

Next generation sequencing panel for hereditary erythrocytosis in adults with otherwise unexplained erythrocytosis unveils additional genomic variants

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Supplemental Table 1. Gene variants identified on next generation sequencing, associated clinical features and management of 23 patients with *otherwise unexplained* erythrocytosis

Patient	Variant	Age/Gender	Hb/Hct	EPO	Thrombosis	Phlebotomy	Aspirin	Anticoagulation
#1	PIEZO1 (VUS) c.7529C>T (p.Pro2510Leu)	51/M	18.6/52.7	8	No	HCT>50%, Unknown	81 mg	None
#2	PIEZO1 (VUS) c.5195C>T (p.Thr1732Met)	70/M	16.3/49.5	9	No	Hb>15-16, Symptom relief	No	None
#3	PIEZO1 (VUS) c.226G>A (p.Ala76Thr) c.5988A>G (p.Ser1996=)	59/M	16.6/51.5	13	Provoked DVT	One time, No symptom relief	325 mg	None
#4	PIEZO1 (VUS) c.7505A>G (p.Lys2502Arg)	62/M	18.4/54.7	22	No	One time, Unknown	81 mg	None
#5	PIEZO1 (VUS) c.7529C>T (p.Pro2510Leu)	41/F	15.8/45.9	5.9	No	No	No	None
#6	PIEZO1 (VUS) c.6506_6508del (p.Lys2169del)	43/M	15.6/44.1	8.1	No	Ferritin >50-100, No symptom relief	No	None
#7	PIEZO1 (VUS) c.3602C>T (p.Thr1201Met)/ HIF1A (VUS) c.1744C>T (p.Pro582Ser)	45/M	15.6/46	19.6	NSTEMI	Every other week, Unknown	81 mg	None
#8	PIEZO1 (VUS) c.7180G>A (p.Gly2394Ser) /HIF3A (VUS) c.1103C>A (p.Ala368Asp)	47/M	14.6/45.2	2.5	No	Every month, Unknown	81 mg	None
#9	ANKRD26 (VUS) c.679C>T (p.Pro227Ser)	40/F	15.4/46.4	12.6	DVT, stroke	No	81 mg	None
#10	ANKRD26 (VUS) c.440A>G (p.Asn147Ser)	47/M	15.3/47.5	17.2	No	Every four weeks, Symptom relief	81 mg	None
#11	ANKRD26 (VUS) c.245C>T (p.Thr82Met) / HIF1A (VUS) c.1744C>T (p.Pro582Ser)	48/M	18.4/52.8	7.2	No	No	no	None
#12	ANKRD26 (VUS) c.1153A>G (p.Thr385Ala) /HIF3A (VUS) c.1672G>A (p.Asp558Asn)	24/M	16.7/49.8	<1	No	No	no	enoxaparin
#13	HIF1A (VUS) c.1744C>T (p.Pro582Ser)	66/M	13.6/44.8	52.9	No	Every month, Symptom relief	No	None
#14	HIF1A (VUS) c.1744C>T (p.Pro582Ser)	29/M	17.5/49.5	9.7	No	Two times, No symptom relief	no	None
#15	HIF1A (VUS) c.1744C>T (p.Pro582Ser)	79/M	18.4/56.6		No	No	81 mg	None
#16	HIF1A (VUS) c.1744C>T (p.Pro582Ser)	55/M	18.6/54.1	6.5	No	No	no	None
#17	HIF1A (VUS) c.1744C>T (p.Pro582Ser)	58/M	17.5/52.5	8.6	No	One time, Unknown	81 mg	None
#18	HIF1A (VUS) c.1744C>T (p.Pro582Ser)/ HIF3A (VUS) c.679C>A (p.Pro227Thr)	21/M	17.2/51.2	7.9	No	No	no	None
#19	SH2B3 (VUS) c.232G>A (p.Glu78Lys)	68/F	15.4/47.9	5.2	No	No	no	None
#20	SH2B3 (VUS) c.452A>G (p.Gln151Arg)	35/M	14.8/43.9	3.7	Stroke	Every week, Unknown	81 mg	apixaban
#21	SH2B3 (VUS) c.586C>T (p.Arg196Cys)	66/M	15.9/46.6	12.4	No	HCT>50%, Symptom relief	81 mg	None
#22	EPO (VUS) c.250G>A (p.Gly84Arg)	45/M	18.5/53.4	5.6	No	No	81 mg	None
#23	BHLHE41 (VUS) c.865_876del (p.Ser289_Gly292del)	32/F	15.1/47.1	7.1	Provoked DVT	Every month, Symptom relief	no	None

Abbreviations: Hb, hemoglobin; HCT, hematocrit ; EPO, erythropoietin; DVT, Deep Vein Thrombosis; NSTEMI, Non–ST-Elevation Myocardial Infarct

Supplemental Table 2. Patients With Unexplained Erythrocytosis with History Of Thrombosis

Patient	Variant	Age at thrombosis/ Gender	Risks factors for thrombosis	Hb/Hct at Thrombosis	Thrombosis	Erythrocytosis Management: Before Thrombosis	Erythrocytosis Management: After Thrombosis workup
#1	PIEZO1 (VUS) c.226G>A (p.Ala76Thr) c.5988A>G (p.Ser1996=)	59/M	Surgery	16.6/51.5	Provoked DVT	rosuvastatin	Aspirin, rosuvastatin
#2	PIEZO1(VUS) c.3602C>T (p.Thr1201Met)/ HIF1A (VUS) c.1744C>T (p.Pro582Ser)	32/M	None	Not available	NSTEMI	No	Aspirin, Phlebotomy
#3	ANKRD26 (VUS) c.679C>T (p.Pro227Ser)	37/F	Surgery, OCP, LACV	Normal 14.6/42.5	Provoked DVT, stroke	No	Aspirin
#4	SH2B3 (VUS) c.452A>G (p.Gln151Arg)	35/M	Carotid Artery Dissection	High 1 st : (20.9/60.7) Normal 2 nd : (12.9/42.9)	Stroke	1 st : No 2 nd : Aspirin, apixaban, Phlebotomy	Aspirin, Ticagrelor
#5	BHLHE41 (VUS) c.865_876del(p.Ser289_Gly 292del)	28	Surgery	Normal 12.5/36.5	Provoked DVT	No	Phlebotomy
#6	None	58/M	None	Unavailable	NSTEMI	No	Apixaban, clopidogrel
#7	None	49/M	APLS	Normal 12.6	Pulmonary Embolism	No	warfarin

Abbreviations: Hb, hemoglobin; HCT, hematocrit; EPO, erythropoietin; CV, cardiovascular; OCP, oral contraceptive pills ; LACV, levoatrial cardinal vein; HH, Hereditary Hemochromatosis; DVT, Deep Vein Thrombosis; NSTEMI, Non–ST-Elevation Myocardial Infarction; APLS, Antiphospholipid syndrome

Supplemental Figure 1. Mayo Clinic Laboratories hereditary erythrocytosis testing algorithm

**Hereditary Erythrocytosis Testing
at Mayo Clinic**

Start with High Oxygen Affinity Variant
analysis

(CEP, HPLC, Mass spec)

Sanger sequencing (HEMP)

(EGLN1, EPAS1, EPOR)

Sanger sequencing

(VHL, BPGM)

Expanded NGS panel

NHEP Comprehensive Panel		
ACO1	EGLN3	JAK2
ANKRD26	EPAS1	KDM6A
BHLHE41	EPO	PFKM
BPGM	EPOR	PIEZO1
CYB5A	GF11B	PKLR
CYB5R3	HIF1A	SH2B3
EGLN1	HIF1AN	SOCS3
EGLN2	HIF3A	VHL

Planned
workflow
change