ARTICLE - Coagulation & its Disorders

Genetic determinants of clinical variability in type 2 von Willebrand disease: bridging genotype and phenotype

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Received: May 30, 2025.
Accepted: August 4, 2025.
Early view: August 14, 2025.

https://doi.org/10.3324/haematol.2025.288342

Supplementary Information

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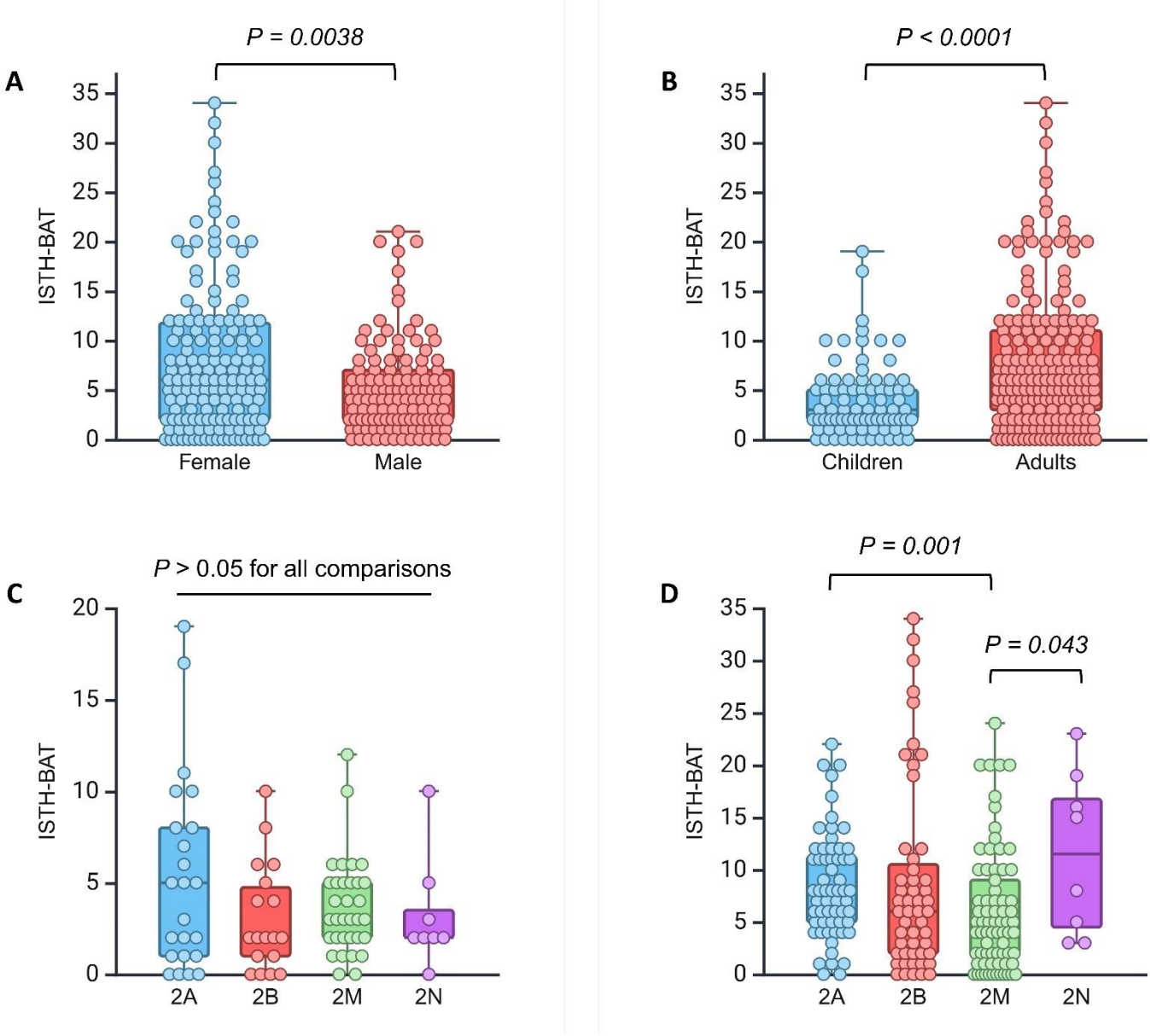

Figure S1. Effect of gender and age on bleeding severity using ISTH-BAT in type 2 von Willebrand disease (VWD). (A) ISTH-BAT scores stratified by gender. (B) ISTH-BAT scores stratified by age. (C) ISTH-BAT scores in children with type 2A, 2B, 2M, or 2N VWD. (D) ISTH-BAT scores in adults with type 2A, 2B, 2M, or 2N VWD**.** Created with BioRender.com.

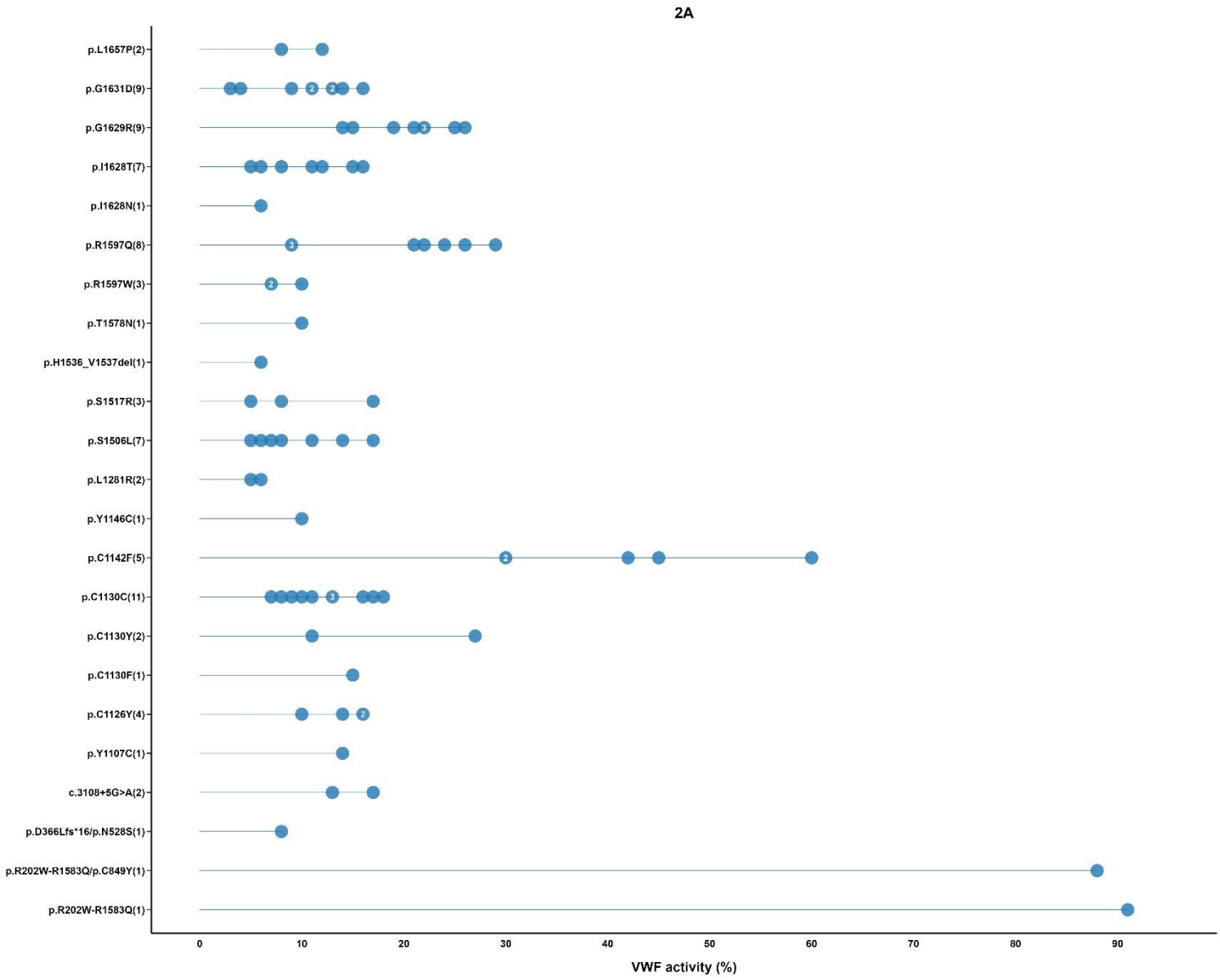

Figure S2. Distribution of VWF activity levels in individuals with type 2A VWD variants.

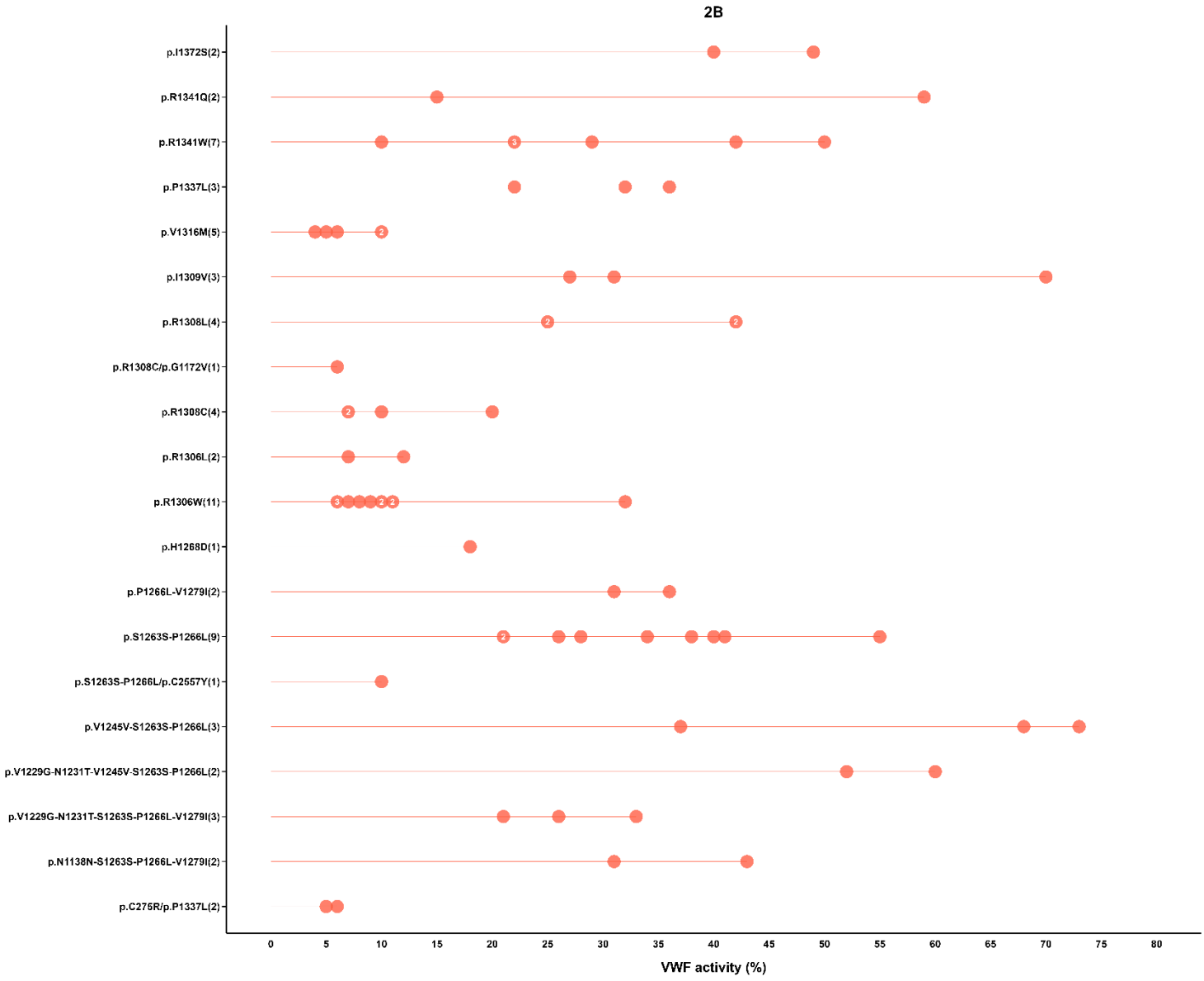

Figure S3. Distribution of VWF activity levels in individuals with type 2B VWD variants.

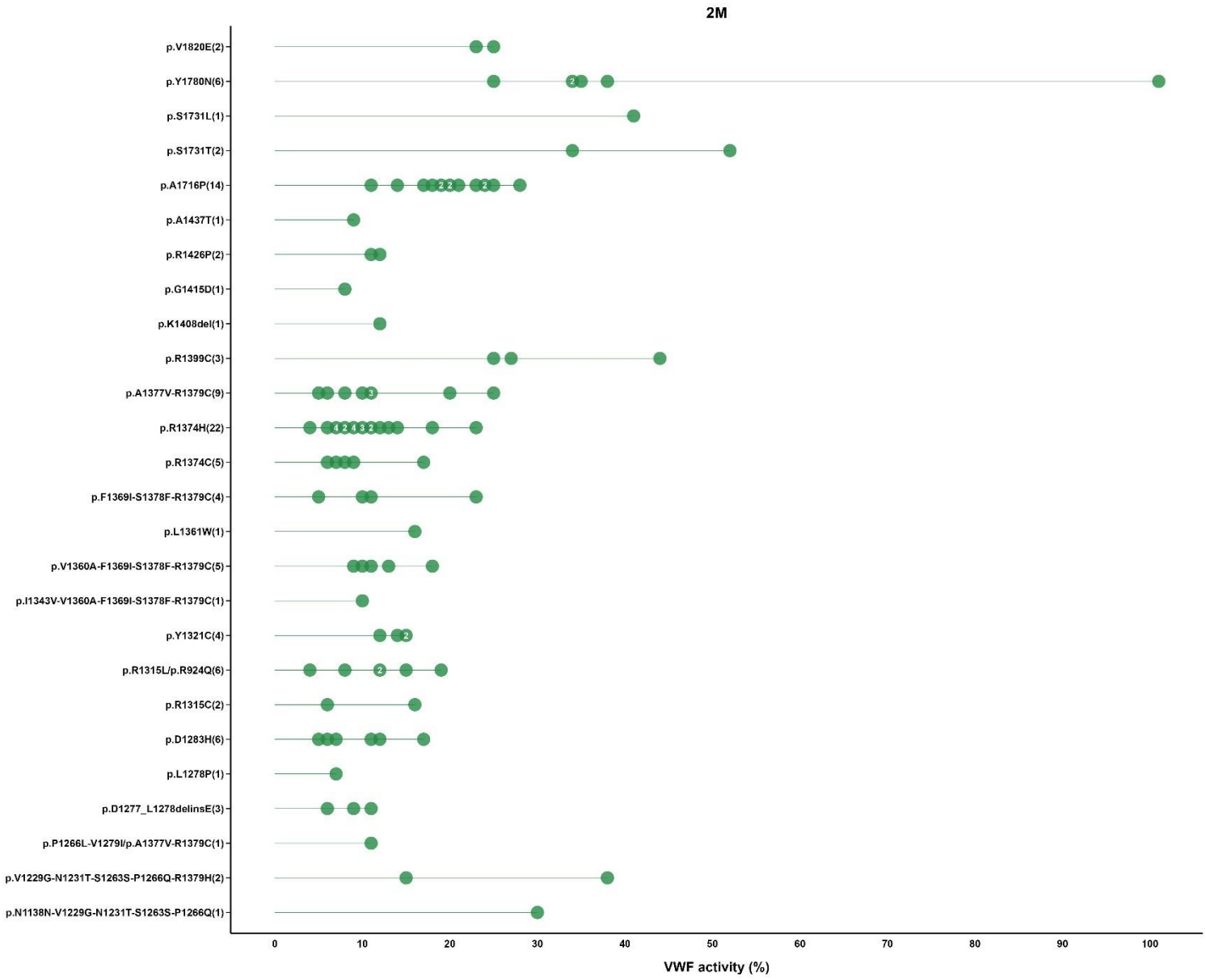

Figure S4. Distribution of VWF activity levels in individuals with type 2M VWD variants.

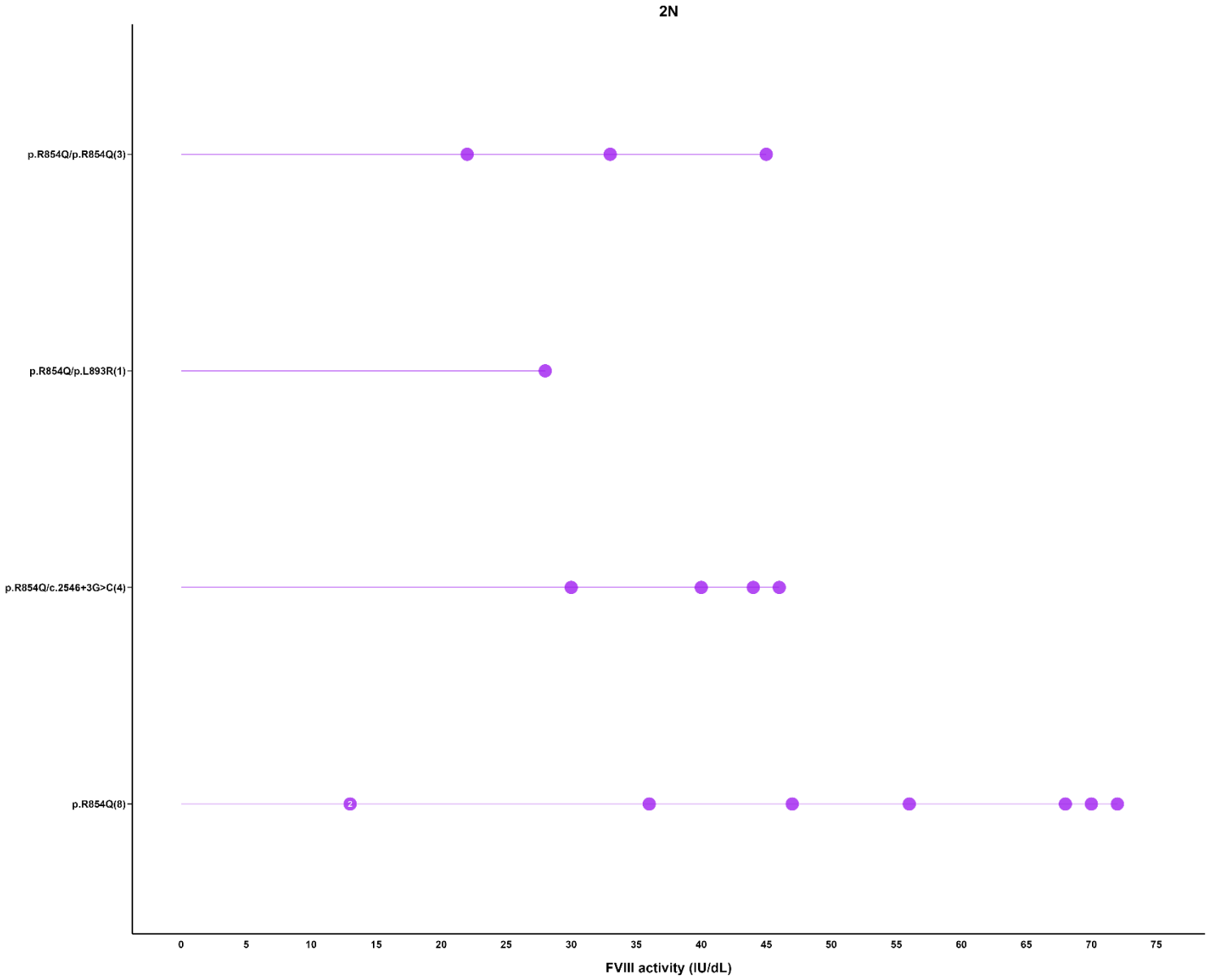

Figure S5. Distribution of FVIII:C levels in individuals with type 2N VWD variants.

Table S1. *In silico* predictions and clinical variant classifications according to ACMG guidelines.

c.DNA	Protein	rsID	CADD	REVEL	ClinVar/Franklin*
c.2546+3G>C[1]	-	rs1565838728	5.925	NA	Likely pathogenic
c.3108+5G>A[2]	-	rs61748495	25.1	NA	Conflicting classifications of pathogenicity
c.2771G>A	p.R924Q	rs33978901	19.36	0.089	Conflicting classifications of pathogenicity
c.4748G>A	p.R1583Q	rs538030800	14.4	0.229	Likely benign
c.3802C>G	p.H1268D	rs61749371	18.21	0.29	Pathogenic
c.604C>T	p.R202W	rs990682639	24.8	0.319	Conflicting classifications of pathogenicity
c.3390C>T	p.C1130C	rs1591865617	8.96	NA	Pathogenic/Likely pathogenic
c.3797C>T	p.P1266L	rs61749370	21.5	0.325	Conflicting classifications of pathogenicity
c.3797C>A	p.P1266Q	rs61749370	22.3	0.405	Conflicting classifications of pathogenicity
c.7670G>A	p.C2557Y	rs774929265	24.4	0.421	Uncertain significance*
c.2561G>A	p.R854Q	rs41276738	29.9	0.487	Pathogenic
c.5338T>A	p.Y1780N	rs372002214	20.1	0.518	Uncertain significance
c.3425G>T	p.C1142F	rs2136417522	27.7	0.543	Uncertain significance
c.3831_3833delCCT	p.D1277_L1278delinsE	rs61749375	20.3	NA	Likely pathogenic
c.1583A>G	p.N528S	rs61754010	25.6	0.555	Pathogenic
c.1092_1093del	p.D366Lfs*16	rs2136470486	23.6	NA	Pathogenic
c.2546G>A	p.C849Y	rs772796741	34	0.579	Likely pathogenic
c.4010C>T	p.P1337L	rs61749400	24.9	0.581	Pathogenic/Likely pathogenic
c.3389G>A	p.C1130Y	rs267607324	27.4	0.583	Likely pathogenic
c.4115T>G	p.I1372S	rs61750070	17.37	0.595	Conflicting classifications of pathogenicity
c.3389G>T	p.C1130F	rs267607324	27.2	0.598	Pathogenic
c.4606_4611delCACGTC	p.H1536_V1537del	rs2136412203	16.45	NA	Pathogenic
c.4136G>A	p.R1379H	rs773292982	22.6	0.611	Likely pathogenic*
c.5191T>A	p.S1731T	rs61750603	21	0.636	Conflicting classifications of pathogenicity

c.4790G>A	p.R1597Q	rs61750577	24.1	0.647	Pathogenic
c.3922C>T	p.R1308C	rs61749387	29	0.673	Pathogenic
c.4222_4224delAAG	p.K1408del	rs61750078	15.2	NA	Pathogenic*
c.4733C>A	p.T1578N	rs2136411988	27.1	0.674	Pathogenic
c.3923G>T	p.R1308L	rs61749388	22.9	0.678	Likely pathogenic
c.4551C>G	p.S1517R	rs2136412350	22.4	0.696	Likely pathogenic
c.4883T>C	p.I1628T	rs61750584	26.3	0.703	Pathogenic
c.2678T>G	p.L893R	rs2136430556	31	0.711	Uncertain significance
c.4195C>T	p.R1399C	rs61750077	25.6	0.712	Likely pathogenic
c.3962A>G	p.Y1321C	rs1591863294	23.5	0.715	Likely pathogenic
c.4277G>C	p.R1426P	rs761308466	20.7	0.724	Uncertain significance
c.4970T>C	p.L1657P	rs61750593	24.2	0.728	Likely pathogenic
c.4135C>T	p.R1379C	rs61750074	32	0.731	Pathogenic/Likely pathogenic
c.3946G>A	p.V1316M	rs61749397	27.1	0.74	Pathogenic
c.5192C>T	p.S1731L	rs764077750	28.7	0.741	Uncertain significance
c.4789C>T	p.R1597W	rs61750117	28.3	0.748	Pathogenic
c.4120C>T	p.R1374C	rs61750071	32	0.757	Pathogenic
c.3916C>T	p.R1306W	rs61749384	29.3	0.769	Pathogenic
c.3943C>T	p.R1315C	rs61749395	33	0.769	Pathogenic/Likely pathogenic
c.3917G>T	p.R1306L	rs61749385	23.4	0.772	Pathogenic
c.4892G>A	p.G1631D	rs2136411659	25.4	0.779	Pathogenic/Likely pathogenic
c.4022G>A	p.R1341Q	rs61749403	27.9	0.792	Pathogenic
c.4885G>C	p.G1629R	rs61750585	24.3	0.796	Likely pathogenic
c.4517C>T	p.S1506L	rs61750100	32	0.796	Pathogenic/Likely pathogenic
c.4883T>A	p.I1628N	rs61750584	27.7	0.797	Pathogenic
c.5146G>C	p.A1716P	rs1194776238	24	0.804	Likely pathogenic
c.4130C>T	p.A1377V	rs141211612	26.9	0.805	Uncertain significance
c.4309G>A	p.A1437T	rs61750084	24.7	0.806	Likely pathogenic
c.3320A>G	p.Y1107C	rs267607319	27.9	0.82	Uncertain significance
c.4244G>A	p.G1415D	rs61750080	24.5	0.823	Likely pathogenic
c.5459T>A	p.V1820E	rs2136405756	27.2	0.833	Uncertain significance
c.3515G>T	p.G1172V	rs1555195293	26.5	0.839	Uncertain significance

c.3842T>G	p.L1281R	rs1591863438	28.6	0.839	Uncertain significance
c.3925A>G	p.I1309V	rs61749389	23.6	0.851	Pathogenic
c.3833T>C	p.L1278P	rs2136413762	27.7	0.854	Uncertain significance
c.3944G>T	p.R1315L	rs61749396	27.8	0.854	Pathogenic
c.4082T>G	p.L1361W	NA	24.3	0.862	Likely pathogenic*
c.3377G>A	p.C1126Y	rs1591866134	26.3	0.871	Uncertain significance
c.3437A>G	p.Y1146C	rs267607326	24.1	0.872	Pathogenic
c.4121G>A	p.R1374H	rs61750072	28.7	0.879	Pathogenic
c.4021C>T	p.R1341W	rs61749402	33	0.889	Pathogenic/Likely pathogenic
c.3847G>C	p.D1283H	rs1219290844	27.5	0.908	Uncertain significance
c.823T>C	p.C275R	rs61753998	27.7	0.918	Likely pathogenic

1. Donor Loss score: 0.66 (NM_000552.5:c.2546+3G>C is predicted to significantly impact splicing, primarily by disrupting the donor splice site). 2. Donor Gain: 0.59 (NM_000552.5:c.3108+5G>A is predicted to alter splicing, primarily through the creation of a novel donor splice site). CADD scores >20 suggest a variant is among the top 1% most deleterious in the genome; higher scores indicate greater predicted pathogenicity. REVEL scores range from 0 to 1, with higher values indicating greater likelihood of pathogenicity; scores ≥0.75 suggest likely pathogenicity, 0.50–0.74 indicate uncertain significance, and <0.50 suggest likely benign effect.