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Examining Rare Instances of Vexas Syndrome in Females

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EXAMINING RARE INSTANCES OF VEXAS SYNDROME IN FEMALES

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ABSTRACT

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is an adult-onset inflammatory condition. Initially thought to only affect males with a specific myeloid-lineage *UBA1* somatic mutation, it was hypothesized that females with the same pathogenic mutation might have a milder form of the condition due to its X-linked inheritance. However, recent research has demonstrated that the genotypic and phenotypic profile of VEXAS patients is expanding, with a recent subset of female patients being identified. This literature review investigates the clinical features and *UBA1* somatic mutations in females with VEXAS, aiming to understand how the condition presents in females compared to males. Notably, this review identified that although VEXAS syndrome presents at a lower frequency in females, the clinical features are similar. The most frequent symptoms among our literature-based cohort in both sexes were rheumatological symptoms. Gastrointestinal involvement and fatigue was exclusively reported in male patients with VEXAS, and the c.122T>C, p.Met41Thr somatic mutation was the most common mutation identified in both sexes. Overall, the findings of this review indicate that female patients who meet the criteria for relapsing polychondritis and/or myelodysplastic syndrome, and have any of the following symptoms: macrocytic anemia, thrombocytopenia, arthritis, fever, chondritis, should undergo somatic *UBA1* genetic testing. Further research with female patients is needed to expand the clinical picture of this disease, and to understand how VEXAS syndrome manifests in this population.

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INTRODUCTION

The term VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) was coined in 2020 by Beck and colleagues to describe a newly discovered adult onset systemic autoinflammatory disorder (Beck et al., 2020). In the original paper, Beck and colleagues used a genotype-first, phenotype-neutral approach to ultimately identify 25 males with the same somatic pathogenic mutation affecting methionine-41 (p.Met41) in the *UBA1* gene, linking a group of patients with a seemingly unrelated autoinflammatory syndrome (Beck et al., 2020). These male patients all presented with similar clinical features in late adulthood, including fevers, cytopenia, dysplastic changes and characteristic vacuoles observed in the bone marrow, inflammation of the skin and lungs driven by neutrophils, chondritis, and vasculitis (Beck et al., 2020). The somatic p.Met41 pathogenic mutation in these 25 patients was also found in more than half of all patients' hematopoietic stem cells, and in their peripheral blood myeloid cells. In a recent study using exome data from 163,096 individuals in a patient population, Beck and colleagues (2023) determined the prevalence of VEXAS syndrome in males as 1:4269 and 1:26,238 for females. This study, which also assessed the phenotypes of patients found that of the 11 patients with a *UBA1* mutation, all exhibited autoinflammatory symptoms consistent with VEXAS syndrome (including two XX females). Although the prevalence in males was found to be higher, this study demonstrated that VEXAS syndrome also occurs in females (Beck et al., 2023).

The *UBA1* gene encodes the E1 enzyme, one of 3 ubiquitin-activating enzymes involved in various protein degradation pathways in the cytoplasm of myeloid cells (Damgaard, 2021). Consequently, myeloid cells with a *UBA1* p.Met41 mutation were found to have a catalytically impaired isoform of the UBA1 protein, which resulted in overall decreased cytosolic

ubiquitination, and an overactive innate immune response, which was suspected to lead to autoinflammatory symptoms (Beck et al., 2020; Grayson et al., 2021). Because somatic mutations in the *UBA1* gene in the myeloid lineage are acquired over time, inflammatory symptoms are observed later in life (Beck et al., 2023). Additionally, somatic mutations in hematopoietic stem cells can lead to myeloid cancer and various benign bone marrow and hematologic syndromes (Dion et al., 2016; Beck et al., 2020). Initially, it was believed that myeloid-restricted somatic mutations in *UBA1* contributed to myelodysplastic disease, often presenting with systemic inflammation. Therefore, it was hypothesized that somatic *UBA1* mutations in patients with both myelodysplasia and relapsing polychondritis or other rheumatologic conditions could be indicative of VEXAS syndrome (Beck et al., 2020). Importantly, because proper *UBA1* function is crucial for intracellular ubiquitin signaling, germline loss of *UBA1* function is expected to be lethal.

VEXAS literature suggests that females with one *UBA1* p.Met41 pathogenic mutation may present with less severe or no symptoms possibly due to a protective effect the second X chromosome (Beck et al., 2020; Stubbins et al., 2022). However, recent studies and case reports have revealed that this may not be the case (Beck et al., 2023; Barba et al., 2021; Diarra et al., 2021; Stubbins et al., 2022; Tsuchida et al., 2021). In fact, some females may have a chromosomal abnormality leading to their VEXAS presentation, such as Turner syndrome (Stubbins et el., 2022). Specifically, Stubbins and colleagues (2022) reported VEXAS syndrome in a female patient, who first presented with myelodysplastic syndrome and relapsing polychondritis, and was found to have low bone marrow vacuolation, and autoinflammation. Sanger sequencing identified the presence of the somatic *UBA1* p.Met41Thr mutation (Stubbins

et el., 2022). This patient was found to have a single X chromosome, indicative of Turner syndrome. This case highlights that while VEXAS can occur in females, other genetic factors may be at play in females with VEXAS syndrome.

A similar case report, described a 51-year-old woman with recurrent episodes of fevers, arthritis, episcleritis, left auricular chondritis and progressive hearing loss (Barba et al., 2021). Following initial clinical evaluations, genetic testing found a *UBA1* pathogenic mutation, as well as monosomy X (Barba et al., 2021). Clinically, this female patient's presentation did not differ from male patients. Although, it was noted that autoinflammatory symptoms appeared earlier than hematologic ones, which can also be variable in male patients. (Barba et al., 2021).

Despite consensus that systemic inflammation is a central manifestation of VEXAS syndrome, the clinical variability makes it difficult to establish classification criteria. For example, Georgin-Lavialle and colleagues (2022) published one of the largest cohort studies to date, involving 116 VEXAS patients (Georgin-Lavialle et al., 2022). Among the 116 patients (comprising 111 males and 5 females), the predominant clinical features included fever (64% of patients), skin lesions (83%), lung involvement (50%), chondritis (36%), ocular involvement (39%), venous thrombosis/vasculitis (35%), and arthritis (28%). Hematological issues were also observed in half of the cases (Georgin-Lavialle et al., 2022). Interestingly, these findings are slightly different from those initially reported by Beck et al. (2020), who observed a greater proportion of patients with fever (92% compared to 64%), chondritis (64% compared to 36%), and arthritis (68% compared to 28%). A higher prevalence of gastrointestinal and neurological involvement were also reported as compared to the Georgin-Lavialle et al. (2022) study.

Another issue in the VEXAS literature is that most studies to date have focused on male patients with VEXAS syndrome. Since there is limited data describing clinical manifestations of the disease in females, it is unclear if the features in females differ than those reported in males. Categorizing the clinical features in female patients, therefore, is necessary to improve not only our understanding of VEXAS syndrome, but also aid in the management of female VEXAS patients.

Finally, in the majority of the VEXAS studies reported, the individuals were first identified via a phenotypic approach and accordingly, some experienced a significant delay in diagnosis (Stubbins et al., 2022). Recently, Corty and colleagues (2023) implemented a large population-based study that used a genotype-driven approach to identify the prevalence and penetrance of VEXAS-associated somatic mutations in a diverse unaffected population. This approach identified significantly more females with a *UBA1* mutation. In fact, compared to the phenotypically-derived data, all the females identified via this genotype-first approach (62/62) had the c.121A>C, p.Met41Leu mutation. In addition, female cases of VEXAS syndrome when compared to controls did not differ significantly in clinical characteristics, thus, this may suggest a mild presentation in affected females and potentially why females with VEXAS experience long diagnostic journeys (Corty et al., 2023). Of note, the affected female population was relatively diverse with 28% identifying as African/African American and 20% identifying as American Admixed/Latino (Corty et al., 2023). Therefore, it is important that VEXAS research continued to be explored on larger scales to fully understand and represent the VEXAS community.

Hence, this literature review investigates the following: (1) Assess the common clinical features in females with VEXAS syndrome. (2) Describe how the clinical features in females with VEXAS differ than those in males. (3) Explore possible reasons for any observed differences in clinical features between males and females, including any differences in observed genotypes.

METHODOLOGY

We conducted a systematic literature review, which enabled a comprehensive, transparent, and reproducible analysis of the current knowledge on female patients with VEXAS syndrome (Siddaway et al., 2019). The aim of this literature review was to collect data on the clinical features of males and females with VEXAS syndrome. We performed an exploratory literature search using the PubMed database and the key word "VEXAS". We first screened articles via the title and abstracts and included only original research and peer reviewed articles. Upon full text review, research articles were included if they described patients with a confirmed VEXAS syndrome diagnosis (due to pathogenic *UBA1* somatic gene mutation), and reported their clinical characteristics. Articles were excluded if they only described VEXAS patient populations in general, and did not describe each patient's manifestations. Furthermore, articles were excluded if they did not confirm the *UBA1* mutation in the patients. This literature search was repeated three independent times between September 2023 and March 2024 to ensure the retrieval of all relevant articles.

We systematically reviewed each article that met our inclusion criteria and recorded the main clinical features seen in each VEXAS patient. We grouped the clinical features into larger overarching clinical categories because not every clinical feature was described for every patient in each article. In Table 3, the clinical features listed were limited to the three most common clinical features per category and additionally, only clinical features that have a total proportion of affected females or males greater than 10% were included. An asterisk (*) in Table 3 indicates that papers referencing only chondritis were included in the final count for both males and females. Nine overarching categories of clinical features were most common in the VEXAS

population: hematologic, rheumatologic, dermatologic, pulmonary, ocular, gastrointestinal, other, and bone marrow status (Table 3).

Given the limited data on females with VEXAS, we determined that a descriptive analysis would be most beneficial in comparing the data between male and female patients (Loeb et al., 2017).

RESULTS

		Barba et al., 2021	*Stubbins et al., 2022*	*Tsuchida et al., 2021*	*Diarra et al., 2021 patient 1*	*Diarra et al., 2021 patient 2*	*Beck et al., 2023 patient 1*	*Beck et al., 2023 patient 2*	*Total* **(n=7)**
	Study location	Lyon, France	Vancouver, Canada	Japan	Paris, France	Paris, France	New York, USA	New York, USA	-
	Age of disease onset	51	67	43	87	78	60-60	70-79	-
Clinical Diagnosis	**Relapsing polychondritis**		Yes	Yes	Yes	Yes			4 (57%)
	Myelodysplastic Syndrome (MDS)	Yes	Yes		Yes				3 (43%)
Clinical Symptoms	**Fever**	Yes		Yes	Yes				3 (43%)
	Arthritis	Yes	Yes				Yes	Yes	4 (57%)
	Pulmonary infiltrates						Yes	Yes	2 (29%)
	Chondritis		Yes	Yes		Yes			3 (43%)
	Hearing loss	Yes						Yes	2 (29%)
	Ocular involvement	Yes							1 (14%)
	Cutaneous / subcutaneous nodules	Yes							1 (14%)
	Macrocytic anemia	Yes	Yes		Yes		Yes	Yes	5 (71%)
	Bone marrow vacuoles	Yes	Yes	Not done	Yes	Yes	Not done	Not done	4
	Thrombocytopenia		Yes		Yes		Yes	Yes	4 (57%
Genotype	**Mutation**	c.122T>C	c.122T>C	c.121A>C	c.121A>G	c.121A>C	c.121A>G	c.118-2A>G	-

	Protein change	p.Met41Thr	p.Met41Thr	p.Met41Leu	p.Met41Val	p.Met41Leu	p.Met41Val	Splice site variant	-
	Karyotype	Monosomy X	Monosomy X	Unknown	Acquired monosomy X in bone marrow	Acquired monosomy X in bone marrow	Normal	Normal	-
	VAF	-	50%	0.14%	-	-	19%	21%	-
Treatment	**Transfusion dependence**		Yes						1 (14%)
	Treatment with steroids	Yes	Yes	Yes	Yes		Yes	Yes	6 (86%)
	Treatment with immunosuppressants	Yes	Yes	Yes	Yes				4 (57%)

Table 1. Summary of clinical characteristics and treatment given to female VEXAS patients.

In total, 7 female VEXAS patients were identified across 5 articles. Among the 7 female patients, the average age at diagnosis was 67 years. The majority (4/7; 57.1%) of female patients met diagnostic criteria for relapsing polychondritis, and 3/7 (42.9%) met diagnostic criteria for myelodysplastic syndrome (MDS). Of the clinical criteria analyzed, the most common symptom was macrocytic anemia, seen in 71.44% of female patients. Thrombocytopenia and arthritis were the second most common symptoms, seen in 57.1% patients each). See table 1 for more detail.

Upon genetic testing, a *UBA1* mutation was identified in all 7 female patients. Six female patients (85.7%) had variants at codon 41 (c.121 A>C; p.Met41Leu, c.121A>G; p.Met41Val, c.122T>C; p.Met41Thr), and 1 (14.3%) had a canonical splice site variant (c.118-2A>G). Complete monosomy X was identified in 2 patients, and acquired monosomy X in bone marrow

was identified in 2 different patients. Two patients showed no evidence of aneuploidy on single nucleotide polymorphism array or exome sequencing. One patient remained untested for aneuploidy. The variant allele frequency (VAF) was reported for 4 patients, ranging from 0.14%-50%.

Table 2 compares the proportion different *UBA1* pathogenic variants between male and female patients. The largest difference observed was of the c.122T>C, p.Met41Thr variant, seen in 56% of male patients versus 28.6% of female patients.

	Total cases (n)	**c.122T>C, p.Met41Thr**	**c.121A>G, p.Met41Val**	**c.121A>C, p.Met41Leu**	**Splice motif mutation**	**Average VAF**
Males	171	96 (56%)	40 (23%)	32 (19%)	3 (2%)	72.5% (32.5%-96.8%)
Females	7	2 (28.6%)	2 (28.6%)	2 (28.6%)	1 (14.2%)	22.5% (0.14%-50%)

Table 2. Comparison of *UBA1* genetic testing results for male versus female VEXAS patients. Splice motif mutation refers to c.118-2A>G, c.118-2A>C and c.119-1G>C variants in *UBA1*.

Table 3 provides a detailed comparison of the most common clinical features in males and females with *UBA1* somatic mutations. As shown, several features present in males were not observed in females. These include, thrombosis, periorbital edema, ocular inflammation, gastrointestinal involvement, fatigue and weight loss. Arthritis, episcleritis, hearing loss and stroke were more frequently noted in females than in males. There were no clinical features observed uniquely in female patients. Table 4 highlights the specific clinical features observed in females and males.

	Hematologic			Rheumatologic			Dermatologic		Pulmonary
	Anemia	Thrombosis	Thrombocytopenia	Fever	Arthritis	Ear Chondritis*	Skin Involvement		Pulmonary Infiltrates
Females	3 (43%)	0 (0%)	1 (14%)	3 (43%)	4 (57%)	3 (43%)	2 (29%)		1 (14%)
Males	130 (71%)	67 (37%)	42 (23%)	151 (83%)	81 (44%)	103 (56%)	152 (83%)		85 (46%)
	Ocular			**GI**	**Other**			**Neurologic**	**Bone Marrow Biopsy**
	Periorbital Edema	Ocular Inflammation	Episcleritis	Gastrointestinal Involvement	Fatigue	Hearing Loss	Weight Loss	Stroke	Vacuolization
Females	0 (0%)	0 (0%)	1 (14%)	0 (0%)	0 (0%)	2 (29%)	0 (0%)	1 (14%)	4 (67%)
Males	34 (19%)	20 (11%)	5 (3%)	46 (25%)	46 (25%)	46 (25%)	28 (15%)	1 (0.5%)	77 (97%)

Table 3. Comparison of the most common clinical features in female and male patients with VEXAS syndrome. This table has been modified from the table found in Beck et al., 2023.

Hematologic	**Rheumatologic**	**Dermatologic**
Thrombosis, venous thromboembolism, unprovoked deep vein thrombosis, arterial thrombosis, thrombocytopenia, macrocytic anemia, pancytopenia, lymphopenia, eosinophilia, monocytopenia, neutropenia, mild dyserythropoiesis, myeloid dyspoiesis, and epistaxis	Fever, nose chondritis, ear chondritis, chondritis, chondritis of possibly the sternum, arthritis and/or arthralgia, rheumatoid arthritis, oligoarthritis, periarthritis of the ankles, polyarthritis, myalgia, vasculitis all localization, spleen or liver enlargement, organomegaly, orchitis, epididymitis, prostatitis, psoriasis, polymyalgia rheumatica, night sweats, hilar and mediastinal lymphadenopathy, cervical lymphadenopathy, and paraaortic lymphadenopathy	Skin involvement**, d**ermatosis**, n**eutrophilic dermatosis with small to medium vessel vasculitis, plaques, skin lesions, leukocytoclastic vasculitis, nodules/erythema nodosum, erythematous plaque and red-purple papules, leucocytoclastic vasculitis small/medium vessels with a monocytic and neutrophilic infiltrate, lymphocytic or eosinophilic vasculitis, urticaria, lymphocytic dermatitis, erythematous subcutaneous nodules, exanthema, erythema exudativum multiforme, subcutaneous inflammatory nodules, and cellulitis
Pulmonary	**Ocular**	**Heart and Vasculature**
Pleural effusions, pulmonary infiltrates, vasculitis of medium-sized bronchial arteries, neutrophilic alveolitis, lymphohistioplasmocellular vasculitis of the larger arterioles, cryptogenic organizing pneumonia, pleuritis,	Periorbital edema, blepharitis, bilateral anterior uveitis and exophthalmos caused by periorbital and intraorbital panniculitis, scleritis, episcleritis, iritis,	ANCA-negative vasculitis, cardiomyopathy, arterial lesions, myocarditis, cardiac tamponade, hypertension, heart vasculitis, and heart

bronchiolitis obliterans, NSIP, vasculitis of the pulmonary vasculature with eosinophilia, cavitation lesion right upper lobe, pulmonary lesions, pleural pathology, and pulmonary embolism	uveitis, and ocular involvement	involvement
Neurologic	**Gastrointestinal**	**Renal**
Possible polyneuropathy, headache, central or peripheral nervous system involvement, aseptic meningitis, polyneuropathy, and vestibular neuritis, stroke, and cerebrovascular accident	Perforation of the bowel, ulcerative lesions in colon and caecum, lesion in pancreas with increased FDG uptake, parotitis, abdominal pain, diarrhea, nausea/vomiting, small bowel inflammation, and gastrointestinal involvement	Progressive renal insufficiency, proteinuria, erythrocyturia, and kidney involvement
Other		
Muscle ache, fatigue, weight loss, infections, progressive hearing loss, sensorineural hearing loss, cochlear/vestibular dysfunction, vestibular symptoms, joint or muscle involvement, and constitutional symptoms		

Table 4. Summary of the observed clinical features in females and males. A comprehensive list of the specific clinical features that fall into each category and the breakdown of these features per publication can be found in the supplementary data.

DISCUSSION

VEXAS syndrome, an acquired systemic autoinflammatory disease was only recently discovered (Beck et al., 2020). Although it was initially found exclusively in males, female patients have now also been reported (Barba et al., 2021; Beck et al., 2023; Diarra et al., 2021; Stubbins et al., 2022; Tsuchida et al., 2021). In this study, we compare the genotypes, and clinical features of 171 (96%) male patients to that of 7 (4%) female patients diagnosed with VEXAS syndrome.

Overall, we found that females exhibited similar clinical features compared to males with VEXAS syndrome, with some subtle differences in frequency of clinical presentation. The most common category of clinical manifestations in both males and females was rheumatological symptoms. In females, hematological symptoms was the second most common category of clinical manifestation, followed by dermatological symptoms and hearing loss. This is compared to males, where the second most common category of clinical manifestation was dermatological manifestations, followed by hematological symptoms and pulmonary manifestations. Both male and female patients also showed high rates of vacuolization found on bone marrow biopsy.

Our study supports the notion that females presenting with a constellation of symptoms from the categories above, including anemia, thrombocytopenia, fever, arthritis, ear chondritis, skin involvement, vacuolization in bone marrow, and/or hearing loss later in life, should be considered for VEXAS syndrome. Specifically, fever, arthritis, and ear chondritis were observed in over 40% of both affected females and males. However, the largest discrepancies between females and males with VEXAS were observed in gastrointestinal involvement and fatigue. No females were reported to have gastrointestinal symptoms or fatigue compared to 46/183 (25%) of

males for both clinical features. Thus, the presence of these clinical features in females may not suggest a VEXAS diagnosis. More plausibly, a larger sample size is needed to truly appreciate the spectrum of disease in this population.

Typically, germline X-linked disorders suggest that the additional X chromosome in females may confer some protective effects, leading to milder symptoms (Migeon, 2020). Luzzato et al. suggested that the *UBA1* gene, which is not subject to X-inactivation, behaves as a recessive allele in females (Echerbault et al., 2024; Luzzatto et al., 2021). Consequently, both copies of the *UBA1* gene must be lost for symptoms to manifest in females. In our study, we reviewed the testing of six female patients who underwent karyotype analysis: two exhibited constitutional monosomy X, two showed acquired monosomy X in the bone marrow, and two had normal karyotypes (Barba et al., 2021; Beck et al., 2023; Diarra et al., 2021; Stubbins et al., 2022; Tsuchida et al., 2021). It would make sense that female patients with a known VEXAS causing variant in one *UBA1* allele, and the loss of function of the other *UBA1* allele through constitutional or acquired X monosomy, would present phenotypically similar to male patients. However, the two women with normal karyotypes do not fit this idea. As more data on female patients with VEXAS syndrome becomes available, it will be crucial to study the mechanisms by which females with a single *UBA1* mutation develop the disease.

The most common *UBA1* variant in both males (98%) and females (85.8%) is a substitution of the methionine 41 codon. A more recently discovered splice motif mutation, occurring at the junction of intron 2 and exon 3 (c.118-2A>C and c.119-1G>C) of the *UBA1* gene, was also reported in patients. This variant was the least common mutation reported in males and females.

More data on splice motif variants is needed to categorize any potential genotype-phenotype correlation.

LIMITATIONS

Our study aggregates the existing data on female patients with VEXAS syndrome. As a result, a key limitation to the current study is the small sample size (n=7). It is possible that the differences we are seeing in clinical manifestations between male and female patients could be related to the small number of females reported. It is also possible that due to publication bias, the female patients we are seeing in the literature present a more severe phenotype than the average female patient would, if they were identified via a genotypic approach. Moving forward, we anticipate the literature on females to increase due to the recognition of VEXAS in females. In fact, during the course of the current study, Echerbault et al., (2024) published a study comparing the clinical features between males and females with VEXAS syndrome. Another limitation of the present study was that we excluded studies that did not include a breakdown of female clinical features due to the varying degrees of how the clinical features were reported. As a result, it is possible that our analysis does not adequately represent the entire clinical picture of female patients. Finally, because of the differences in reporting of clinical features between studies, it was difficult to determine whether clinical features were excluded because they were absent in patients versus not reported because they were not assessed. This is an important note for future studies in order to get a more complete clinical pictures of the manifestations of the disease in patients.

CONCLUSION

This literature review demonstrated that the most common clinical features in females are macrocytic anemia, thrombocytopenia, arthritis, fever, chondritis, and the presence of bone marrow vacuoles. However, compared to males, females were more likely to present with arthritis, episcleritis, hearing loss and stroke. No females were reported to have gastrointestinal symptoms or fatigue. Interestingly, the c.122T>C, p.Met41Thr mutation was found to be the most common *UBA1* mutation in VEXAS patients, regardless of biological sex. Finally, no genotype-phenotype correlations were identified. Based on our findings, female patients who meet the criteria for relapsing polychondritis, myelodysplastic syndrome (MDS), and/or have a combination of the symptoms described in Table 3, should consider somatic *UBA1* genetic testing. As the female VEXAS literature expands, further studies should be performed to explore the mechanism of action and clinical manifestations of females with VEXAS syndrome. Further research is also needed to better understand the disease course in females. This is imperative as VEXAS syndrome is associated with significant morbidity, and concerning, a high mortality rate. As such, it is important that studies on female patients are conducted to ensure equitable and timely care.

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SUPPLEMENTARY MATERIAL

Supplementary data file 1