

## ABSTRACT

### Sickle Cell Beta<sup>+</sup> Thalassaemia In Jamaica: A Heterogeneous Disorder

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This thesis reports the hematological, clinical and molecular defects of sickle cell  $\beta^+$  thalassaemia ( $S\beta^+$  thalassaemia) subjects in Jamaica. 197 subjects with  $S\beta^+$  thalassaemia have been studied.  $S\beta^+$  thalassaemia subjects are phenotypically heterogeneous resulting from varying levels of Hb A determined by the type of  $\beta^+$  thalassaemia gene inherited. The methodology for identifying the mutations included amplifying genomic DNA utilizing two polymerase chain reaction (PCR) procedures, the Amplification Refractory Mutation System (ARMS) and the Dynabead methods. 10 different  $\beta^+$  mutations were identified, seven by the ARMS-PCR [(1)-29 (A→G), (2)-88 (C→T), (3) CD-24 (T→A), (4) Poly-A (T→C), (5) IVSI nt 5(G→C), (6) IVS-II-nt-654 (C→T), and (7) IVSI nt 6 (T→C) ], and three by the Dynabead method, [a new frame shift mutation, (FS cd59-83 (+71), in one subject, one subject with homozygous -88(C→T) and Hb-Monroe or IVSI (-1) G→C  $\alpha_2\beta_2^{30}$ , in nine subjects]. Although rare, the Hb Monroe has been previously described in African patients.

The high frequency of the -29 (A→G) and -88 (C→T) mutations in this population was consistent with other studies. Examination of the Hb A level showed a wide range of concentrations within each of the -29 (A→G) and -88 (C→T) mutation groups. The

determinants of this variability in Hb A levels are currently unknown. An Indian mutation, [IVS-I nt 5(G→C)], was found to be relatively common.

Four groups were designated after information was received from the patients or relatives regarding the various racial groups within their family. African, Indian, Others, Chinese and No Ethnic Information (NEI). As expected, the type of  $\beta^+$  thalassaemia mutation varied according to these groups.

Blood samples were quantitated for Hb A in 94 subjects and the Hb A level varied from 1.1 to 33%. The molecular characterisation of the  $\beta$ -thalassaemia alleles and the quantitation of Hb A resulted in the designation of two  $S\beta^+$  thalassaemia phenotypic groups for the Jamaican population.  $S\beta^+$  thalassaemic subjects with Hb A levels reading less than or equal to 10% were designated phenotype I, which included those who inherited the more severe forms of the  $\beta^+$  thalassaemia genes such as the IVS-I nt 5 (G→C), IVS-II nt 654 (C→T) and subjects with Hb-Monroe. Subjects with Hb A levels of 10% or more, with milder forms of the  $\beta^+$  thalassaemia genes such the -29 (A→G), -88 (C→T), CD-24 (T→A) Poly-A (T→C) and IVSI-6 (T→C)), were designated  $S\beta^+$  thalassaemia phenotype II.

Two sample statistical tests were used to determine whether these two groups differed with respect to the following indices: Hb F, Hb A<sub>2</sub>, MCHC, reticulocytes, MCV and total haemoglobin. The two sample t-test revealed that the Phenotype II individuals had significantly higher Hb and MCV readings than did the Phenotype I individuals ( $P < 0.05$ ).

It was demonstrated that Phenotype I individuals had significantly higher reticulocyte counts than did the Phenotype II individuals ( $P < 0.01$ ). A non-parametric two-sample test revealed that the MCHC values for Phenotype I individuals were significantly lower than those for Phenotype II ( $P < 0.01$ ). Analysis of the clinical manifestations suggests that Jamaican  $S\beta^+$  thalassaemia subjects have a mild to moderate clinical severity.

**KEY WORDS:**  $S\beta^+$  thalassaemia; Hb A levels;  $\beta^+$  thalassaemia mutations; Phenotypes