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**Systematic Review and Meta Analysis**

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# Clinical features in VEXAS syndrome: a systematic review

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## Abstract

**Objective:** To systematically characterize the complete phenotypic spectrum of VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome through comprehensive analysis of all published cases since its discovery in 2020.

**Methods:** We conducted a systematic review following PRISMA guidelines across five databases. Studies reporting genetically confirmed VEXAS cases were included. To minimize duplicate counting while maximizing data utility, we applied stringent inclusion criteria. Prevalence estimates were calculated using Wilson score intervals. Results were discussed, with secondary analysis focusing on rare manifestations of the disease, and clinical recommendations as appropriate.

**Results:** Analysis of 720 patients from 33 case reports and 21 case series across 32 countries revealed cutaneous involvement as the predominant manifestation (81.8%, 95% CI: 78.8–84.5%), followed by constitutional symptoms (69.4%, 95% CI: 66.0–72.7%) and respiratory disease (61.3%, 95% CI: 57.6–64.7%). Joint involvement (47.3%, 95% CI: 43.5–51.2%), ocular disease (44.3%, 95% CI: 40.5–48.2%) and venous thromboembolism (41.8%, 95% CI: 38.3–45.4%) were also common. Myelodysplastic syndrome occurred in 35.8% (95% CI: 32.3–39.4%) of patients. Previously under-recognized manifestations included significant respiratory involvement and a broad spectrum of vascular complications. Rare but clinically significant features included cardiac involvement (7.6%), renal disease (7.0%) and CNS manifestations (7.8%).

**Conclusion:** This systematic review provides the most comprehensive characterization of VEXAS syndrome to date, establishing robust prevalence estimates across all organ systems and identifying rare manifestations with important clinical implications. These findings will facilitate earlier diagnosis, inform monitoring strategies and guide future research priorities.

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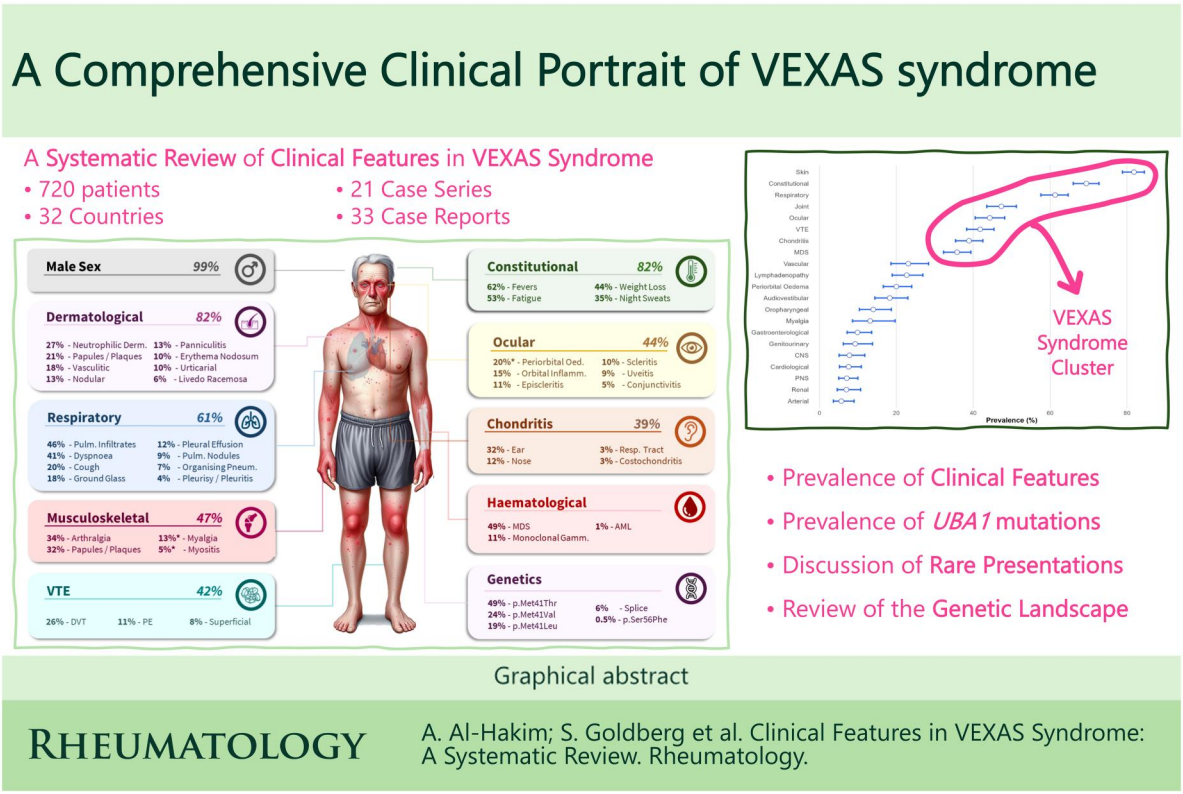
## Graphical abstract




**Keywords:** systematic review, VEXAS, UBA1, X-linked, somatic mutation, haematoinflammatory, autoinflammatory, myelodysplasia

**Rheumatology key messages**

- VEXAS syndrome presents with diverse manifestations affecting multiple systems, requiring multidisciplinary management and standardized diagnostic criteria.
- Cutaneous (81.8%), constitutional (69.4%), respiratory (61.3%), joint (47.3%) and ocular (44.3%) manifestations are most prevalent in VEXAS syndrome.
- VEXAS likely represents a spectrum of UBA1-related disorders requiring comprehensive diagnostic frameworks and treatments.

## Introduction

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is an adult-onset systemic autoinflammatory disorder with significant morbidity and mortality. Recent population-based studies suggest a prevalence of ∼1 in ∼4000 men over 50 years old [1]. The condition manifests as combined systemic inflammation and bone marrow dysfunction, with up to half of patients dying withing 5 years of diagnosis [1–3]. The disease is characterized by a highly heterogeneous clinical presentation across multiple systems. Patients experience recurrent fevers, profound fatigue, skin lesions and progressive cytopenias, leading to substantial disability and frequent hospitalizations [4]. The economic burden is considerable, with many patients requiring long-term corticosteroid therapy, repeated transfusions and intensive specialist care across multiple disciplines.

This systematic review aims to comprehensively catalogue and analyse all reported clinical manifestations of VEXAS syndrome since its discovery. By synthesizing data from all published case series and reports, we seek to establish the relative frequency of different disease features and identify rare but significant manifestations. This information will be crucial for improving disease recognition, developing standardized diagnostic criteria and guiding therapeutic decision-making.

## Methods

This systematic review was conducted according to PRISMA guidelines with prospective PROSPERO registration (CRD42024539750). We searched five databases (PubMed, Embase, Web of Science, Scopus and Cochrane) for studies reporting genetically confirmed VEXAS cases published between December 2019 and July 2024 (Fig. 1). Studies were included if they reported clinical features in adult patients with confirmed UBA1 mutations. To minimize duplicate counting while maximizing data utility, we applied stringent inclusion

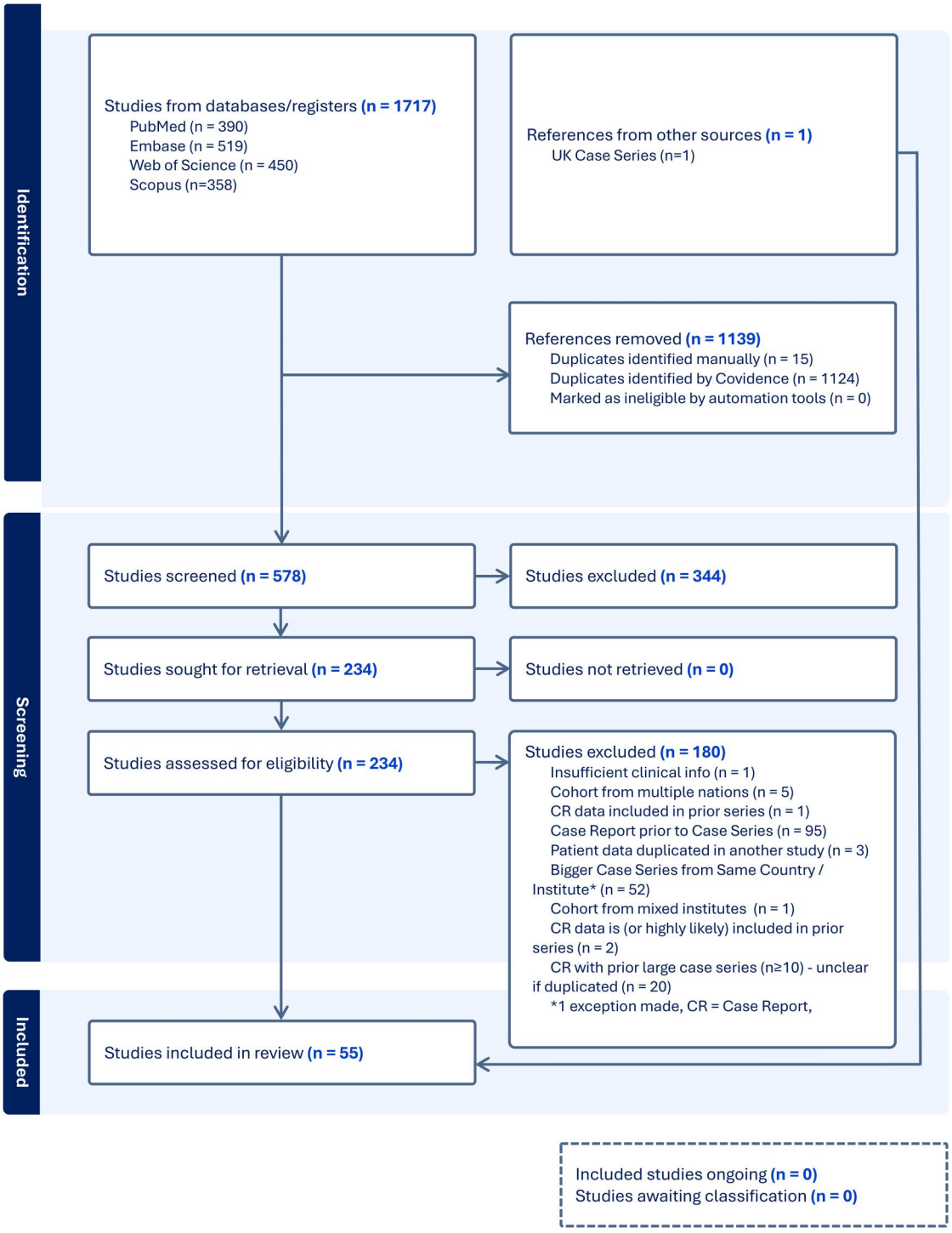



**Figure 1.** PRISMA flow diagram detailing the systematic review process

criteria. During analysis, for overlapping French cohorts ($n = 256$ and $n = 116$), we used the larger cohort as primary data source except where specific features were only reported in the smaller cohort. For each clinical feature, prevalence was calculated with corresponding 95% CIs using Wilson score intervals. To prevent artificial deflation of prevalence estimates, larger studies ($n > 20$) were excluded from denominator calculations when features were not explicitly assessed. Detailed methodology including search strategy, inclusion/exclusion criteria, data extraction protocols and statistical approaches are provided in the supplementary methods.

## Results

Our systematic review analysed clinical manifestations in up to 720 VEXAS patients across 33 case reports and 21 case series from 32 countries (Fig. 2 and Table 1). The largest contributions came from France (256 or 116 patients), USA

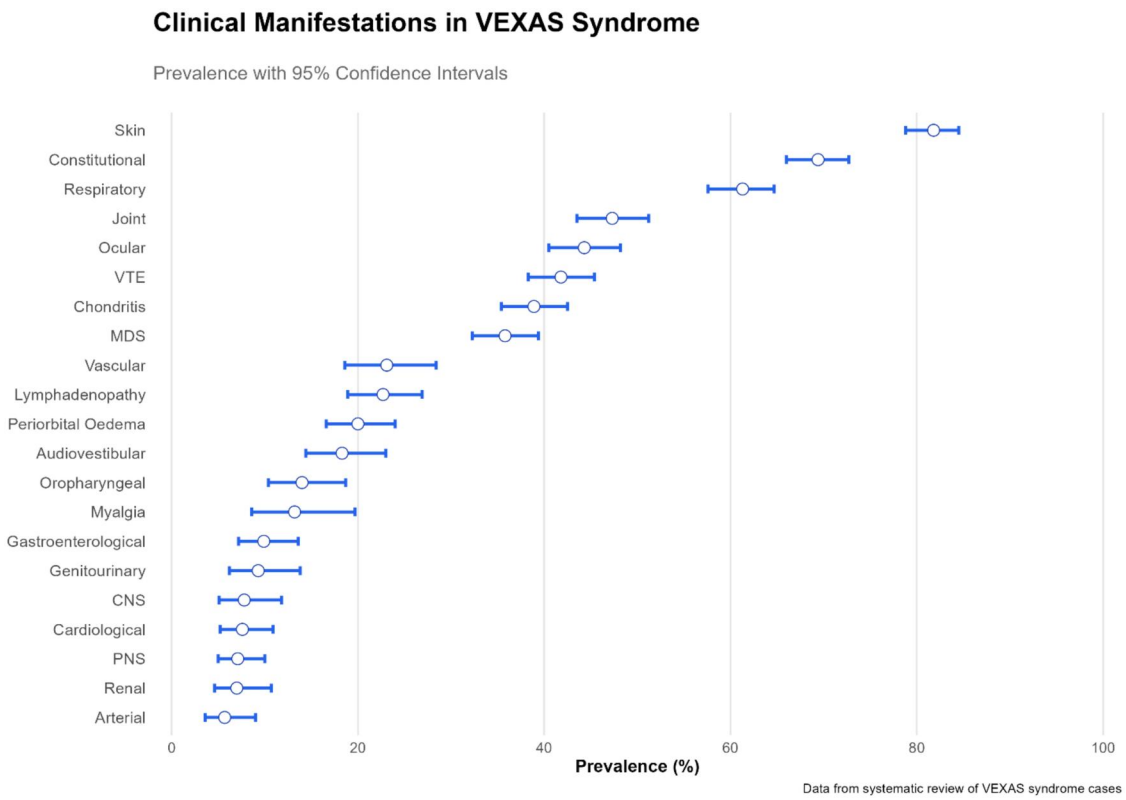



**Figure 2.** Forest plot showing the prevalence (%) of major clinical manifestations in VEXAS syndrome with 95% CIs. VTE: venous thromboembolism; MDS: myelodysplastic syndrome; PNS: peripheral nervous system

(157 patients), UK (82 patients), Italy (41 patients) and Japan (40 patients) (Table 2). The reported population were almost exclusively male (98.6%, 95% CI: 97.3–99.3%) (Table 3).

Cutaneous involvement was the most prevalent manifestation, affecting 81.8% (95% CI: 78.8–84.5%) of patients. Neutrophilic dermatoses were most frequent (27.0% [23.2–31.3%]), followed by papules/plaques (20.8% [16.3–26.1%]) and vasculitic lesions (18.1%).

Constitutional symptoms were the second most common presentation (69.4% [66.0–72.7%]), dominated by fevers (62.1% [58.5–65.6%]), fatigue (52.7% [46.2–59.1%]) and weight loss (44.2% [39.0–49.5%]).

Respiratory involvement affected 61.3% (57.6–64.7%) of patients, most commonly manifesting as pulmonary infiltrates (46.2% [41.7–50.8%]) and dyspnoea (41.3% [35.6–47.3%]), while ground glass changes (17.6%) and pleural effusions (12.2%) occur less frequently. Rarer manifestations include cryptogenic organizing pneumonia (6.9%) and pleurisy (3.5%).

Joint involvement occurred in 47.3% (43.5–51.2%) of patients, presenting as either arthralgia (34.2% [30.0–38.8%]) or inflammatory arthritis (31.7% [28.3–35.3%]). Ocular disease affected 44.3% (40.5–48.2%) of patients, while venous thromboembolism (VTE) occurred in 41.8% (38.3–45.4%). Chondritis was present in 38.9% (35.4–42.5%), predominantly affecting the ears (31.7% [26.7–37.1%]).

Among haematological manifestations, myelodysplastic syndrome was present in 35.8% (32.3–39.4%) of patients, while paraproteinemia occurred in 10.9%. Progression to acute myeloid leukaemia was rare (1.3%).

Less common but clinically significant manifestations included vascular involvement (23.1% [18.6–28.4%]), lymphadenopathy (22.7% [18.9–26.9%]) and periorbital oedema (20.0% [16.6–24.0%]). Notably rare manifestations included cardiac involvement (7.6%), renal disease (7.0%) and CNS involvement (7.8%).

Genetic analysis demonstrated that the p.Met41Thr variant (c.122T>C) was most prevalent, accounting for 49.3% (45.1–53.4%) of cases. The p.Met41Val variant (c.121A>G) was identified in 23.9% (20.6–27.6%) of cases, while p.Met41Leu (c.121A>C) was present in 19.4%. Splice variants constituted 5.9% of cases, with rarer variants including p.Ser56Phe (0.5%) and other novel mutations (0.9%) making up the remainder.

## Discussion

This systematic review provides the most comprehensive phenotypic analysis of VEXAS syndrome to date, examining manifestations across 720 patients. Here, we present a system-based analysis incorporating both prevalence data from our systematic review, findings from specialist reports, and notable rare manifestations from the literature.

Overall, our results clearly demonstrate a cluster of features (skin, constitutional, respiratory, joint, ocular, VTE, chondritis and MDS) that have come to define VEXAS (Fig. 2). VEXAS syndrome demonstrates heterogeneity of inflammatory manifestations, both overall, and within each commonly affected system. Work is urgently required to better understand the associations and clinical significance of each feature and whether they correspond with a subset of the disease, helping predict outcomes, or identify targeted therapeutic regimes.

**Table 1.** Included studies

| No. | Title | Authors | PMID | Country | Cases |
|---|---|---|---|---|---|
| 1 | VEXAS syndrome: still expanding the clinical phenotype [5] | Oganesyan *et al.* | 33693570 | Armenia | 1 |
| 2 | Inflammatory pseudotumour arising secondary to VEXAS syndrome [6] | Holmes *et al.* | 35843757 | Australia | 1 |
| 3 | Clinical images: ureteritis in VEXAS syndrome [7] | Raman and Damodaran | | Australia | 1 |
| 4 | Orbital inflammatory disease due to VEXAS syndrome: an entity to consider [8] | Ang *et al.* | 38133613 | Australia | 1 |
| 5 | The first case of VEXAS syndrome in Austria [9] | Strasser and Haushofer | 37287250 | Austria | 1 |
| 6 | Pulmonary manifestations of VEXAS syndrome with acute interstitial pneumonia and diffuse alveolar hemorrhage: a case report and literature review [10] | Puseljic *et al.* | 38956997 | Austria | 1 |
| 7 | Bone marrow reinvestigation leading to the diagnosis of VEXAS syndrome [11] | Strasser *et al.* | 38530637 | Austria | 1 |
| 8 | Case report: diagnosis of VEXAS syndrome in a patient with therapy-resistant large vessel vasculitis [12] | Boret and Malfait | | Belgium | 1 |
| 9 | Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome (VEXAS syndrome) with prominent supraglottic larynx involvement: a case-based review [13] | Guerrero-Bermúdez *et al.* | 35986821 | Colombia | 1 |
| 10 | Novel somatic UBA1 variant in a patient with VEXAS syndrome [14] | Stiburkova *et al.* | 36762418 | Czech Rep | 1 |
| 11 | Case report of a patient with VEXAS syndrome [15] | Tsourveloudis *et al.* | 38206689 | Greece | 1 |
| 12 | Cutaneous manifestations of VEXAS syndrome: multiple changing faces in the same patient [16] | De *et al.* | | India | 1 |
| 13 | VEXAS syndrome with systemic lupus erythematosus: expanding the spectrum of associated conditions [17] | Sharma *et al.* | 34463053 | India | 1 |
| 14 | VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) [18] | Varadarajan *et al.* | 36409014 | India | 1 |
| 15 | A truly VEXing diagnosis [19] | Lynch *et al.* | | Ireland | 1 |
| 16 | VEXAS, a newly reported hemato-immune disease presenting with striking ocular and systemic inflammatory features [20] | Dinneen *et al.* | | Ireland | 1 |
| 17 | VEXAS syndrome as a cause for multifocal, relapsing head and neck inflammation [21] | Heeney *et al.* | 38947541 | Ireland | 1 |
| 18 | Challenging the paradigm: a case of early-onset VEXAS syndrome [22] | Sanchez-Hernandez *et al.* | 37740251 | Mexico | 1 |
| 19 | Orbital and periorbital inflammation in VEXAS syndrome [23] | Martin-Nares *et al.* | 35302406 | Mexico | 1 |
| 20 | A man in his sixties with chondritis and bone marrow failure [24] | Midtvedt *et al.* | 35239266 | Norway | 1 |
| 21 | VEXAS syndrome in a patient with myeloproliferative neoplasia [25] | Austestad *et al.* | 36879894 | Norway | 1 |
| 22 | VEXAS syndrome without the V: a New Zealand case report [26] | Leightell-Brown and Sommer | | NZ | 1 |
| 23 | Case report: VEXAS as an example of autoinflammatory syndrome in pulmonology clinical practice [27] | Więsik-Szewczyk *et al.* | 38343641 | Poland | 1 |
| 24 | VEXAS syndrome diagnosis starting from ultrasound findings: a case report [28] | Rácz *et al.* | 38805617 | Romania | 1 |
| 25 | Vexas syndrome: on the threshold of changing perceptions of known diseases [29] | Chaltsev *et al.* | | Russia | 1 |
| 26 | VEXAS syndrome with cutaneous nodules [30] | Argobi | 35795842 | Saudi Arabia | 1 |
| 27 | The first Korean case of VEXAS syndrome caused by a UBA1 somatic variant [31] | Yoon *et al.* | 36281520 | South Korea | 1 |
| 28 | A case of VEXAS syndrome manifesting as Kikuchi-Fujimoto disease, relapsing polychondritis, venous thromboembolism and macrocytic anaemia [32] | Lee *et al.* | 33630036 | Singapore | 1 |
| 29 | VEXAS syndrome and thrombosis: findings of inflammation, hypercoagulability, and endothelial dysfunction [33][a] | Fan *et al.* | 38181815 | Singapore | 1 |
| 30 | Case report: lower limb pseudocellulitis due to calf myositis in VEXAS syndrome [34] | Lim and Chua | 39045896 | Singapore | 1 |
| 31 | Rhombencephalitis in a patient with VEXAS syndrome [35] | Johnsson | | Sweden | 1 |
| 32 | An unusual initial presentation of VEXAS syndrome [36] | Galindo-Feria and Chatzidionysiou | | Sweden | 1 |
| 33 | VEXAS syndrome with severe multisystem involvement: rapid recovery after splenectomy [37] | Yildirim *et al.* | 36544349 | Turkey | 1 |
| 34 | Challenges in diagnosis and treatment of VEXAS syndrome: two case reports [38] | Raj and Sadawarte | | Australia | 2 |

(continued)

**Table 1.** (continued)

| No. | Title | Authors | PMID | Country | Cases |
|---|---|---|---|---|---|
| 35 | Case report: VEXAS syndrome: from mild symptoms to life-threatening macrophage activation syndrome [39] | Staels *et al.* | 34046042 | Belgium | 2 |
| 36 | VEXAS-syndrome, a newly described autoinflammatory systemic disease with dermatologic manifestations [40] | Baur *et al.* | 37953404 | Germany | 2 |
| 37 | VEXAS syndrome: complete molecular remission after hypomethylating therapy [41] | Sockel *et al.* | 38214707 | Germany | 2 |
| 38 | Venous inflammation might be one of the features of VEXAS syndrome and associated thrombosis [42] | Karadeniz *et al.* | 37099698 | Turkey | 2 |
| 39 | VEXAS syndrome: lessons learnt from an early Australian case series [43] | Islam *et al.* | 35419965 | Australia | 3 |
| 40 | Tofacitinib as a biologic response modifier in VEXAS syndrome: a case series [44] | Salehi *et al.* | 37337622 | Australia | 3 |
| 41 | VEXAS syndrome: a report of three cases [45] | Ciferská *et al.* | 35238760 | Czech Rep | 3 |
| 42 | VEXAS and myelodysplastic syndrome: an interdisciplinary challenge [46] | Kreutzinger *et al.* | 38398362 | Germany | 4 |
| 43 | VEXAS syndrome: clinical case series from a Canadian cohort [47] | Williams *et al.* | 38490666 | Canada | 6 |
| 44 | VEXAS syndrome: a call for diagnostic awareness based on a case series of seven patients [48] | Pinto *et al.* | 37071935 | Portugal | 7 |
| 45 | Adult-onset autoinflammation caused by somatic mutations in UBA1: A Dutch case series of patients with VEXAS [2] | van der Made *et al.* | 34048852 | Netherlands | 12 |
| 46 | Treatment experiences with focus on IL-6R inhibition in patients with VEXAS-syndrome and a case of remission with azacytidine treatment [49] | Johansen *et al.* | 38141211 | Denmark | 16 |
| 47 | VEXAS syndrome: a national retrospective cohort study [50] | Wolff *et al.* | | Switzerland | **17** |
| 48 | Spanish cohort of VEXAS syndrome: clinical manifestations, outcome of treatments and novel evidences about UBA1 mosaicism [51] | Mascaro *et al.* | 37666646 | Spain | 30 |
| 49 | Efficient detection of somatic UBA1 variants and clinical scoring system predicting patients with variants in VEXAS syndrome [52] | Maeda *et al.* | 37606963 | Japan | 40 |
| 50 | Diagnostic capabilities, clinical features, and longitudinal UBA1 clonal dynamics of a nationwide VEXAS cohort [53] | Gurnari *et al.* | 38108611 | Italy | 41 |
| 51 | Pulmonary manifestations in VEXAS syndrome [54] | Moura *et al.* | 37062498 | USA Mayo | 45 |
| 52 | Treatment outcomes in VEXAS syndrome: a retrospective study from the UK VEXAS interest group (VEXNET-UK) [55] | Al-Hakim *et al.* | | UK | 82 |
| 53 | Skin manifestations of VEXAS syndrome and associated genotypes [56] | Tan *et al.* | | USA NIH | 112 |
| 54 | Further characterization of clinical and laboratory features in VEXAS syndrome: large-scale analysis of a multicentre case series of 116 French patients [3] | Georgin-Lavialle *et al.* | 34632574 | France | 116 |
| 55 | Biologics and JAK inhibitors efficacy in VEXAS syndrome from French multicenter case series of 256 patients [57] | Mekinian *et al.* | | France | 256 |

Comprehensive overview of published VEXAS syndrome studies included in the systematic review. Studies are listed with details including title, authors, PubMed ID (PMID), country of origin and number of cases reported. Articles are numbered 1–55 for reference.
[a] Case report extracted from $n = 2$ where patient 1 was duplicated.

## Cutaneous manifestations

Our analysis confirms cutaneous involvement as the predominant feature of VEXAS syndrome of patients, in-keeping with previously reported prevalences (Fig. 3) 6].

Cutaneous manifestations represent a common and often initial feature of VEXAS syndrome. Skin disease frequently appears early, presenting as the first manifestation in 45–61% of patients in separate case series [56, 58]. The pattern of cutaneous involvement demonstrates genotype-specific associations, with Tan *et al.* demonstrating an association between p.Met41Leu variants and neutrophilic dermatosis (82% [14/17] of cases), while p.Met41Val variants more commonly manifested with vasculitic lesions (55% [11/20] of cases) with a mixed leukocytic infiltrate (85% [17/20]) [56]. Treatment responses vary, with corticosteroids showing high initial efficacy (92% response rate) but limited long-term utility due to toxicity concerns [56].

Recent histopathological analyses suggest two distinct patterns of skin involvement: 'clonal' lesions containing *UBA1*-mutated cells (neutrophilic dermatoses) and 'paraclonal' manifestations driven by inflammatory mediators (leukocytoclastic vasculitis), suggesting distinct pathophysiological drivers in manifesting cutaneous disease [59]. The high expression of chemokine receptors CXCR3 and CCR4 on dysfunctional monocytes, coupled with their localization near dermal blood vessels, provides mechanistic insight into

**Table 2.** Contribution of cases by country

| Country ($n = 32$) | Cases | Case reports ($n = 1$) | Case series ($n > 1$) |
|---|---|---|---|
| Armenia | 1 | 1 | |
| Australia | 11 | 3 | 3 |
| Austria | 3 | 3 | |
| Belgium | 3 | 1 | 1 |
| Canada | 6 | | 1 |
| Colombia | 1 | 1 | |
| Czech Rep | 4 | 1 | 1 |
| Denmark | 16 | | 1 |
| France | 256/116 | | 1 or 1 |
| Germany | 8 | | 3 |
| Greece | 1 | 1 | |
| India | 3 | 3 | |
| Ireland | 3 | 3 | |
| Italy | 41 | | 1 |
| Japan | 40 | | 1 |
| Mexico | 2 | 2 | |
| Netherlands | 12 | | 1 |
| Norway | 2 | 2 | |
| NZ | 1 | 1 | |
| Poland | 1 | 1 | |
| Portugal | 7 | | 1 |
| Romania | 1 | 1 | |
| Russia | 1 | 1 | |
| Saudi Arabia | 1 | 1 | |
| Singapore | 3 | 3 | |
| South Korea | 1 | 1 | |
| Spain | 30 | | 1 |
| Sweden | 2 | 2 | |
| Switzerland | 17 | | 1 |
| Turkey | 3 | 1 | 1 |
| UK | 82 | | 1 |
| USA (two sites) | 157 | | 2 |
| Total | 580/720 | 33 | 21 |

Geographic distribution of reported VEXAS syndrome cases in the literature. Data is presented by country, showing total cases and their distribution between individual case reports and case series ($n > 1$). France reports two different totals due to potential overlap between cohorts, with these studies used for separate prevalence calculations.

the tissue-specific inflammatory response [60]. Rarer cutaneous manifestations include pyoderma gangrenosum, granulomatous dermatitis and neutrophilic eccrine hidradenitis.

Given the high prevalence and early presentation of skin manifestations in VEXAS, clinicians should maintain a high index of suspicion for this diagnosis in older male patients presenting with neutrophilic dermatoses or vasculitic lesions, particularly when accompanied by systemic inflammation or cytopenias. Early genetic testing is warranted, as the specific *UBA1* variant may help predict the pattern of cutaneous involvement, guiding therapeutic decision-making [56].

## Constitutional features

Constitutional symptoms affect 69.4% of patients, with fevers, fatigue and weight loss forming a characteristic triad. The specific pattern and periodicity of fevers in VEXAS syndrome requires further characterization through prospective studies.

Anecdotally, fatigue is increasingly recognized as a key complaint in the clinical setting, and it may be that these studies are under-reporting this feature due to its inherent subjectivity, mixed aetiology (inflammation *vs* cytopenias) and the underuse of standardized clinical scores to capture it. Certainly, further work is required to characterize the cause and responsiveness of fatigue, especially when considering its use in disease activity indices, as prospective treatment trials are developed.

## Respiratory disease

The 61.3% prevalence of respiratory involvement represents a higher disease burden than previously recognized, though it is a well-known feature of the disease [61].

Borie *et al.* showed VEXAS syndrome CT scan patterns demonstrating three distinct phenotypes: organizing pneumonia-like changes, nonspecific unilateral involvement and a pattern mimicking heart failure with bilateral involvement and mediastinal adenopathy [61]. The therapeutic response pattern provides compelling evidence for direct VEXAS-mediated pathology, as pulmonary infiltrates resistant to both diuretics and antibiotics demonstrated consistent resolution with prednisolone >20 mg/d. *UBA1* mutations in bronchoalveolar lavage samples (82% macrophages) and the temporal correlation between systemic disease flares and pulmonary manifestations support this further [61]. In a separate study, analysis of bronchoalveolar lavage data revealed neutrophilic alveolitis in 42% of cases, suggesting active inflammatory processes within the lung parenchyma [54]. The range of manifestations from interstitial lung disease to organizing pneumonia suggests multiple pathophysiological mechanisms, potentially including both direct tissue infiltration by mutated cells and secondary inflammatory damage.

The role for routine chest imaging and pulmonary function tests in patients with VEXAS syndrome has yet not been agreed and should be a subject of future prospective studies. There should be early consideration of high-dose glucocorticoid therapy when inflammatory pulmonary involvement is identified, as these manifestations appear to represent direct disease activity rather than secondary complications.

## Musculoskeletal system

Though many studies report arthralgia or inflammatory arthritis in VEXAS, it is noteworthy that most studies (including all case series $n > 20$) did not specify their methodology for assessing joint involvement, with few reporting radiological findings. The lack of standardized assessment protocols and limited use of advanced imaging modalities (e.g. ultrasound or MRI) may lead to underestimation of both the prevalence and severity of joint involvement. Comprehensive musculoskeletal imaging studies are needed to properly characterize the pattern, extent and evolution of joint disease and to evaluate genotype-phenotype patterns.

While rare, VEXAS-associated myositis has been documented in three cases, characterized by MRI-confirmed muscle inflammation despite normal or minimally elevated creatine kinase levels [62, 63, 34]. Muscle biopsies revealed distinctive macrophage infiltration, differing from typical inflammatory myopathies. This pattern, along with reported orbital muscle involvement, suggests a unique pathophysiological mechanism warranting further investigation [8, 21, 23].

Overall, clinicians should be aware of the possibility of underlying muscle inflammation in patients with VEXAS syndrome with persistent myalgias despite a normal creatine kinase level.

## Vascular and thrombotic disease

Vascular manifestations in VEXAS present a complex spectrum of pathology. We recognize here a high rate of VTE with deep vein thrombosis (DVT) predominating over

**Table 3.** Overall prevalence of clinical features in systematic review

| Clinical feature | Prevalence | Cases | Percentage (95% CI) |
|---|---|---|---|
| Demographics | | | |
| Male sex | 572 | 580 | 98.6% (97.3–99.3%) |
| Overall dermatological | 589 | 720 | 81.8% (78.8–84.5%) |
| Neutrophilic dermatoses | 123 | 455 | 27.0% (23.2–31.3%) |
| Papules/plaques | 54 | 260 | 20.8% (16.3–26.1%) |
| Vasculitic | 88 | 485 | 18.1% (15.0–21.8%) |
| Nodular | 15 | 114 | 13.2% (8.1–20.6%) |
| Panniculitis | 19 | 144 | 13.2% (8.6–19.7%) |
| Erythema nodosum | 24 | 230 | 10.4% (7.1–15.1%) |
| Urticarial | 31 | 305 | 10.2% (7.3–14.1%) |
| Livedo racemosa | 9 | 144 | 6.2% (3.3–11.5%) |
| Overall constitutional | 500 | 720 | 69.4% (66.0–72.7%) |
| Fevers | 447 | 720 | 62.1% (58.5–65.6%) |
| Fatigue | 119 | 226 | 52.7% (46.2–59.1%) |
| Weight loss | 151 | 342 | 44.2% (39.0–49.5%) |
| Night sweats | 78 | 226 | 34.5% (28.6–40.9%) |
| Anorexia | 1 | 114 | 0.9% (0.2–4.8%) |
| Overall respiratory | 441 | 720 | 61.3% (57.6–64.7%) |
| Pulmonary infiltrates | 211 | 457 | 46.2% (41.7–50.8%) |
| Dyspnoea | 112 | 271 | 41.3% (35.6–47.3%) |
| Cough | 32 | 159 | 20.1% (14.6–27.0%) |
| Ground glass change | 28 | 159 | 17.6% (12.5–24.3%) |
| Pleural effusion | 52 | 427 | 12.2% (9.4–15.6%) |
| Pulmonary nodules | 15 | 159 | 9.4% (5.8–15.0%) |
| Cryptogenic organizing pneumonia | 11 | 159 | 6.9% (3.9–12.0%) |
| Pleurisy/pleuritis | 4 | 114 | 3.5% (1.4–8.7%) |
| Overall joint | 302 | 638 | 47.3% (43.5–51.2%) |
| Arthralgia | 151 | 441 | 34.2% (30.0–38.8%) |
| Inflammatory arthritis | 215 | 679 | 31.7% (28.3–35.3%) |
| Overall ocular | 281 | 634 | 44.3% (40.5–48.2%) |
| Orbital inflammation | 17 | 114 | 14.9% (9.5–22.6%) |
| Episcleritis | 32 | 300 | 10.7% (7.7–14.7%) |
| Scleritis | 32 | 315 | 10.2% (7.3–14.0%) |
| Uveitis | 39 | 440 | 8.9% (6.6–11.9%) |
| Conjunctivitis | 10 | 184 | 5.4% (3.0–9.7%) |
| Overall VTE | 301 | 720 | 41.8% (38.3–45.4%) |
| DVT | 68 | 266 | 25.6% (20.7–31.1%) |
| PE | 30 | 266 | 11.3% (8.0–15.6%) |
| Superficial | 13 | 159 | 8.2% (4.8–13.5%) |
| Overall chondritis | 280 | 720 | 38.9% (35.4–42.5%) |
| Ear | 95 | 300 | 31.7% (26.7–37.1%) |
| Nose | 37 | 300 | 12.3% (9.1–16.5%) |
| Respiratory tract | 5 | 184 | 2.7% (1.2–6.2%) |
| Costochondritis | 3 | 114 | 2.6% (0.9–7.5%) |
| Overall vascular | 65 | 281 | 23.1% (18.6–28.4%) |
| Small vessel | 28 | 199 | 14.1% (9.9–19.6%) |
| Medium vessel | 7 | 159 | 4.4% (2.1–8.8%) |
| Large vessel | 7 | 230 | 3.0% (1.5–6.1%) |
| Overall lymphadenopathy | 94 | 415 | 22.7% (18.9–26.9%) |
| Mediastinal/hilar | 35 | 275 | 12.7% (9.3–17.2%) |
| Cervical | 9 | 230 | 3.9% (2.1–7.3%) |
| Periorbital oedema | 91 | 454 | 20.0% (16.6–24.0%) |
| Overall oropharyngeal | 38 | 271 | 14.0% (10.4–18.7%) |
| Laryngitis | 17 | 114 | 14.9% (9.5–22.6%) |
| Parotitis | 5 | 114 | 4.4% (1.9–9.9%) |
| Oral ulcers | 8 | 226 | 3.5% (1.8–6.8%) |
| Audiovestibular | 57 | 311 | 18.3% (14.4–23.0%) |
| Hearing loss | 29 | 159 | 18.2% (13.0–25%) |
| Muscular | | | |
| Myalgia | 19 | 144 | 13.2% (8.6–19.7%) |
| Myositis | 6 | 114 | 5.3% (2.4–11.0%) |
| Overall gastroenterological | 34 | 342 | 9.9% (7.2–13.6%) |
| Hepatosplenomegaly | 25 | 342 | 7.3% (5.0–10.6%) |
| Colitis | 7 | 226 | 3.1% (1.5–6.3%) |
| Overall genitourinary | 21 | 226 | 9.3% (6.2–13.8%) |
| Epididymitis/orchitis | 20 | 226 | 8.8% (5.8–13.3%) |
| Overall cardiological | 26 | 342 | 7.6% (5.2–10.9%) |
| Pericardial effusion | 4 | 114 | 3.5% (1.4–8.7%) |
| Pericarditis | 8 | 342 | 2.3% (1.2–4.5%) |
| Myocarditis | 7 | 342 | 2.0% (1.0–4.2%) |
| Overall renal | 19 | 270 | 7.0% (4.6–10.7%) |
| AIN | 1 | 114 | 0.9% (0.2–4.8%) |
| Overall PNS | 29 | 410 | 7.1% (5.0–10.0%) |
| Peripheral neuropathy | 21 | 410 | 5.1% (3.4–7.7%) |
| Multineuritis | 3 | 370 | 0.8% (0.3–2.4%) |
| CIPD | 5 | 370 | 1.4% (0.6–3.1%) |
| Overall CNS | 20 | 256 | 7.8% (5.1–11.8%) |
| CVA | 10 | 226 | 4.4% (2.4–8.0%) |
| Overall arterial | 17 | 296 | 5.7% (3.6–9.0%) |
| Haematological | | | |
| MDS | 247 | 690 | 35.8% (32.3–39.4%) |
| Monoclonal gammopathy | 71 | 650 | 10.9% (8.8–13.6%) |
| AML | 2 | 155 | 1.3% (0.4–4.6%) |
| Genetics | | | |
| 122T>C (p.Met41Thr) | 274 | 556 | 49.3% (45.1–53.4%) |
| 121A>G (p.Met41Val) | 133 | 556 | 23.9% (20.6–27.6%) |
| 121A>C (p.Met41Leu) | 108 | 556 | 19.4% (16.4–22.9%) |
| Splice | 33 | 556 | 5.9% (4.3–8.2%) |
| c.167C>T (p.Ser56Phe) | 3 | 556 | 0.5% (0.2–1.6%) |
| Other | 5 | 556 | 0.9% (0.4–2.1%) |

Prevalence of clinical manifestations in VEXAS syndrome based on systematic review of published cases. Features are grouped by organ system with total cases, number affected and calculated prevalence with 95% CIs. Hierarchical organization shows both overall system involvement and specific manifestations within each category. AIN: acute interstitial nephritis; CVA: cerebrovascular accident; CIDP: chronic inflammatory demyelinating polyneuropathy VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; PNS: peripheral nervous system; MDS: myelodysplastic syndrome; AML: acute myeloid leukaemia.

pulmonary embolism (PE). There has been one report of cerebral sinus vein thrombosis and clinicians should be mindful of this possibility [64]. It has previously been reported that two-thirds of VTEs occur within the first 2 years of inflammatory manifestations, while the recent UK treatment outcome study demonstrated a low incidence of thrombosis while on treatment, suggesting inflammatory control may ameliorate thrombotic risk [55, 65]. Generally, the high thrombotic burden appears independent of traditional risk factors, suggesting disease-specific prothrombotic mechanisms [66].

Beyond thrombosis, vasculitis affected a quarter of patients, with a propensity for small vessels over medium and large vessels, as noted in other studies focused on the manifestation [67]. This hierarchical distribution pattern may reflect the tissue distribution of *UBA1*-mutated cells.

We identified eight instances of aortitis across six studies in the selected literature, with one occurrence of aortic dissection, highlighting the potential severity and consequences of this feature [3, 12, 24, 39, 45, 50, 68]. In a French cohort of 116 patients with VEXAS syndrome, the prevalence of aortitis was 1.7% [3]. Aortitis can only be diagnosed with advanced radiography, thus clinicians should maintain a high index of suspicion for this potentially serious manifestation.

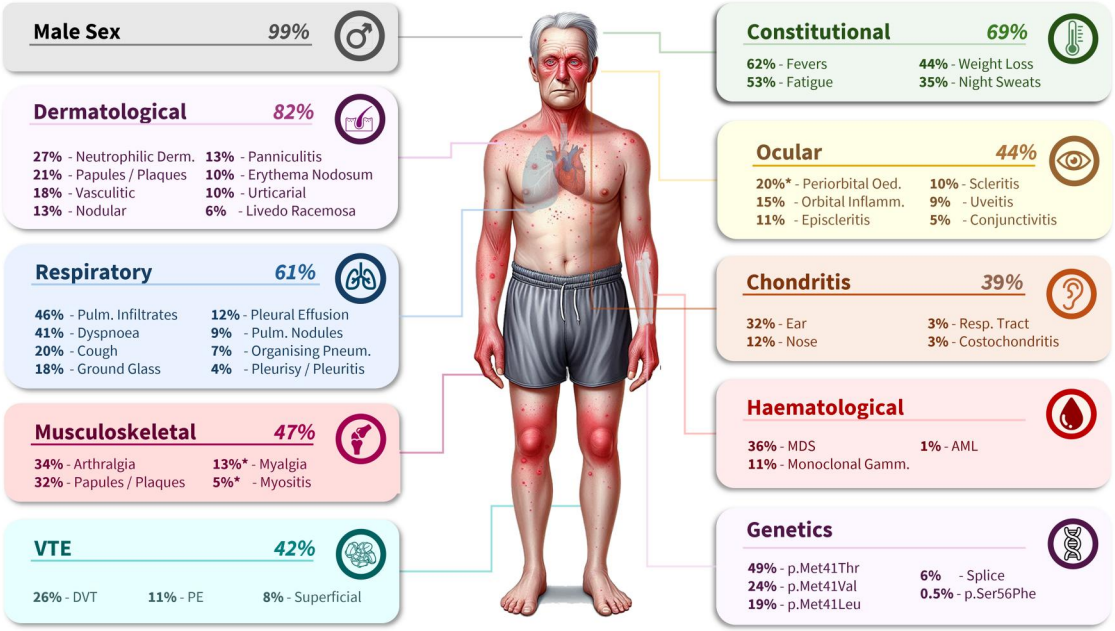



**Figure 3.** Diagram summarizing the major clinical manifestations (prevalence >25%) of VEXAS syndrome. *Data for this feature was not used for the prevalence calculations of the assigned category. VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; MDS: myelodysplastic syndrome; AML: acute myeloid leukaemia

### Neurological manifestations

The relative rarity of neurological features suggests potential protective mechanisms against *UBA1*-mutated cell infiltration of neural tissues, though further research is needed to clarify to what extent these manifestations are caused by a VEXAS-mediated process, and if they can be predicted or prevented.

One case reported VEXAS with Lewis and Sumner syndrome, an immune-mediated peripheral neuropathy, with abnormal nerve conduction studies and characteristic biopsies, who demonstrated dramatic improvement following therapy with azacitidine [69]. This suggested mechanistic link between VEXAS and immune-mediated neuropathy warrants further investigation [2, 70].

Rare neurological manifestations include optic neuritis, aseptic meningitis, inflammatory pseudotumor, CNS vasculitis and rhombencephalitis [2, 6, 8, 35, 40, 71]. Given the potential severity of CNS involvement, early neuroimaging and CSF analysis should be considered after excluding other inflammatory, autoimmune and neoplastic conditions.

## Cardiac disease

Though relatively uncommon, cardiac manifestations warrant vigilance given their potential severity. The predominance of inflammatory over structural cardiac disease suggests systemic inflammation, rather than direct tissue infiltration, as the primary pathogenic mechanism.

Recent data from a large French cohort of 299 patients provides additional insight, demonstrating cardiac events in 2.7% and non-ischemic events in 1.7% [72]. The paper noted that these non-ischemic events occurred during inflammatory flares, suggesting a mechanistic link between systemic inflammation and cardiac pathology. The high mortality rate in cardiac-affected patients, and positive response to targeted anti-inflammatory therapy in some cases, reinforces the need for optimal cardiac surveillance in VEXAS syndrome.

## Ophthalmic disease

Our analysis identified orbital inflammation (14.9%), episcleritis (10.7%), scleritis (10.2%), and uveitis (8.9%) as significant components of ocular disease in VEXAS syndrome. While periorbital oedema (20.0%) is a well-recognized manifestation of VEXAS, clinicians should be mindful of the heightened risk of associated ocular damage in patients with evident or suspected orbital inflammation, which may involve dacryoadenitis, choroidal detachment and orbital muscle myositis [8, 21, 23, 44, 73].

Clinical outcomes suggest a favourable prognosis in patients with isolated ocular involvement when treated with medium-dose glucocorticoids (20–40 mg/day), with rapid and good responses observed in most cases [68, 74]. However, the same study also noted that orbital/ocular manifestations were often relapsing-remitting, with recurrent episodes occurring in 75% of cases, requiring careful monitoring. Notably, the international AIDA network registry study found a significant association between relapsing polychondritis (RP) and orbital/ocular involvement in VEXAS syndrome (relative risk: 2.37, 95% CI: 1.03–5.46, $P = 0.048$), suggesting potential shared pathogenic mechanisms [75].

Given the high frequency of ocular involvement, significant recurrence rate and potential for structural damage, patients with VEXAS syndrome and eye disease should undergo regular ophthalmological screening, with particular attention paid to those presenting with RP. Early recognition and appropriate immunosuppressive therapy may help prevent permanent ocular complications in those at risk.

## Chondritis

Our study found that chondritis in VEXAS predominantly affects the ears over the nose, with respiratory tract involvement notably rare. As previously reported, this distribution

pattern differs from traditional RP, offering diagnostic utility [76].

Studies have established important genotype-phenotype correlations in VEXAS-RP, with patients carrying the p.Met41Val variant being less likely to develop ear chondritis (22% *vs* 53–66%, $P < 0.01$) [77]. A detailed comparison by Khitri *et al.* found VEXAS-RP demonstrates distinct clinical features from idiopathic RP (I-RP), including lower rates of nasal chondritis, significantly higher inflammatory markers (median CRP 64 mg/l *vs* 10 mg/l, $P < 0.001$) and greater prevalence of systemic manifestations [76]. Notably, their analysis revealed VEXAS-RP patients had poorer outcomes, with markedly lower remission rates compared with I-RP (27% *vs* 90%, $P < 0.001$), and significantly higher mortality, though ear chondritis is actually associated with a lower risk of mortality within the VEXAS population itself [76, 77]. Ferrada *et al.* demonstrated VEXAS-RP could be predicted with 100% sensitivity and 96% specificity in men with chondritis, macrocytosis and platelets $<200 \times 103/\mu l$ [78].

Overall, clinicians should be highly suspicious of VEXAS in older men with chondritis with raised CRPs, systemic features, macrocytosis and cytopenias. This constellation should necessitate genetic screening and referral given the likelihood of VEXAS syndrome.

## Genitourinary and renal systems

Epididymitis/orchitis represented the predominant genitourinary feature of VEXAS syndrome. Acute tubulointerstitial nephritis, while rare (0.9%), may represent an under-recognized complication, due to the need for biopsy, and clinicians should be aware of the possibility in the event of renal dysfunction [79–81].

## Oropharyngeal and audiovestibular disease

Audiovestibular disease affected almost one-fifth of patients, with hearing loss representing the majority of cases. A recent case report documented successful treatment of sensorineural hearing loss with intratympanic steroid injections in early-onset VEXAS syndrome [22]. Though an isolated case, it suggests that prompt ENT evaluation may be warranted when audiovestibular symptoms develop, particularly given the risk of permanent hearing loss.

## Lymphoid system

Lymphadenopathy presents in almost one-fifth of patients, with a predilection for mediastinal/hilar involvement over cervical disease. The pattern and distribution of lymphoid involvement may have diagnostic utility in distinguishing VEXAS from other inflammatory conditions and haematological malignancies.

## Haematological features and plasma cell dyscrasias

Myelodysplastic syndrome represents a defining feature, present in around one-third of patients. Recent evidence suggests VEXAS represents a unique entity within the myeloid neoplasm spectrum, characterized by clonal cytopenia with inflammatory features rather than traditional MDS [4]. This distinction has important implications for prognostication and treatment selection.

Unlike traditional MDS, VEXAS-associated MDS reportedly demonstrates a less complex mutational profile, with patients typically having fewer additional myeloid driver mutations and a higher frequency of mutations restricted primarily to epigenetic regulators like *DNMT3A* and *TET2* [82, 83]. These cases predominantly manifest as MDS with single-lineage dysplasia or multilineage dysplasia, with 73% (27/37) of evaluable patients presenting with very-low/low risk disease according to the IPSS-M risk stratification system, which poorly predicts the mortality of VEXAS-MDS [82].

Notably, while traditional MDS can progress to acute myeloid leukaemia (AML) in around one-third of cases, transformation to acute leukaemia appears rare in VEXAS-MDS, supported by an prevalence of 1.3% in our review [84]. The molecular mechanisms of progression were highlighted in a recent case, where transformation coincided with acquisition of a *RUNX1* mutation in a VEXAS patient with pre-existing *ASXL1/SF3B1*-mutant MDS, with a second reported in a *TET2*-mutant MDS [85]. VEXAS patients that evolved to AML harboured strong AML drivers such as RUNX1 and ASXL1 (which are infrequent in VEXAS), suggesting potent secondary events are required to induce AML [53, 85, 86].

Monoclonal gammopathy occurred in 10.9% of patients, comparing to a normal prevalence of 3.7–5.6% in men aged 60–79 years old [87]. Recent analysis of 28 VEXAS patients demonstrated a higher frequency of plasma cell disorders, with 28.6% having clonal plasma cells in bone marrow (three MGUS and five multiple myeloma) [88]. These clonal plasma cells showed distinctive molecular features, including frequent t(11; 14) translocations and cyclin D1 expression, suggesting a potential mechanistic link between defective *UBA1* function and plasma cell dysregulation.

Macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH) represents a rare but clinically significant haematological complication of VEXAS syndrome, documented in several published case reports [39, 63, 89, 90]. The literature demonstrates diverse presentations, including cases triggered by Epstein–Barr virus (EBV) viremia and *Campylobacter jejuni* bacteraemia, as well as cases developing in the context of severe underlying inflammation. Where done, bone marrow examination in these cases consistently revealed haemophagocytosis, accompanied by marked hyperferritinemia and progressive cytopenias. Various therapeutic approaches have been documented, including JAK inhibition, IL-6 blockade and high-dose corticosteroids, with variable outcomes. Given the potentially life-threatening nature of this complication, clinicians should maintain vigilance for MAS/HLH development in VEXAS patients.

## Genetics

The male predominance in VEXAS syndrome reflects its X-linked inheritance pattern. Most reported symptomatic female cases are explained by chromosomal abnormalities, typically monosomy X [91]. Of note, analysis in the NIH All of Us cohort identified p.Met41Leu variants in 74 asymptomatic participants, predominantly women (84%), with ages ranging from 20–83 years, suggesting factors beyond the UBA1 mutation are required for clinical VEXAS development [92].

Research has demonstrated that specific variants correlate with distinct clinical phenotypes and outcomes. The p.Met41Val variant, present in approximately one-quarter of cases in our study, is associated with more severe disease and shorter survival compared with other variants [77]. Conversely, the p.Met41Leu variant typically confers a better prognosis [3]. These genotype-phenotype correlations are

increasingly recognized as crucial for risk stratification and treatment planning.

The relative rarity of splice variants and novel mutations (collectively ~7%) suggests that most pathogenic *UBA1* mutations cluster around the Met41 position. However, Collins *et al.* recently identified six novel somatic mutations that lead to VEXAS syndrome by impacting UBA1 catalytic function, rather than isoform expression [93]. Similarly, the p.Ser56Phe (S56F) variant affects UBA1 enzyme efficiency in a temperature-dependent manner, and drive a milder inflammatory phenotype, characterized by mainly cytopenias [94]. The emergence of these functionally distinct variants suggests VEXAS represents a spectrum of UBA1-related disorders, necessitating comprehensive characterization of genotype-phenotype correlations to inform diagnosis and therapeutic strategies.

In light of canonical mutations in asymptomatic individuals and the widening spectrum of *UBA1*-related disease, there is now a pressing need to develop a comprehensive diagnostic framework for VEXAS syndrome; incorporating both clinical and genetic features to optimize trial recruitment and accelerate the development of effective therapies [92].

## Clinical and research implications

This comprehensive characterization has immediate implications for clinical practice. It enhances understanding of the disease's diverse presentations, facilitating earlier diagnosis and providing a foundation for developing formal diagnostic criteria and trial inclusion guidelines. The broad spectrum of manifestations necessitates a multidisciplinary approach to patient care, with particular emphasis on respiratory, vascular, ocular, and haematological surveillance.

The identified high-prevalence features should inform diagnostic strategies, particularly in older male patients presenting with these manifestations alongside cytopenias.

Several critical research priorities emerge from this analysis. International VEXAS registries and large-scale prospective cohort studies are urgently needed to validate prevalence estimates and better define the syndrome's natural history. These collaborative platforms would enable standardized data collection across multiple centres, facilitating robust analysis of treatment outcomes and disease patterns. Furthermore, comprehensive genotype-phenotype correlation studies to map specific UBA1 variant clinical manifestations and mechanistic investigations into tissue-specific inflammatory processes are required. Longitudinal tracking of clonal evolution and progression remains essential, alongside the urgent development of standardized disease activity measures.

## Limitations

Several important limitations should be considered when interpreting our findings. The relative novelty of VEXAS syndrome means our analysis primarily draws from retrospective data, introducing potential reporting and publication bias. More severe or unusual manifestations may be overrepresented. Our conservative approach to handling potential duplicate patients may have led to the exclusion of some unique cases, particularly in regions with large case series. This strategy prioritized data integrity over absolute case numbers but may have impacted the precision of our prevalence estimates. The variable depth and quality of clinical documentation across studies posed challenges for data synthesis. Some manifestations, particularly subjective symptoms, may be inconsistently reported. Our denominator calculation strategy represents a pragmatic but arbitrary threshold. While this approach helps prevent artificial deflation of prevalence estimates, it may introduce its own forms of bias.

## Data availability

All data supporting this manuscript are available from the corresponding author upon reasonable request.

## Contribution statement

Adam Al-Hakim, Ségolène Gaillard, Maël Heiblig, Sinisa Savic and David B. Beck conceived the study. Adam Al-Hakim and Scott Goldberg collected the data. Adam Al-Hakim and Scott Goldberg analysed the data. Adam Al-Hakim wrote the first draft. All authors read, edited and approved the manuscript.

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Systematic Review and Meta Analysis