Haematologica HAEMATOL/2018/204784 Version 3

Sphingolipid dysregulation due to lack of functional KDSR impairs proplatelet formation causing thrombocytopenia

Tadbir K Bariana, Veerle Labarque, Jessica Heremans, Chantal Thys, Mara De Reys, Daniel Greene, Benjamin Jenkins, Luigi Grassi, Denis Seyres, Frances Burden, Deborah Whitehorn, Olga Shamardina, Sofia Papadia, Keith Gomez, NIHR BioResource, Chris Van Geet, Albert Koulman, Willem H Ouwehand, Cedric Ghevaert, Mattia Frontini, Ernest Turro, and Kathleen Freson

Collaborative Groups: NIHR BioResource (Jayanthi Alamelu, Raza Alikhan, David Allsup, Arif Alvi, Steve Austin, Trevor Baglin, Tamam Bakchoul, Gareth Baynam, Neha Bhatnagar, Tina Biss, Sara Boyce, Elizabeth Chalmers, Melissa V Chan, Janine Collins, Peter W Collins, Nicola S Curry, Kate Downes, Tina Dutt, Wendy N Erber, Gillian Evans, Tamara Everington, Remi Favier, Bruce Furie, Michael Gattens, Greinacher Andreas, Gresele Paolo, Daniel Hart, Yvonne M C Henskens, Rashid Kazmi, David Keeling, Anne M Kelly, Michael A Laffan, Michele Lambert, Claire Lentaigne, Ri Liesner, Bella Madan, Mike Makris, Carolyn Millar, Andrew D Mumford, Sarah Mangles, Mary Mathias, Paquita Nurden, Samya Obaji, K John Pasi, Jeanette H Payne, Kathelijne Peerlinck, Fernando Pinto, Shoshana Revel-Vilk, Sylvia Richardson, Mike Richards, Matthew T Rondina, Catherine Roughley, Sol Schulman, Harald Schulze, Suthesh Sivapalaratnam, Ilenia Simeoni, Marie Scully, Susan E Shapiro, Keith Sibson, Matthew C Sims, Matthew J Stubbs, R Campbell Tait, Kate Talks, Gordon B Taylor, Jecko Thachil, Cheng-Hock Toh, Minka J A Vries, Timothy Warner, Henry G Watson, Sarah K Westbury, John-Paul Westwood)

Haematologica HAEMATOL/2018/204784 Version 3

Disclosures: Funding - T.K.B is supported by the British Society of Haematology and NHS Blood and Transplant. K.F and C.V.G. are supported by the Fund for Scientific Research-Flanders (FWO Vlaanderen, Belgium; G.0B17.13N) and by the Research Council of the University of Leuven (BOF KU Leuven, Belgium; OT/14/098). C.V.G is holder of the Bayer and Norbert Heimburger (CSL Behring) Chairs. The structured illumination microscope was acquired through a CLME grant from Minister Lieten to the VIB Biolmaging Core, Leuven. J.H is supported by the Fund for Scientific Research-Flanders (FWO Vlaanderen, Belgium) grant no.1S00816N. A.K and B.J are funded by the National Institute for Health Research (NIHR) Biomedical Research Centre (RG64245). M.F. is supported by the British Heart Foundation (BHF) Cambridge Centre of Excellence (RE/13/6/30180). The Ouwehand laboratory receives support from the BHF, Bristol-Myers Squibb, European Commission, MRC, NHS Blood and Transplant, Rosetrees Trust, the NIHR Biomedical Research Centre based at Cambridge University Hospitals NHS Foundation Trust, and the University of Cambridge. The Tg(cd41:EGF)11 line was a gift from Professor Leonard Zon (Hematology Division, Brigham and Women's Hospital, Boston, MA).

Contributions: T.K.B analysed the results, performed the iPSC and iMK experiments, and wrote the manuscript. E.T and D.G performed statistical analyses and E.T edited the manuscript. C.T. performed stem cell differentiations. J.H. performed granule immunostainings and quantifications. M.D.R. performed zebrafish experiments. F.B assisted with cDNA library synthesis. L.G and D.S performed RNA-seq analysis. B.J performed mass spectrometry of sphingolipids. M.F and A.K analysed results and edited the paper. D.W provided sample logistics, QC and whole genome sequencing oversight. O.S analysed the sequencing results. C.G and K.G edited the paper. V.L and C.V.G are clinicians following up this pedigree. W.H.O leads the NIHR BioResource- Rare Diseases and co-wrote the paper. K.F. designed the study and analysis plan, and co-wrote the paper.