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PB2240 SILENT GLOBIN MUTATIONS. 10 YEARS REFERRALS FOR GENETIC COUNSELING.

Topic: 27. Thalassemias

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Background:

Haemoglobinopathies, constitute the most frequent monogenic disorders worldwide and in Greece. Silent β and α globin mutations may be missed during screening programs. The identification of combinations of silent defects with severe thalassemia mutations is essential for the genetic counseling of at-risk couples.

Aims:

We report the results of the molecular analysis of 241 subjects with borderline hematologic indices or HbA2 levels respectively, without iron deficiency, during a ten year period in order to provide the appropriate genetic counseling for couples at-risk.

Methods:

The screening methodology of identifying the carriers is simple and low cost based on determination of red cell indices (RBC, Hb, Ht, MCV, MCH, RDW) and quantification of HbA, F, A_2, S, C, and other haemoglobins with the HPLC (Bio-Rad Variant Haemoglobin Testing System) and Capillary electrophoresis (Minicap). The practice guidelines are similar throughout the prevention network laboratoties of the country. The screening methods used for DNA analysis, all performed in the National Thalassemia Centre, were denaturating gradient gel electrophoresis (DGGE), allele-spesific oligonucleotide (ASO) analysis, high resolution melting analysis and other polymerace chain reaction directed methods and DNA sequencing.

Results:

162 subjects (67,2%) were found carriers of a silent thalassemic mutation. Among the subjects with MCH<27,5 pg, we found 147(89%) with a silent mutation. Most common was the -α 3.7 , -101(C>T) (68,7%). Other α deletions were found and some unstable variants as Hb Icaria, Hb Adana, Hb Agrinio, Hb Constant Spring, triplication of α genes and Termination Cd +6 C-G in the 3' untranslated region (3'UTR of the β-globin gene (+1480 C→ G) and silent Cap+1570(T>C) (HBB:c*96T>C), .

Among 76 subjects with borderline Hb A2 values (3,1-3,9%), 29 (39%) had a molecular defect in the β or α-globin genes. No molecular defects were found in the remaining 47 individuals. Among the positive samples the most common silent mutation was the-101(C>T)(n=15). In our study group the -101 (C>T) mutation shows an elevated Hb A2, Term+ 6 and silent Cap+1570(T>C) (HBB:c*96T>C), have a phenotype closer to normal. The -α3,7 deletion can be suspected when MCH is below 27,5 and triplication of a genes (ααα anti–3.7/αα) is often silent.

Summary/Conclusion:

Current application of molecular techniques to the study of borderline heamatologic measurements is important in the field of thalassemia diagnosis and the genetic counseling of couples at risk.