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A Twenty-Five Year Prospective Clinical Review and Family Studies Revealed New Globin Gene Regulators for Hb F Induction

Alex E. Felice, Joseph J. Borg, Laura Grech, Christian A. Scerri, Ruth Galdies & Sjaak Philipsen

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ABSTRACT

A Twenty-Five Year Prospective Clinical Review and Family Studies Revealed New Globin Gene Regulators for Hb F Induction

Alex E. Felice[a,b], Joseph J. Borg[a], Laura Grech[a], Christian A. Scerri[a,b], Ruth Galdies[b] and Sjaak Philipsen[c]

[a]Thalassaemia Testing and Haemoglobin Research Laboratory, Faculties of Health Science and Medicine and Surgery, Centre of BioBanking and Molecular Medicine, University of Malta, Msida, Malta; [b]Thalassaemia Clinic, Sptar Mater Dei, Malta; [c]Department of Cell Biology and Genetics, Erasmus Medical Center, Rotterdam, The Netherlands

The long-term goal of our research is to understand the genomics underlying clinical expression of β-thalassemia (β-thal) with a particular interest in the developmental regulation of globin gene switching and the pharmacogenomics re-activation of Hb F. Our approach follows two lines of investigation; clinical and experimental, by which observations in patients and families are done followed by experimental genomics. Prospective clinical data were collected over 25 years from patients with homozygous β-thal with different mild or severe mutations, using an innovative clinical severity score that served to quantify minimal response to transfusion and Hb F induction. The data indicated the requirements for transfusion even of mild thalassemia in children and that splenectomy was largely ineffective. Small doses of hydroxyurea (HU) resulted in aggravation of hematological parameters presumably due to medullary inflammation. A small number of critical families with a phenoypic thalassemia variant, or pseudo-thalassemia, due to various degrees of Krüppel-like factor 1 (KLF1) deficiency and various levels of Hb F in adulthood were identified and followed. Extensive experimental genomics confirmed the role of the KLF1 locus both directly and indirectly in regulating γ- to β-globin gene switching within a complex interactome that included FLVCR1 isoforms and that regulated the inter-erythrocytic distribution of the Hb F. Further research is intended to explore the interplay between the loci and the possible effects of new Hb F-inducing agents acting on new pathways in the clinical setting to improve patient outcomes.

KEYWORDS: Thalassemia; globin gene mutations; natural history; fetal hemoglobin; globin gene; Krüppel-like factor 1 (KLF1)

CONTACT Alex E. Felice alex.felice@um.edu.mt Thalassaemia Testing and Haemoglobin Research Laboratory, Faculties of Health Science and Medicine and Surgery, Centre of BioBanking and Molecular Medicine, University of Malta, Msida, Malta