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Features of Vascular Ehlers-Danlos Syndrome among Biobank Participants Harboring Predicted High-Risk *COL3A1* Genotypes

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Vascular Ehlers-Danlos syndrome (vEDS), caused by damaging variants in the type III procollagen gene, *COL3A1*, has a median survival of 51 years.[1] Dominant-negative (DN) variants, missense glycine substitutions within the triple helical domain and splicing variants altering in-phase exons, are considered more severe than haploinsufficiency (HI) variants, premature termination codons causing mRNA instability (*i.e.*, frameshift, non-sense, large deletions).[1,2] Penetrance, estimated from patients with vEDS, is high; ≥ 80% of genotype-positive individuals have ≥ one major complication.[3] Increasingly, deleterious *COL3A1* genotypes are identified through genomic screening programs, yet clinical risks in such unselected populations are not yet defined. We therefore used a genotype-first approach to minimize ascertainment bias, investigating vEDS-associated phenotypes among *COL3A1*$^{+}$ biobank participants.

Mount Sinai's Bio*Me* biobank (median age 64, IQR 49–75 years; 58.4% Female; 22% African American (AA), 27% European American, 34% Hispanic/Latinx, 4% Asian), links 32,344 patients' exome sequences to their longitudinal electronic health records (EHR), and the United Kingdom Biobank (UKBB), a prospective cohort study, contains phenotypic data and exome sequences for 200,643 participants (median age 57 ± 8 years; 54% Female; 94% white, 2% Asian, 2% Black). Exomes were queried for putatively damaging *COL3A1* variants: rare (minor allele frequency < 0.1% in gnomAD) and (1) triple helical domain (exons 6–47)[3] missense glycine substitutions; (2) stop-loss/start-gain; (3) frameshift insertion/deletion; or (4) canonical splice site variant within two base pairs of the exon.

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Variants with ≥ 1 likely benign/benign ClinVar designation were excluded. Mount Sinai's IRB approved this study; informed consent was obtained at enrollment. Data supporting study findings are available from the corresponding author upon reasonable request.

Eighteen Bio*Me* (11 females; 1 in 1,797, 95% C.I. 1:2,500–1:3,344) and 63 UKBB (33 females; 1 in 3,185, 95% C.I. 1:2,554–1:4,229) were *COL3A1*$^{+}$ (Figure, A). vEDS-related phenotypes including major/minor diagnostic criteria,[4] age/cause of death, and obstetric/surgical histories were assessed from EHRs (Bio*Me*) or database entries (UKBB). Median age was 50 (Bio*Me*) and 54 (UKBB) years, exceeding the median age when patients with vEDS are diagnosed following clinical events.[3] No *COL3A1*$^{+}$ individual was diagnosed with vEDS or a genetic arteriopathy.

Although > 75% of included variants were DN (Bio*Me*: 17, 94%; UKBB: 45, 71%) and predicted to cause severer phenotypes, no genotype-positive participant experienced organ rupture or fatal, unprovoked arterial rupture/dissection. Major vEDS criteria were met in two (11%) Bio*Me* (aneurysm; family history) and two (3%) UKBB (aneurysm) participants. Minor criteria were met in four (22%) Bio*Me* (varicose veins, talipes equinovarus) and six (10%) UKBB (varicose veins, easy bruising) participants (Figure, B). None had organ rupture, carotid-cavernous sinus arteriovenous fistula, tendon/muscle rupture, pneumothorax/hemopneumothorax, congenital hip dislocations, joint or craniofacial/skin features. Association with any vEDS criteria was not different between individuals harboring DN or HI variants (15, 24% vs. 3, 16%, p=0.4). Sixteen (20%) *COL3A1*$^{+}$ individuals harbored variants previously reported as likely pathogenic or pathogenic (LP/P) in ClinVar (Figure, C); none met major and three (19%) met minor criteria. Amongst the remaining 65 with novel (n=55) or VUS (n=10) variants, 4 (6%) met major and 7 (11%) met minor criteria. Prevalence of any criteria was not different in those with LP/P versus novel/VUS variants (p=0.9).

84% of *COL3A1*$^{+}$ participants had no documented vEDS features. Surgeries, including major surgeries, occurred in 89% of Bio*Me* (with no major complications) and 90% of UKBB *COL3A1*$^{+}$ participants. No pregnancy complications were noted for five Bio*Me* (45%) and 30 UKBB (91%) *COL3A1*$^{+}$ females with obstetric histories. Three participants were deceased, one (UKBB) from a subarachnoid hemorrhage secondary to an unspecified surgery.

The higher prevalence of relevant variants in Bio*Me* versus UKBB may be due to health system rather than population level recruitment. Prevalence of deleterious *COL3A1* variants in UKBB was still higher than previously cited for vEDS (~1:50,000–1:200,000).[5] The four individuals who met major vEDS criteria, however, equate to a point prevalence between 1:16,172 and 1:100,322, consistent with previous estimates. Interestingly, 44% of *COL3A1*+ individuals in Bio*Me* (none related) were AA, although vEDS has no known racial predilection.

Study limitations are those inherent to EHR/database phenotyping, including incompleteness. Outward criteria of vEDS may be subtle, missed even by clinical geneticists. Aneurysms are often asymptomatic preceding dissection or rupture. Phenotypic

features may have been present in *COL3A1*$^{+}$ participants but not suspected in routine clinical care. We do expect to have captured the severest manifestations of *COL3A1*$^{+}$-related disease (*i.e.*, arterial dissection/rupture, organ rupture) with our methods. Finally, *COL3A1*$^{+}$ cases with fatalities at young ages would not be included in these biobanks, conferring a survival bias.

In summary: 1) relevant *COL3A1* variants are commoner than previously understood; 2) *COL3A1*$^{+}$ status, even for DN variants, does not reliably predict vEDS phenotypes or dangerous outcomes; 3) penetrance may be lower than previously predicted; and 4) assigning rare *COL3A1* variants as putatively damaging based on the criteria used for this study is at least as predictive as established ClinVar classifications.

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Nonstandard Abbreviations and Acronyms

EHR	electronic health record
DN	dominant negative
HI	haplo-insufficiency
UKBB	United Kingdom Biobank
vEDS	vascular Ehlers-Danlos syndrome

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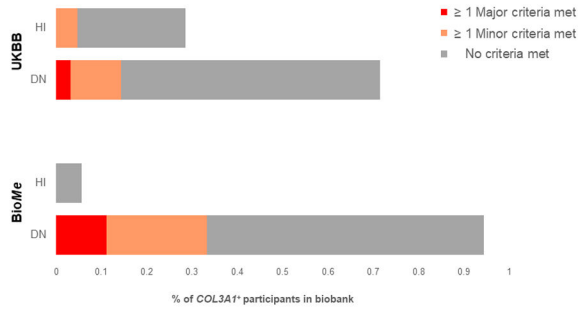
A

	Bio*Me*	UKBB
N	18	63
Age at enrollment (years), median (IQR)	50 (44-57)	54 (48-62)
Female	11 (61)	33 (52)
White/European	6 (33)	56 (89)
African American/Black/Caribbean	8 (44)	0
Asian	0	5 (8)
Hispanic/Latin American	1 (6)	0
Mixed	0	1 (2)
Other/Unknown	4 (22)	1 (2)

Variant types	*VUS*	*LP/P*	*Total*	*VUS*	*LP/P*	*Total*
Glycine substitution	3	4	15 (83)	6	9	38 (59)
Frameshift insertion/deletion	0	0	1 (6)	0	1	12 (19)
Splicing	0	0	2 (11)	1	1	7 (11)
Start loss/ stop gain	0	0	0	0	2	7 (11)

B



C

CASE	SEX	AGE (Y)	VARIANT	TYPE	DIAGNOSTIC CRITERIA	NOTABLE FEATURES	OBSTETRIC HISTORY
BIOME-1	F	34	c.G2627C, p.G876A	Gly	-	-	G7P2
BIOME-2	F	48	c.G2123T, p.G708V	Gly	Minor-1	Retinal detachment, Mild aortic root dilatation; multifocal stenosis infrapopliteal arteries; Fatal stroke in father	G5P3
BIOME-3	F	50†	c.G2464A, p.G822S	Gly	-	Mild aortic root dilatation	None
BIOME-4	F	54	c.G2627C, p.G876A	Gly	Minor-1	Normal thoracic aortic dimension; Varicosities	G2P2
UKBB-1	F	43	c.G2257T; p.G753C	Gly	-	Obstetric laceration of vagina and pelvic floor	G2P2
UKBB-2	M	45	c.G944C; p.G315A	Gly	-	-	-
UKBB-3	F	47	c.G1996A; p.G666S	Gly	-	Musculoskeletal/connective tissue disease	G1P1
UKBB-4	F	53	c.3966delG:p.K1323Rfs*64	Del	-	Stroke	G1P1
UKBB-5	M	54	c.G1996A; p.G666S	Gly	-	-	
UKBB-6	F	56	c.G1258A; p.G420S	Gly	-	Hematemesis	G4P3
UKBB-7	M	57	c.G2257T; p.G753C	Gly	-	Retinal detachment with retinal break	-
UKBB-8	M	61	c.G1996A; p.G666S	Gly	-	-	-
UKBB-9	M	62	c.C3496T, p.R1166X	SG	-	-	-
UKBB-10	M	62	c.G862T; p.G288C	Gly	-	-	-
UKBB-11	F	64	c.G30A; p.W10X	SG	-	-	G0P0
UKBB-12	F	68	c.2283+1G>A	Splice	Minor - 1	-	G3P3
UKBB-13	M	68	c.G2257T; p.G753C	Gly	-	-	-

Figure 1.

Demographic and clinical data, distribution of variant types and individuals meeting vEDS diagnostic criteria and selection of detailed cases among Bio*Me* and UKBB participants with putatively deleterious *COL3A1* variants. **A,** Demographic data and types of variants for Bio*Me* and UKBB participants with putatively deleterious *COL3A1*$^{+}$ genotypes. **B,** Distribution of vEDS major and minor criteria for Bio*Me* and UKBB participants with putatively deleterious *COL3A1* variants stratified according to haplo-insufficiency or dominant-negative variant types.. **C**, Table of biobank participants harboring *COL3A1* variants previously reported in association with vEDS (likely pathogenic or pathogenic designations in ClinVar).A: Table entries are number (%) unless otherwise noted; Designations of variants in ClinVar are listed: VUS- variant of uncertain significance; LP- likely pathogenic; P- pathogenic; total indicates all variants including those not classified in ClinVar; B: HI- “haplo-insufficiency” variant; DN- “dominant negative” variant; C: Age listed is at last EHR entry (BioMe) or first assessment (UKBB); Gly- glycine substitution; SG- stop-gain; Spice- essential splice site mutation; Del- frameshift deletion; † - Participant died at age 50 of septic shock from sternal wound infection following mitral/aortic valve replacement