



β -Thalassemia: Genotype-Phenotype Relationship

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Genotype-phenotype relationship is the mainstay of studies in medical genetics. In the light of genetic counseling for example and prenatal diagnosis in particular, the knowledge becomes even more important for decision-making during pregnancy termination. The most common Mendelian-inherited disease, thalassemia, causes by defective synthesis of either α - or β -globin chain. Key pathologic determinant deserves mention that is the continuing production of the counterpart globin chain in excess--overproduction of β -globin in case of α -thalassemia and α -globin for β -thalassemia.

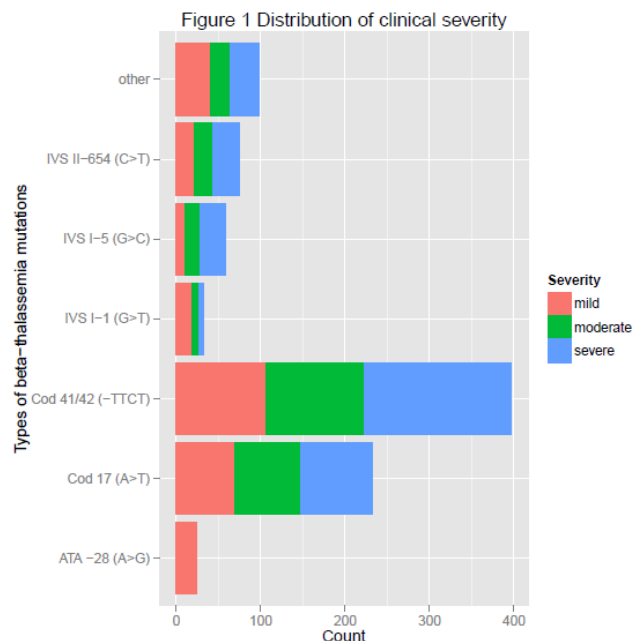
β -Thalassemia mutations

Mutations cause null output from β -globin gene designated β^0 -thalassemia while those causing partial reduction of the output define β^+ -thalassemia. The most prevalent β^+ -thalassemia in Thailand is β^E hemoglobin [1] (varying from 3% in the central and upto 50-70% in the Northeast) occurred as a result of substitution mutation in codon 26 leading to glutamic instead of lysine residue (c.76G>A according to recommended nomenclature [2], in addition activation of cryptic splice site culminating in nonproductive mRNA [3]. The combination of β^E together with β^0 - or other β^+ -thalassemia constitutes the majority of β -thalassemic patients. Their peripheral blood contains no Hb A ($\alpha^2 \beta^2$) but Hb F ($\alpha^2 \beta^2$), Hb E ($\alpha^2 \beta^E$) and Hb A2 ($\alpha^2 \beta^2$). However, predicting clinical severity of these patients are not always simple. In fact, clinical presentation could be classified as mild, moderate and severe forms according to scoring system [4].

Detailed data presented here are as published elsewhere [5]. Figure 1 demonstrates severity of various forms of β -thalassemia mutations with β^E (917 patients). Obviously, all patients with mutation at -28 A to G are clinically mild and the mutation considered β^+ -thalassemia. The remaining categories classified as β^0 -thalassemia mutations are codon 41/42 (-TTCT) (or c.121_124delTTCT), codon 17 (A>T) (c.48A>T), IVS II-654(C>T), IVS I-5(G>C), IVS I-1(G>T) and other. Noteworthy, all β^0 -thalassemia mutations when inherited with β^E result in unpredictable severity.

Coinheritance with α -thalassemia

Considering the high frequency of α -thalassemia in this region, Table 1 illustrates the tendency of having milder forms if there coexists whether deletion of one of both α -globin genes— $\alpha^{3.7}$, $\alpha^{4.2}$ or α^{SEA} and nondeletion as $\alpha^{Constant}$ Spring and α^{PakSe} . Both forms of α -thalassemia ameliorate the symptoms due to reduced output from the mutated genes thereby decreasing the excess α -globin chains in β -thalassemia. However, coinheritance together with α^{SEA} -thalassemia (both α -globin gene deleted) in Table 1 is not the exception because this patient carries codon 121(G>T) (c.361G>T) mutation when inherited as heterozygote alone is enough to produce severe disease (dominant β -thalassemia) [6]. The concepts are appreciated by considering triplicated α -globin genes expected to increase α -globin chain output indeed aggravate the diseases [7].



Using multinomial regression of severity outcome and predictors as β -thalassemia mutations, α -globin genotypes as well as sex, age and clinical centers where patients were recruited, the results indicate that types of β 0-thal mutations do not grossly confer significant difference in terms of clinical severity whereas identity of α -globin genotypes coinherited differentially affects in severity modification. Author therefore supports the notion that β 0-thalassemia/Hb E patients with apparent mild symptoms should be screened for α -thalassemia [7]. Other covariates such as age and sex have small influence. With the exception of patients with IVS-I-1(G > T), they tend to be moderate rather than severe when compare to other β 0-thalassemia mutations.

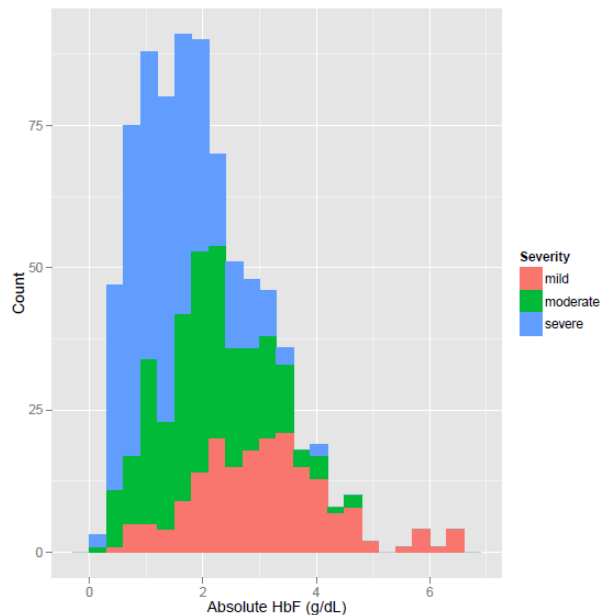


Table 1: alpha.globin \times Severity

| alpha.globin | Severity | | | Total |
|---------------------------------------|---------------|---------------|---------------|-------------|
| | mild | moderate | severe | |
| Normal | 221 26.50% | 258 30.97% | 354 42.50% | 833 100% |
| Hb CS trait | 13 92.90% | 1 7.14% | 0 0% | 14 100% |
| Hb Pakse trait | 2 100% | 0 0% | 0 0% | 2 100% |
| Hetero 3.7 kb deletion | 50 90.90% | 4 7.27% | 1 1.82% | 55 100% |
| Hetero 4.2 kb deletion | 4 66.00% | 2 33.33% | 0 0% | 6 100% |
| Hetero SEA deletion | 0 0% | 0 0% | 1 100% | 1 100% |
| Hetero triplicated alpha-globin genes | 0 0% | 0 0% | 4 100% | 4 100% |
| Homo 3.7 kb deletion | 2 100% | 0 0% | 0 0% | 2 100% |
| Total | 292 31.80% | 265 28.90% | 360 39.26% | 917 100% |

Genetic modifiers

Large deletions, dominant and unknown β -thalassemia mutations are excluded. Still, β 0-thalassemia/Hb E patients with comparable β 0-mutations without any forms of α -thalassemia virtually manifest variable phenotypes. With the

advent of genome-wide association studies, other major loci modifying disease severity (mild vs severe) becomes appear i.e. BCL11A, HBS1L-MYB intergenic region and polymorphisms within β -globin locus [8-10]. These three major loci are believed to modify disease severity via modulation of percentage of fetal hemoglobin (%Hb F). Other genetic loci responsible for remaining proportions of variations in %Hb F expectedly exist in the genome, this is termed missing heritability or hidden heritability (11).

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