. Rheumatologic diseases may be well suited to this approach because of their complex and highly variable clinical presentations.

In the current study, we used a genotype-driven approach to identify a genetic cause of inflammatory disease. We thereby identified recurrent and inactivating acquired mutations in *UBA1*, a gene encoding the ubiquitin-activating enzyme 1, in men with a late-onset, treatment-refractory inflammatory syndrome with associated hematologic abnormalities. UBA1 is necessary for the initiation of ubiquitylation, a type of post-translational modification of proteins that is used to regulate diverse aspects of cellular biology, including intracellular signaling and protein degradation through the proteasome or the autophagy–lysosome system. We named this disorder the VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome.

METHODS

PARTICIPANTS

Three affected men, each with a somatic *UBA1* variant, were identified by analysis of exome data from genetic databases at the National Institutes of Health (NIH) Clinical Center. Fifteen additional men in observational cohorts at the NIH Clinical Center were identified on the basis of clinical similarities to the previous three affected men: their somatic *UBA1* variants were confirmed by Sanger sequencing. Seven other participants were identified in study populations at University College London and Leeds Teaching Hospitals NHS Trust in the United Kingdom. All participants were enrolled in research studies that had been approved by the respective institutional review boards and provided written informed consent. Clinical diagnoses were defined according to standard criteria.[10-16]

GENETIC AND FUNCTIONAL ANALYSIS

We sequenced the exomes of the first 3 participants and 3 additional participants and sequenced *UBA1* in the other 19 participants and their unaffected family members. We prioritized genes involved in the post-translational process of ubiquitylation because of its

regulation of innate immune responses.[17] We analyzed fractionated cell types in blood and fibroblast samples obtained from the participants using digital droplet polymerase-chain-reaction assay, immunoblotting, immunohistochemical testing, electron microscopy, flow cytometry, and cytokine profiling. To study the effect of presumed etiologic variants on *UBA1* function, we edited the genome of zebrafish using the CRISPR (clustered regularly interspaced short palindromic repeats)–Cas9 (CRISPR-associated protein 9) system. The Supplementary Appendix, available with the full text of this article at NEJM.org, includes a description of the methods used for these procedures.

STATISTICAL ANALYSIS

Continuous variables are presented as means with standard deviations or medians with interquartile ranges and were compared with the use of parametric or nonparametric tests as appropriate. Categorical variables are expressed as absolute numbers and percentages and were compared with the use of the chi-square test. Statistical methods for the transcriptomic analyses are described in the Supplementary Appendix. Post hoc Bonferroni correction was performed for experiments with multiple comparisons, and the results are presented as adjusted P values.

RESULTS

GENOTYPE-FIRST SCREENING TO IDENTIFY THE VEXAS SYNDROME

We screened the exomes and genomes of 1477 persons referred because of undiagnosed recurrent fevers, systemic inflammation, or both and 1083 persons affected by atypical, unclassified disorders who were identified through the Undiagnosed Diseases Program.[18] The combined population of participants was roughly balanced with respect to sex and spanned a wide range of ages (Fig. 1A). We identified 3 men, all with novel (absent from public databases including the Genome Aggregation Database), predicted deleterious, and apparently heterozygous variants at the same codon, methionine-41 (p.Met41) of the X-linked gene *UBA1*, which is highly intolerant to haploinsufficiency (as indicated by a "probability of being loss-of-function intolerant" [pLI] score of 1.0, on a range of 0.0 to 1.0, with a higher score indicating a greater degree of intolerance for loss-of-function variants in healthy persons). The seemingly heterozygous variants seen in these 3 affected men raised questions of mosaicism or aneuploidy, because males usually have only one copy of X-chromosomal genes. Mindful of the potential role of somatic mutations in adult-onset disease, we evaluated all the variants, including those with a lower-than-expected allele frequency.

We confirmed all *UBA1* variants of interest using Sanger sequencing (Fig. 1A and Fig. S1 in the Supplementary Appendix) and determined that the variants were absent from fibroblasts in the tested participants (Fig. S2). None of the 25 affected men had affected family members, and all 8 available relatives tested negative for the mutation. The participants did not have aneuploidy on karyotype analysis, nor were X-chromosomal copy-number variations present, as determined by high-density single nucleotide polymorphism array analysis (Fig. S2C). We therefore predicted that these apparently heterozygous variants were

somatic (also known as mosaic or postzygotic) mutations, with genetically heterogenous cells carrying either hemizygous wild-type or mutated *UBA1*.[20]

To corroborate these findings, we interrogated exome data primarily from whole-blood samples obtained from 141,600 persons (77,162 unaffected adults and 64,438 persons who had been referred for diagnostic testing, mostly for neurodevelopmental diseases) who had undergone sequencing at a diagnostic company (GeneDx). None of the unaffected persons had a *UBA1* p.Met41 allele fraction exceeding 5%. As for the affected persons, only 5%, the majority of whom were children, had immune phenotypes. However, we identified 3 men with *UBA1* p.Met41 variants exceeding 71% variant allele frequency (Table S1), all with late-onset inflammatory disease. Thus, both screens identified *UBA1* p.Met41 somatic mutations exclusively in men with adult-onset inflammatory disorders.

GENETIC FEATURES OF THE VEXAS SYNDROME

To characterize mosaicism, we isolated and sequenced different hematopoietic cell populations. The participants with *UBA1* mosaic mutations had predominantly wild-type lymphocytes (T and B cells) and predominantly mutant myeloid cells (neutrophils and monocytes) in peripheral blood (Fig. 1B and 1C). Despite *UBA1* mutations being lineage-restricted in the blood, early marrow progenitor cells showed mosaicism. Hematopoietic stem cells and multipotent progenitors, granulocyte–monocyte progenitors, megakaryocyte–erythroid progenitors, and lymphoid progenitors isolated from bone marrow had abundant mutant cells, but mutations were absent in mature lymphocytes. The participants had decreased peripheral lymphocyte counts, which suggests that the mutant cells either did not proliferate or were eliminated, an outcome that resulted in an increased proportion of the wild-type genotype (Fig. S3).

CLINICAL FEATURES OF THE VEXAS SYNDROME

The first 3 participants were men in whom severe inflammatory syndromes had developed in the fifth to seventh decade of life. Common clinical features included alveolitis, ear and nose chondritis, skin lesions, and thromboembolic disease (Fig. 2). Each participant had progressive hematologic abnormalities, including macrocytic anemia, thrombocytopenia, and myeloid dyspoiesis, but none had an overt hematologic malignant condition. The only common genetic lesion among these 3 participants was a nonsynonymous missense mutation at *UBA1* p.Met41 (Fig. S4). We identified 22 additional participants who had overlapping clinical phenotypes; 7 of these participants were from an existing cohort of patients with relapsing polychondritis (ClinicalTrials.gov number, NCT02257866) (Table 1; see also the Supplementary Appendix). Among 18 participants who had undergone genetic screening on the basis of their clinical characteristics (male with adult-onset inflammatory syndrome and cytopenia, as well as chondritis, vasculitis, neutrophilic dermatosis, or a combination of these), 14 (78%) were found to have *UBA1* mutations.

The 25 participants with confirmed mutations in *UBA1* underwent extensive clinical assessment (Tables S2 through S8). All were male with a median age at disease onset of 64 years. Each of these participants had one of three somatic variants in codon 41 in *UBA1* (predicting amino acid substitutions p.Met41Val [NM_003334.3:c.121A→G; ClinVar

accession number, SCV001438043], p.Met41Thr [NM_003334.3:c.122T→C; ClinVar accession number, SCV001438045], or p.Met41Leu [NM_003334.3:c.121A→C; ClinVar accession number, SCV001438044]). The majority of these participants had recurrent fevers, pulmonary involvement, dermatologic manifestations (including neutrophilic dermatoses and cutaneous vasculitis), macrocytic anemia, hematopoietic dyspoiesis, and bone marrow vacuolization restricted to myeloid and erythroid precursor cells (Table 1, Fig. 2, Table S3, and Figs. S5 and S6). Electron microscopy revealed myeloid cells that were undergoing cell death and had vacuoles consisting of lipid droplets and disordered cellular organelles, including degenerating mitochondria.

Subgroups of participants met or partially met established diagnostic or classification criteria for a number of clinical conditions (Table 1 and Table S2). Transformation into a myelodysplastic syndrome with excess blasts or acute myeloid leukemia did not occur in any participant. All 25 participants had highly elevated levels of acutephase reactants and had no response to multiple disease-modifying antirheumatologic drugs (Tables S4 and S5). Glucocorticoids, often administered in high doses, were the only treatment that consistently ameliorated severe inflammatory symptoms. Of the 25 participants, 10 (40%) died from disease-related causes (respiratory failure or progressive anemia) or complications related to treatment.

IMMUNOLOGIC FEATURES OF THE VEXAS SYNDROME

Transcriptome analysis of the peripheral blood of participants revealed a shared gene expression signature consistent with the activation of multiple innate immune pathways (Fig. S7A and S7B and Table S9). Gene-expression profiling of isolated monocytes and neutrophils that were studied during a clinically quiescent period during which the participants had been receiving minimal treatment showed highly activated inflammatory signatures in multiple pathways including tumor necrosis factor, interleukin-6, and interferon-γ, a finding that is consistent with cell-intrinsic severe myeloid inflammation (Fig. S7C and Tables S10 through S12). Activation of pathways affecting the unfolded protein response and integrated stress response was identified only in myeloid cells (Fig. S8).[21] Elevated levels of multiple cytokines in the serum were consistent with the findings from the transcriptome analysis (Fig. 3). Peripheral B cells and monocytes showed atypical differentiation, with loss of immature B cells and nonclassical and intermediate monocyte populations (Fig. S9). Functional studies of neutrophils obtained from the participants with the VEXAS syndrome, as compared with those from age- and sex-matched healthy controls, showed preserved phagocytic capacity in mutant cells but enhanced spontaneous neutrophil extracellular trap formation, findings that are consistent with dysregulated proinflammatory neutrophil activation (Fig. S10).

VEXAS SYNDROME AND LOSS OF CYTOPLASMIC *UBA1* FUNCTION

UBA1 encodes the major E1-activating enzyme required for initiation of all cellular ubiquitin signaling.[22-25] UBA1 is expressed as two isoforms differing in translation start site — nuclear UBA1a (initiated at p.Met1) and cytoplasmic UBA1b (initiated at p.Met41) (Fig. 4A). Unexpectedly, monocytes obtained from the participants with the VEXAS syndrome, as compared with those from the controls, and ectopically expressed UBA1 Met41Val, as

compared with the wild-type enzyme, had similar nuclear and cytoplasmic localization, despite loss of the initiating methionine for UBA1b (Fig. S11A through S11C).

We next analyzed the expression of UBA1 Met41 variants in human embryonic kidney (HEK293T) cells by immunoblotting, which revealed loss of UBA1b and an unanticipated faster-migrating band (Fig. 4B and Fig. S11B). We hypothesized that the protein generating the faster-migrating band might be an isoform generated by translation initiation from a downstream start codon (Fig. 4A). Indeed, introduction of a mutation targeting the Met67 codon resulted in the disappearance of the faster-migrating band, suggesting that the transcription of the messenger RNA of this novel isoform of UBA1, denoted here as UBA1c, is initiated from the Met67 codon. UBA1c localized to the cytoplasm (Fig. S11A), a finding consistent with our observations regarding monocytes from the participants with the VEXAS syndrome. Purified recombinant UBA1c was catalytically impaired in thioester assays, as compared with purified recombinant UBA1a and UBA1b, a finding that was indicated by the predominance of the faster-migrating uncharged form in the UBA1c lane in contrast to the excess of charged forms with other tested UBA1 proteins (Fig. 4C). We therefore concluded that Met41 variants result in the reduction of cytoplasmic *UBA1* function by favoring the production of a catalytically deficient UBA1c over that of a catalytically proficient UBA1b.

We then attempted to confirm this cytoplasmic isoform switch by investigating the consequences of such a switch in the cells from the participants. Purified T cells from the participants, which were predominantly wild type, and from the unaffected controls had equivalent amounts of UBA1a and UBA1b proteins (Fig. 4D). In contrast, monocytes, which predominantly carried mutated *UBA1* variants in the participants, had decreased levels of UBA1b and detectable levels of UBA1c, which confirmed the results of the transfection studies (Fig. 4D). Mutant monocytes were defective in ubiquitylation, as shown by a loss of polyubiquitin species and a concomitant increase in free ubiquitin (Fig. 4D). These cells also showed increased eIF2α phosphorylation and altered LC3 levels, which suggests that loss of ubiquitylation activates cellular stress responses that lead to up-regulation of the unfolded-protein response (as indicated by increased eIF2α phosphorylation) and dysregulation of autophagy (as indicated by altered LC3 levels) (Fig. 4D).

To study the contribution of nuclear and cytoplasmic UBA1 isoforms to inflammatory disease in vivo, we established CRISPR-Cas9–edited zebrafish models (Table S13). Zebrafish *uba1* and human *UBA1* are highly homologous (Fig. S12). Because *uba1* is essential for viability,[26-28] we assessed inflammation during early development. Homozygous loss of all isoforms of Uba1 (Δ*uba1* [Δ indicates loss of protein]) or loss of Uba1b alone (Δ*uba1b*) but not Uba1a (Δ*uba1a*) in transgenic Tg(*mpx*:EGFP [*mpx* promoter controlling expression of enhanced green fluorescent protein]) zebrafish led to lower numbers of neutrophils than the numbers in sibling control heterozygous or wild-type fish (Fig. S13). All three zebrafish lines deficient in *uba1* also showed growth abnormalities and early death between 7 and 21 days after fertilization, a finding that may be due in part to the germline nature of these mutations as compared with the somatic variants found in the participants with the VEXAS syndrome. Finally, Δ*uba1* or Δ*uba1b*, but not Δ*uba1a*, led to up-regulation of the expression of inflammatory genes in zebrafish, similar to that seen in

the participants (Fig. 4E). Taken together, these results support the concept that systemic inflammation results from disruption of cytoplasmic UBA1 and its zebrafish homologue.

DISCUSSION

The genotype-first, phenotype-neutral strategy to understand human disease has yielded a positive outcome — the identification of a cause of severe adult-onset inflammatory disease. We identified myeloid lineage-restricted *UBA1* somatic mutations as the common cause of clinically complex and seemingly disparate diagnoses with overlapping hematologic features.

Ubiquitylation is a three-step process performed by the concerted actions of ubiquitin-activating enzymes (E1), which include 2 unique enzymes[29]; ubiquitin-conjugating enzymes (E2), which include approximately 40 unique enzymes[30]; and substrate specific ligases (E3), which include more than 600 unique enzymes.[31] Physiologic regulation of ubiquitin signaling often occurs at the level of E2 and E3 enzymes, but much less is known about control of ubiquitin activation. Our finding that a major cause of the VEXAS syndrome is a depletion of cytoplasmic UBA1 supports a critical function of subcellularly regulated ubiquitin activation during hematopoiesis.

UBA1 is required for nearly all cellular ubiquitin signaling and is essential in model organisms and cultured cells. The identification of *UBA1* variants exclusively in the somatic state probably reflects the finding that mutations affecting p.Met41 are lethal when they are germline and that this mutation is compatible with life only when mosaic in specific cell types.[32,33] We observed that inflammation in the participants with the VEXAS syndrome is driven by mutant myeloid cells, which outnumber wild-type myeloid cells. These findings suggest that myeloid precursor cells can survive with this somatic mutation and that mutant lymphocytes are negatively selected within bone marrow, observations that are consistent with the selective toxicity of the unfolded protein response and proteotoxic stress in lymphocytes as compared with myeloid cells.[34] The fact that we identified this mutation only in men, all of whom were clinically affected, suggests that the additional allele in women protects against effects of the mutant allele, although it is possible that, owing to skewed X-inactivation, the disease is milder in women. More generally, our findings suggest that X-linked mosaic mutations may cause other diseases.

Somatic mutations in hematopoietic stem cells have long been known to be associated with myeloid cancers and bone marrow failure syndromes and benign hematologic conditions such as paroxysmal nocturnal hemoglobinuria and, more recently, have been recognized as common, age-related processes, referred to as clonal hematopoiesis of indeterminate potential.[35,36] Somatic mutations are also causally linked to T-cell–mediated dysregulation in pure red-cell aplasia[37,38] and large granular lymphocytosis.[39] Myeloid-restricted somatic mutations in *UBA1* may underlie myelodysplastic disease, accompanied by systemic inflammation. For example, hematologic abnormalities in the spectrum of myelodysplastic syndrome develop in older men with relapsing polychondritis, with an increased risk of death.[40] The co-occurrence of relapsing polychondritis with myelodysplasia may be explained by the VEXAS syndrome. Similarly, concomitant myelodysplasia has been

reported in each of the rheumatologic conditions that were linked to the VEXAS syndrome in the current study, including polyarteritis nodosa, Sweet's syndrome, and giant-cell arteritis.[41] Given the increased mortality among patients with the VEXAS syndrome, efforts to identify effective treatment strategies that target the clonal somatic process, such as bone marrow transplantation or gene-editing therapies, should be considered.

Using a genotype-driven approach, we identified a disorder that connects seemingly unrelated adult-onset inflammatory syndromes. We named this genetic disorder the VEXAS syndrome, which is caused by myeloid-restricted somatic missense mutations in *UBA1*. Our findings show that somatic mutations can cause severe inflammatory conditions that manifest in adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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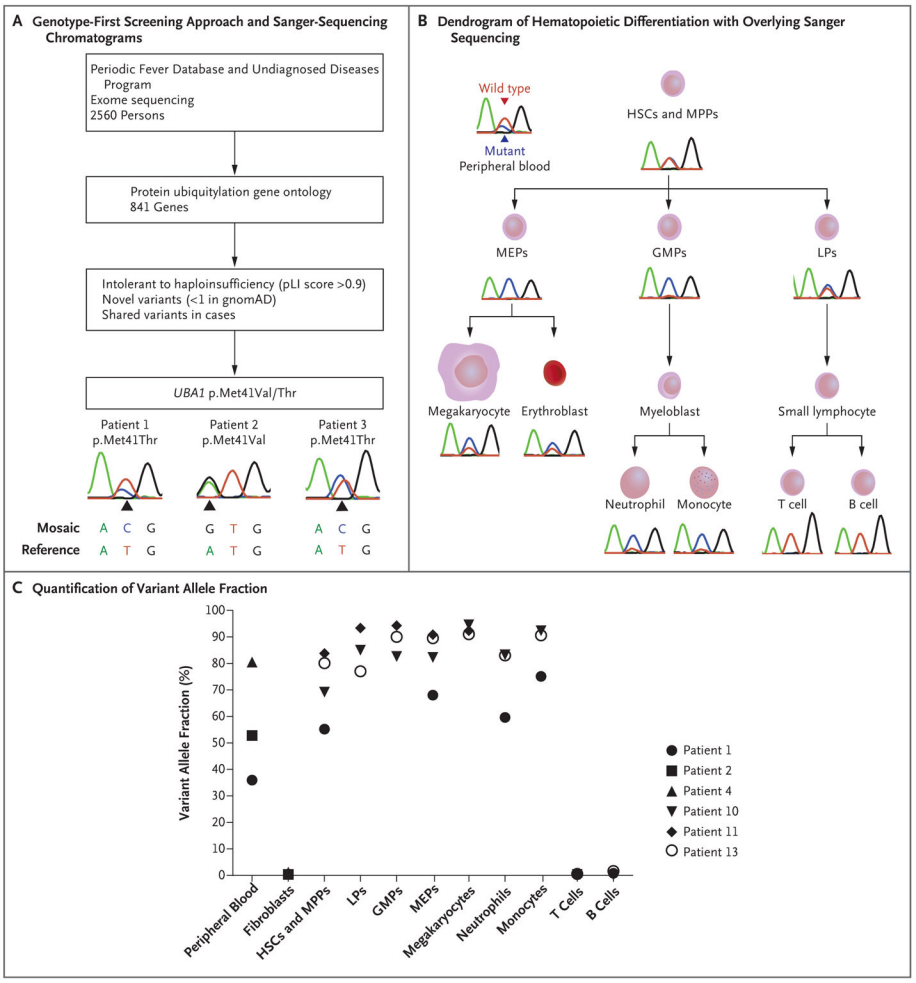

Figure 1 (facing page). Identification of Lineage-Restricted *UBA1* Somatic Variants in the VEXAS Syndrome.

Panel A shows a schematic representation of a genotype-first screening approach to identify novel disease-causing variants and Sanger-sequencing chromatograms for mosaic variants in Patients 1 through 3 at *UBA1* methionine-41 (p.Met41); the black triangles indicate the bases with distinct nucleotides. The term gnomAD denotes Genome Aggregation Database,[19] pLI probability of being loss-of-function intolerant (scores on the pLI range from 0.0 to 1.0, with a higher score indicating a greater degree of intolerance for loss-of-function variants in healthy persons), and VEXAS vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic. Panel B shows a dendrogram of hematopoietic differentiation with overlying Sanger sequencing of sorted bone marrow progenitors and peripheral-blood lineages from a representative case (in Patient 1). *UBA1* mosaic variants were enriched in progenitor cells and myeloid lineages and were absent in lymphocytes. GMPs denotes granulocyte–monocyte progenitors, HSCs hematopoietic stem cells, LPs lymphoid progenitors, MEPs megakaryocyte–erythroid progenitors, and MPPs multipotent progenitors. Panel C shows quantification of variant allele fraction with the use of digital droplet polymerase-chain-reaction assay in isolated cell lines including peripheral blood, fibroblasts, HSCs and MPPs,

LPs, GMPs, and MEPs sorted from bone marrow–biopsy samples and neutrophils, monocytes, and T cells and B cells sorted from peripheral-blood samples.

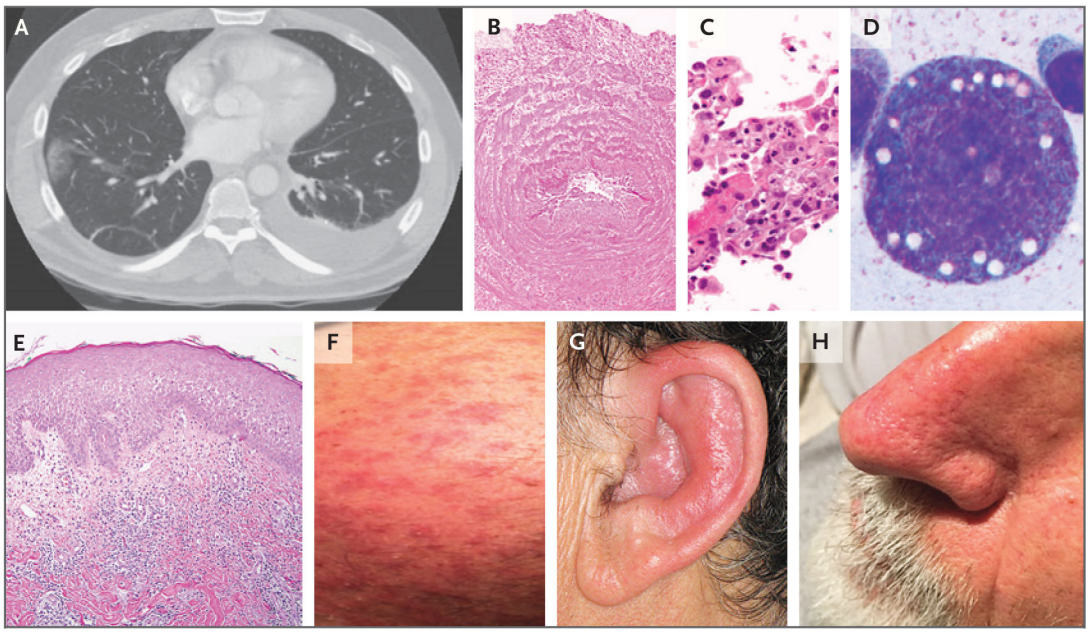

Figure 2. Clinical Manifestations of the VEXAS Syndrome.

Lung involvement included pulmonary infiltrates and pleural effusions (Panel A), vasculitis of medium-sized bronchial arteries (Panel B), and neutrophilic alveolitis (Panel C). Characteristic vacuoles were present in myeloid precursor cells from bone marrow aspirates (Panel D). Cutaneous manifestations included neutrophilic dermatosis with small- to medium-vessel vasculitis (Panel E) and tender plaques (Panel F). Cartilaginous involvement included auricular chondritis (Panel G) and nasal chondritis (Panel H), which were sometimes associated with periorbital inflammation. Hematoxylin and eosin staining was used in Panels B, C, and E, and Wright–Giemsa staining was used in Panel D.

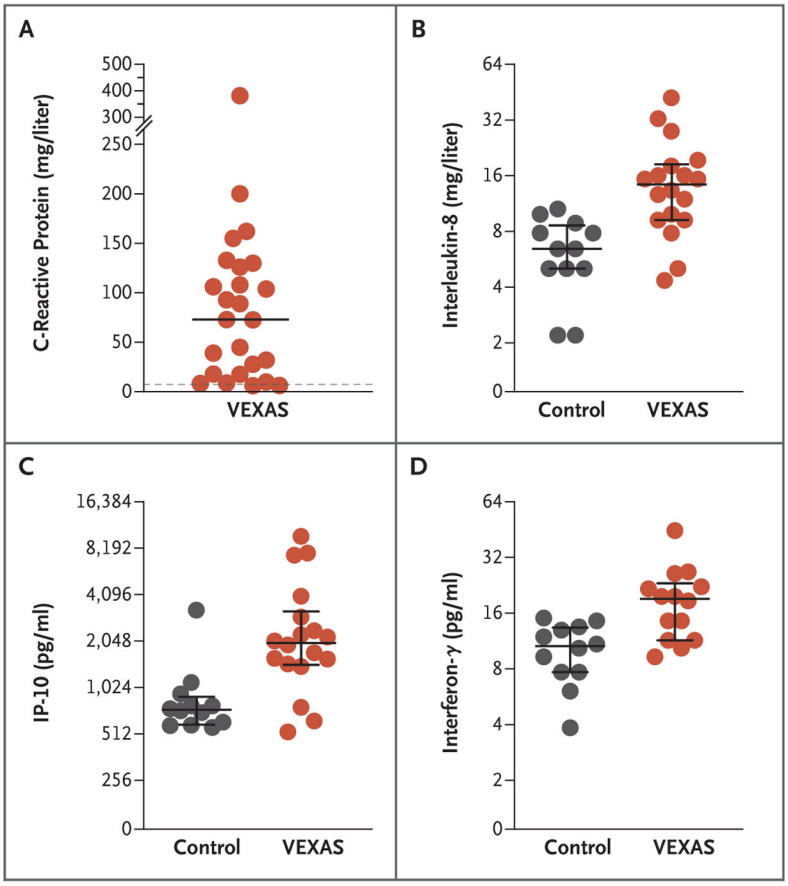

Figure 3. Serum Cytokines in Men with the VEXAS Syndrome.

Cytokine profiling was performed with the use of serum samples obtained from patients with the VEXAS syndrome, and the results were compared with those from controls. Enzyme-linked immunosorbent assay revealed higher inflammatory markers in the patients with the VEXAS syndrome than in the controls. Panel A shows the results for C-reactive protein values in the 25 participants with the VEXAS syndrome (values for the controls are not shown). The dashed line indicates the upper limit of the normal range (<5 mg per deciliter). Panel B shows the results for interleukin-8, with median values of 14.4 mg per liter (interquartile range, 9.2 to 18.5) among 18 samples from 13 participants with the VEXAS syndrome and 6.5 mg per liter (interquartile range, 5.1 to 8.6) among 12 controls. Panel C shows the results for interferon-inducible protein 10 (IP-10), with median values of 1995 pg per milliliter (interquartile range, 1443 to 3201) among 18 samples from 13 participants with the VEXAS syndrome and 734 pg per milliliter (interquartile range, 564 to 893) among 12 controls. Panel D shows the results for interferon-γ, with median values of 19.2 pg per milliliter (interquartile range, 11.4 to 23.3) among 14 samples from 13 participants with the VEXAS syndrome and 10.6 pg per milliliter (7.7 to 13.4) among 12 controls. In Panels B, C, and D, the long horizontal line represents the median value, and shorter bars represent the interquartile range.

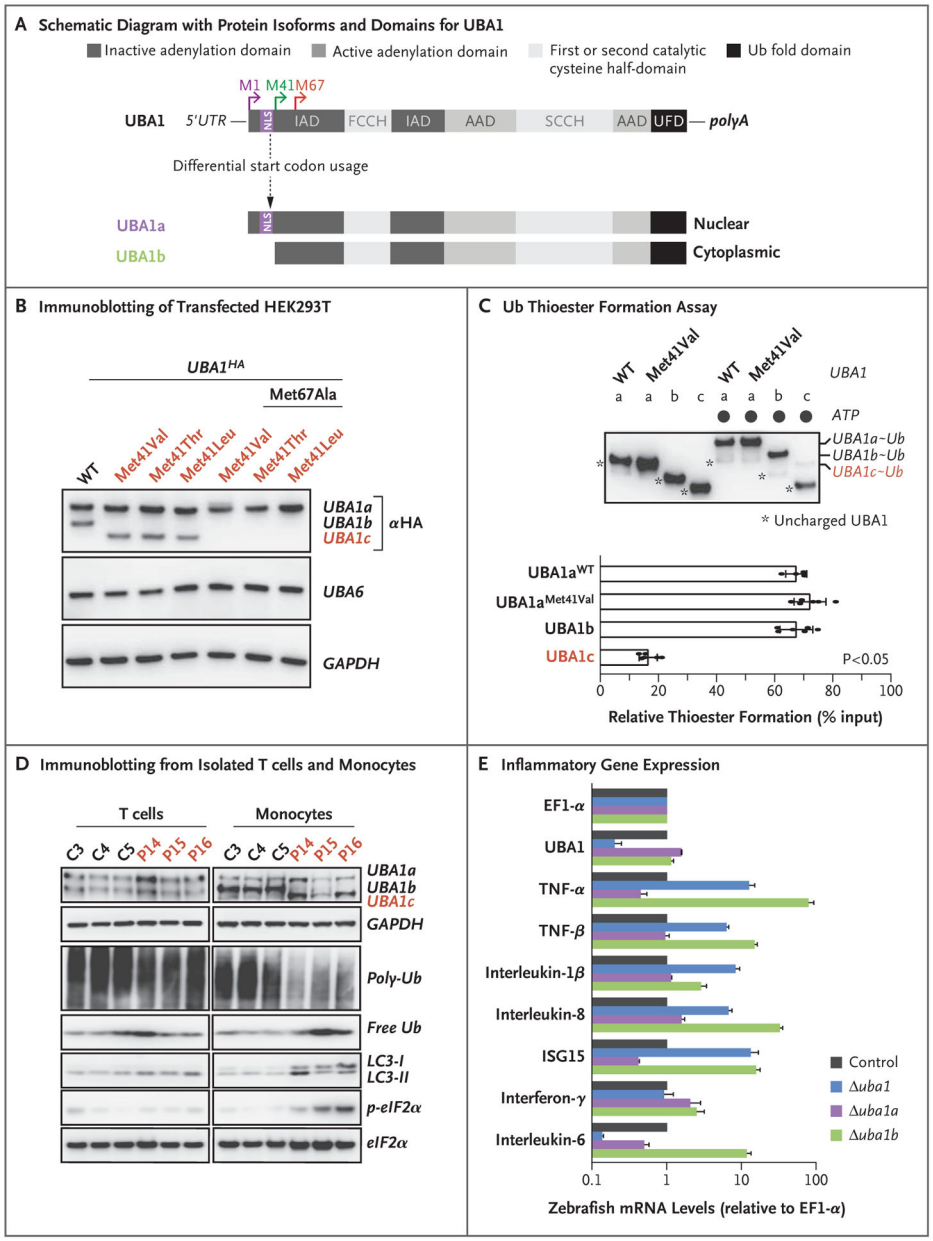

Figure 4 (facing page). Loss of Cytoplasmic *UBA1* Function Leading to Inflammation.

Panel A shows a schematic diagram with protein isoforms and domains for UBA1. UBA1a is a long isoform with a nuclear localization sequence (NLS) and a translation start site at p.Met1, and UBA1b is a short isoform without an NLS with a translation start site at p.Met41. AAD denotes active adenylation domain, FCCH first catalytic cysteine half-domain, IAD inactive adenylation domain, SCCH second catalytic cysteine half-domain, Ub ubiquitin, and UFD Ub fold domain. Panel B shows immunoblots of transfected human embryonic kidney (HEK293T) cells. Hemagglutinin (HA)-tagged UBA1 Met41 constructs lead to expression of a novel short isoform, abrogated by the introduction of a Met67Ala mutation. The term αHA denotes anti-HA, and WT wild type. Panel C shows a representative Ub thioester formation assay with the use of purified recombinant UBA1

isoforms. UBA1c shows impaired activity, whereas UBA1a p.Met41Val activity is similar to that in a UBA1a WT control. Ub thioester–charged forms of UBA1 variants are labeled with "~Ub." The quantification of five replicates is shown below in a bar chart. Thioester formation activity differed significantly between UBA1c and UBA1a WT (adjusted $P<0.05$). Panel D shows immunoblots of isolated T cells and monocytes from three participants with the VEXAS syndrome and age-matched controls. In the participants with the VEXAS syndrome, T cells are primarily WT and monocytes are primarily mutant. Mutant cells show decreased UBA1b and polyubiquitylation (Poly-Ub) levels, an increased free Ub level, and increased eIF2α phosphorylation (p-EIF2α) and LC3 levels. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as a loading control. Panel E shows higher levels of inflammatory gene expression in Δ*uba1* and Δ*uba1b* embryos than in Δ*uba1a* and sibling control heterozygous or WT control embryos (calculated as $\log_{10}$ factor change in the messenger RNA [mRNA] level). A Δ indicates loss of protein, and T bars standard errors. EF1-α denotes elongation factor 1α, ISG15 interferon-stimulated gene 15, and TNF tumor necrosis factor.

Table 1.

Demographic and Clinical Characteristics of Participants with the VEXAS Syndrome.*

Characteristic	Participants (N = 25)
Demographic characteristics	
Male sex — no. (%)	25 (100)
Median age at onset (range) — yr	64 (45–80)
Died before the current study — no. (%)	10 (40)
Genetic characteristics	
Somatic *UBA1* (NM_003334.3) variant (p.Met41) — no. (%)	25 (100)
p.Met41Thr (c.122T→C)	15 (60)
p.Met41Val (c.121A→G)	5 (20)
p.Met41Leu (c.121A→C)	5 (20)
Key clinical features	
Fever — no. (%)	23 (92)
Skin involvement — no. (%)†	22 (88)
Pulmonary infiltrate — no. (%)	18 (72)
Ear and nose chondritis — no. (%)	16 (64)
Venous thromboembolism — no. (%)	11 (44)
Macrocytic anemia — no. (%)	24 (96)
Bone marrow vacuoles — no./total no. (%)	18/18 (100)
Laboratory findings	
Median C-reactive protein (IQR) — mg/liter	73 (18–128)
Median ESR (IQR) — mm/hr	97 (64–124)
Current or past treatment	
Glucocorticoids — no. (%)	25 (100)
Median no. of synthetic DMARDs (IQR)	2 (1–3)
Median no. of biologic or target synthetic DMARDs (IQR)	2 (0.5–3)
Diagnostic or classification criteria that were met — no. (%)	
Relapsing polychondritis	15 (60)
Sweet's syndrome	8 (32)
Myelodysplastic syndrome	6 (24)
Multiple myeloma or monoclonal gammopathy of undetermined significance	5 (20)
Polyarteritis nodosa	3 (12)
Giant-cell arteritis	1 (4)

*DMARDs denotes disease-modifying antirheumatic drugs, ESR erythrocyte sedimentation rate, IQR interquartile range, and p.Met41 methionine-41.

†The most common skin-biopsy findings were neutrophilic dermatosis (in 8 participants), leukocytoclastic vasculitis (in 7 participants), and medium-vessel arteritis (in 3 participants).