The molecular spectrum of hemoglobinopathy; Thalassemia and Hb variants

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The hemoglobinopathies constitute the most common recessive monogenic disorders worldwide [1, 2]. Over 1700 different mutations have been reported which either affect the synthesis of globin chains (causing thalassemia) or alter the structure and properties of the hemoglobintetramer (hemoglobin variants or abnormal hemoglobins) [3]. Hemoglobinopathies are mostly autosomal recessive disorders and heterozygotes are symptom-free but present various hematological characteristics which are used for their identification in carrier screening programs. The homozygous states andcompound-heterozygous states result in four main groups of clinically significant conditions, each witha variable degree of phenotypic severity: the- thalassemias,-thalassemias, sickle cell syndromes, and Hb E syndromes [4]. The heterogeneity of the hemoglobinopathies is caused by the numerous types of thalassemia and abnormal hemoglobin genotypes which can interact when co-inherited, creating a complex range of hematological phenotypes that often cause difficultiesin interpretation. Moreover, some phenotypes can arise from several different genotypes, such as heterozygous alpha zero thalassemia and homozygous alpha plus thalassemia, and the genotypes cannot be distinguished by simple hematological parameters. Finally, the electrophoresis or chromatography techniques used to screen for abnormal hemoglobins only provide a presumed diagnosis for the variant, and further tests are required for a definitive diagnosis. Thus in many cases of carrier screening, an accurate diagnosis requires expertise in the interpretation of the hematological results and confirmation of the genotypes by DNA analysis [1].
The presentation will highlight some unexpected molecular mechanisms showing interesting genotype-phenotype correlations, either ameliorating or deteriorating the clinical presentation of hemoglobinopathy.

[1] John Old , Cornelis Harteveld , Carrier Screening for the Haemoglobinopathies: Past, Present and Future, https://www.lidsen.com/journals/genetics/genetics-01-03-005
[2] Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bulletin of the World Health Organization. 2008;86(6):480-7.
[3]Giardine B, Borg J, Viennas E, Pavlidis C, Moradkhani K, Joly P, et al. Updates of the HbVar database of human hemoglobin variants and thalassemia mutations. Nucleic acids research. 2014;42(Database issue):D1063-9.
[4] Weatherall DJ, Clegg JB. The thalassaemia syndromes: John Wiley & Sons; 2008.