LETTER TO THE EDITOR

Scott syndrome with novel compound heterozygous pathogenic variants in ANO6 and reduced thrombin generation

Authors

Amna Ahmed,[1] Samantha J. Montague,[1] Hrushikesh Vyas,[1] Jayna Mistry,[1] Natasha J. Pavey,[1] Sophie R.M. Smith,[1] Liam Griffith,[1] Isobel Clothier,[1] Roseanne Hudson,[1] Emma Faulkner,[1] Richard Buka,[1] Patricia Bignell,[2] Carl Fratter,[2] Kathryn Marshall,[3] Ben Bailiff,[3] Natalie S. Poulter,[1] Bas de Laat,[4] Dana Huskens,[4] Gillian C. Lowe,[5] Steven G. Thomas[1] and Neil. V. Morgan [1]

[1]Department of Cardiovascular Sciences, School of Medical Sciences, College of Medicine and Health, University of Birmingham, Birmingham, UK; [2]Oxford Genetics Laboratories, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; [3]Department of Haematology, University Hospitals Coventry and Warwickshire, Coventry, UK; [4]Synapse Research Institute, Maastricht, the Netherlands and [5]Comprehensive Care Haemophilia Centre, University Hospital Birmingham NHS Foundation Trust, Birmingham, UK

Correspondence:
N.V. MORGAN - N.V.Morgan@bham.ac.uk

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Scott syndrome with novel compound heterozygous pathogenic variants in *ANO6* and absent thrombin generation

Amna Ahmed [1], Samantha J. Montague [1], Hrushikesh Vyas [1], Jayna Mistry [1], Natasha Pavey [1], Sophie R. M. Smith [1], Liam Griffith [1], Isobel Clothier [1], Roseanne Hudson [1], Emma Faulkner [1], Richard Buka [1], Patricia Bignell [2], Carl Fratter [2], Kathryn Marshall [3], Ben Bailiff [3], Natalie S. Poulter [1], Bas de Laat [4], Dana Huskens [4], Gillian C. Lowe [5], Steven G. Thomas [1], Neil. V Morgan [1]*

Supplementary Data

Comprising:

Supplementary Table 1: Haematological Parameters for index patient II:2

Parameter	II:2	Reference Ranges*
Age (y)	60	-
ISTH BAT score**	8	0 – 3 (Males)
Sex	Male	-
White Blood Cells (x10^9/L)	8.22	3.26 – 11.2
Red Blood Cells (x10^9/L)	5.20	3.9 – 5.77
Haemoglobin (g/L)	148	130 – 171
Mean corpuscular volume (fL)	93.8	83 – 103
Platelets (x10^9/L)	363	150 – 400
Mean platelet volume (fL)	9	9-12
Lymphocytes (x10^9/L)	2.87	0.5 – 4.0
Monocytes (x10^9/L)	0.53	0.3 – 0.9
Neutrophils (x10^9L)	4.18	1.5 – 7.0
Prothrombin time (s)	14.9	10-14
Activated partial thromboplastin time ratio	1	0.8-1.2
von Willebrand Factor Antigen (vWF:Ag)	166	48 – 175
von Willebrand factor activity level (Ristocetin Co-Factor (vWF:RCo) (IU/dL)	205	47 – 154
von Willebrand Factor Antigen (vWF:Ag)	166	48 – 175
von Willebrand Factor Collagen binding activity (vWF:CBA)	155	57 – 164
FVIII:C (IU/dL) * **	>150	>40
FIX (IU/dL)	160	>40

* Reference ranges taken from document HAE.N002 Version 21.04 available at https://qehbpathology.uk/images/files/PUB_040.pdf

** International Society for Thrombosis and Haemostasis – Bleeding Assessment Tool (ISTH BAT) score comprised of Epistaxis (3), Surgery (3), Haematuria (2)

*** - reference range for FXIII:C was from UHCW – https://www.uhcw.nhs.uk/download/clientfiles/files/CWPS%20Handbook%20V17%20November%202025.pdf

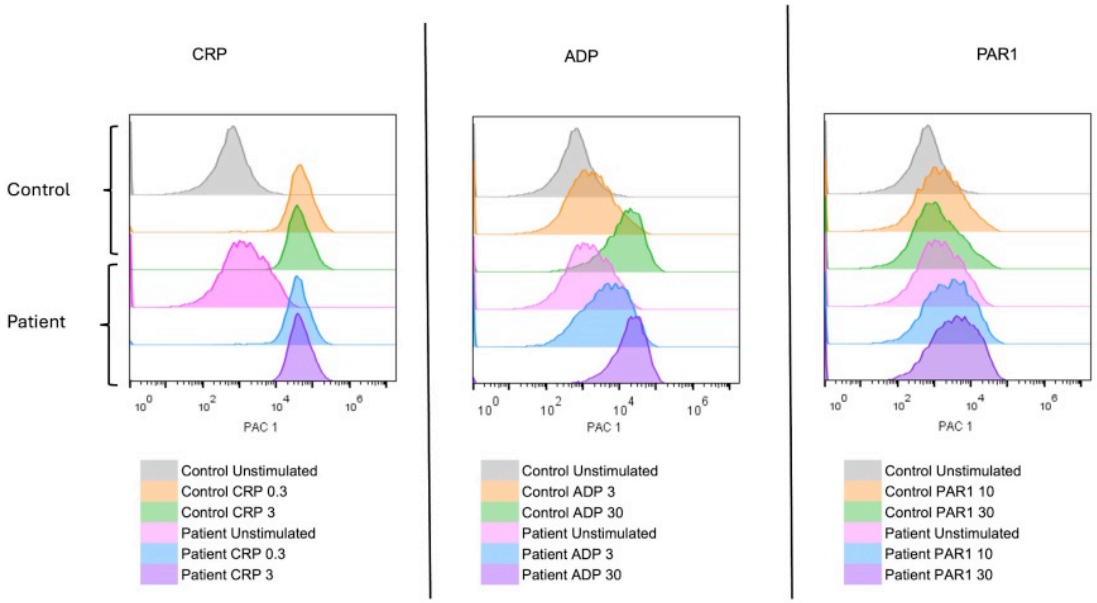
A

Platelet Aggregation

Agonist	Control Normal Ranges *				Patient ***	Same Day Control ***
	Mean	*SD*	*Lower **	*Upper **		
ADP 10	85	15	55	114	92	81
Adren 10	73	22	29	116	102	91
PAR1 30	*nd*	*nd*	*nd*	*nd*	94	90
Col 1	61	30	0.1	121	42	81
Col 3	66	21	23	109	110	90
CRP 3	*nd*	*nd*	*nd*	*nd*	112	85
Risto 1.5	85	17	51	118	107	120

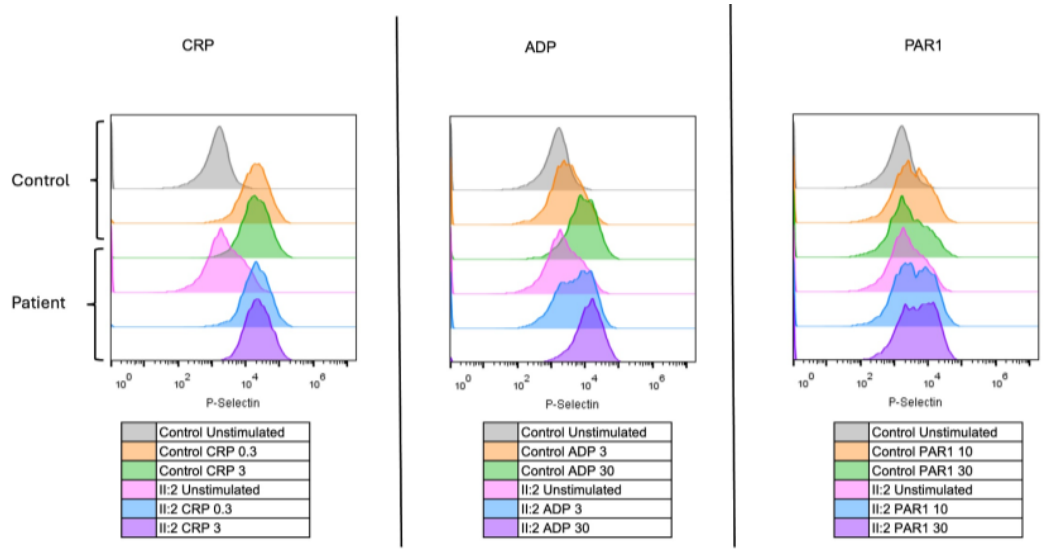
B

Platelet Activation

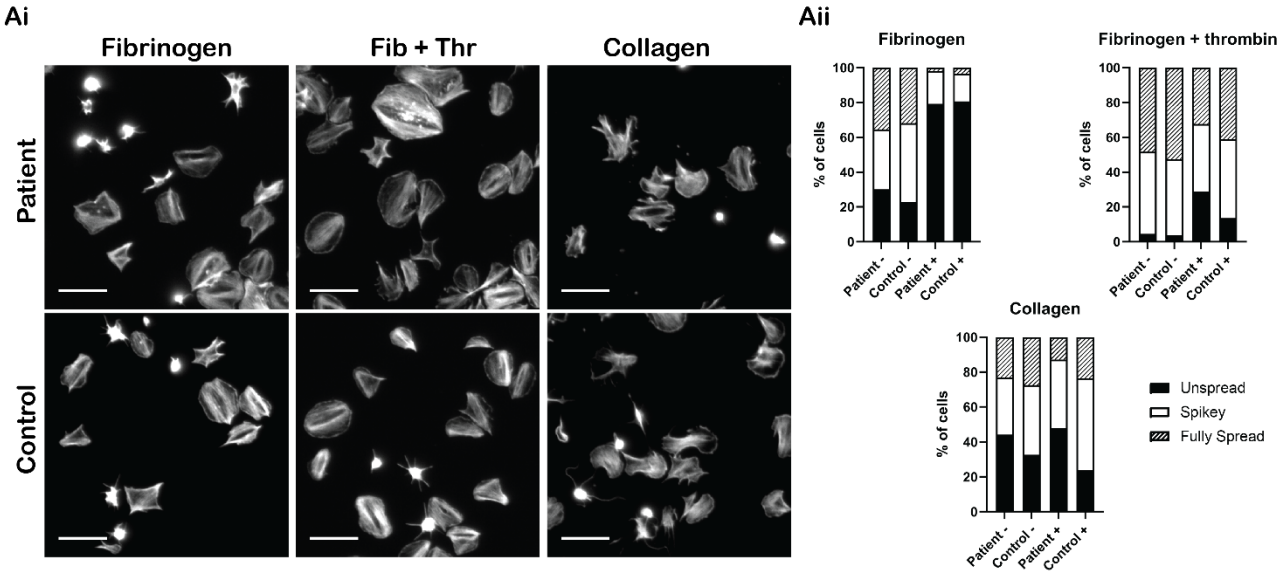


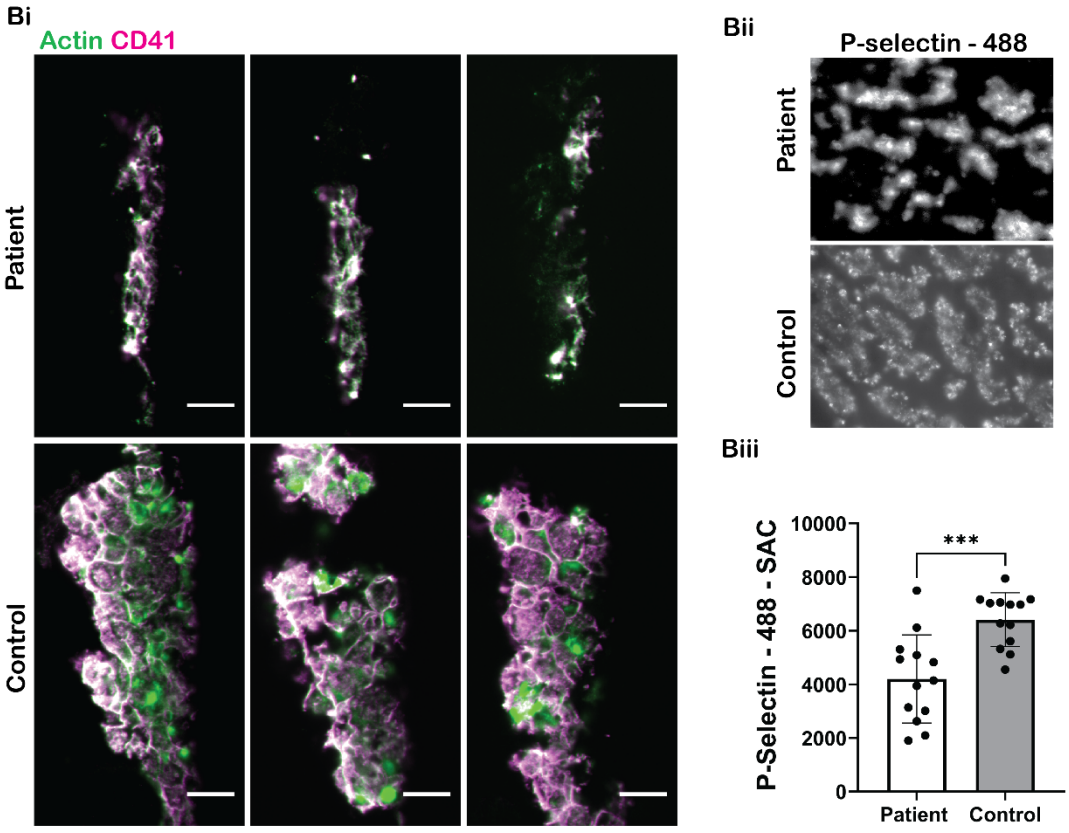
C

Platelet Secretion



Supplementary Figure 1. Platelet function analysis of the Scott patient compared to same-day healthy control. A) Percentage aggregation for index patient II:2 and same day control. PRP from patient II:2 and same-day healthy control, patient was stimulated with a range of platelet agonists for 7 min and aggregation and measured by light transmission aggregometry (LTA, Chrono-log model 700). ADP; Adenosine diphosphate (µM), Adren; Adrenaline (µM), PAR1; PAR1 peptide (TRAP6, µM), Coll; collagen (µg/mL), CRP; collagen-related peptide (µg/mL), Risto; ristocetin (mg/mL). * Control ranges taken from 33 healthy volunteer controls. ** Lower and upper values are ± 2 x SD, *** Green indicates value is within control normal range, red that it is outside. *nd* – Agonist/concentration not routinely performed with healthy control panels**. B)** Histograms of median fluorescence intensity (MFI) of PAC1-FITC and **C)** CD62P-APC (P-selectin) positive (platelets after stimulation with 0.3, 3 µg/mL CRP, 3, 30 µM ADP and 10, 30 µM PAR1 measured using flow cytometry.


Ai
Fibrinogen
Fib + Thr
Collagen
Patient
Control
Aii
Fibrinogen
Fibrinogen + thrombin
Collagen
% of cells
Patient -
Control -
Patient +
Control +
Unspread
Spikey
Fully Spread


Bi
Actin CD41
Patient
Control
Bii
P-selectin - 488
Patient
Control
Biii
P-Selectin - 488 - SAC
***
Patient
Control

Supplementary Figure 2. Platelet spreading and thrombus formation of patient compared to same-day control. A) Washed platelets (2×10^7 /mL) were spread on fibrinogen (100 µg/mL), fibrinogen and thrombin (Fib + Thr, 100 µg/mL and 0.1 UI/mL respectively) and collagen (10 µg/mL). **Ai)** Representative images for patient (II:2) and same-day control. **Aii)** distribution of spread platelet phenotype for platelets on fibrinogen, fibrinogen+ thrombin and collagen in the absence (−) and presence (+) of apyrase (2 U/mL) and indomethacin (10 µM). **B)** Thrombus formation on collagen (100 µg/mL) microspots in the Maastricht flow chamber at 1500 s^{-1}. **Bi)** Expansion microscopy images of selected regions of interest of thrombi using selective plane illumination microscopy (SPIM) stained for CD41 and actin**.** Scale bar = 20 µM. **Bii)** Representative images of patient thrombi and same-day healthy control stained for P-selectin. Scale = 50 µm. **Biii)** Quantitation of surface area coverage (SAC) of P-selectin images (13 fields of view per individual, mean ± SD). Unpaired T-test, *** = P <0.005