



From Genotype to Phenotype in Thalassaemia

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Outline

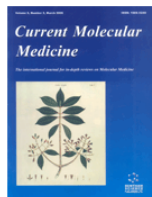


-
- ✓ Introduction, general aspects
 - ✓ Genotype-phenotype in patients
 - ✓ Genotype-phenotype in carriers
 - ✓ Conclusions



Genetic modifiers of β -thalassemia

Swee Lay Thein



Genetic modifiers in hemoglobinopathies.

Rund D, Fucharoen S.

Current Molecular Medicine

Volume 8 Issue 7

2008

Galanello and Origa *Orphanet Journal of Rare Diseases* 2010, 5:11
<http://www.orphandis.com/content/5/1/11>



ORPHANET JOURNAL
OF RARE DISEASES

REVIEW

Open Access

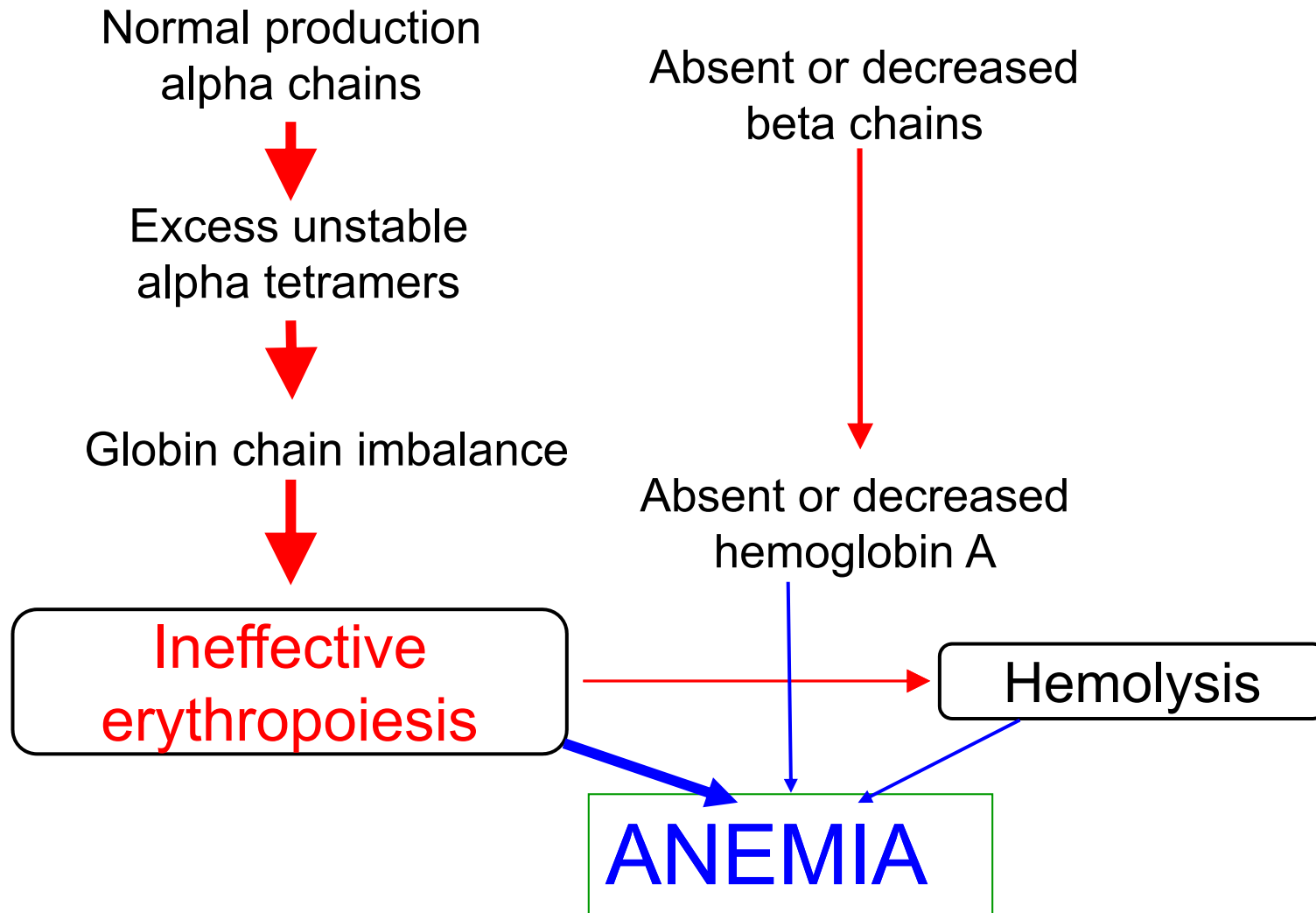
Beta-thalassemia

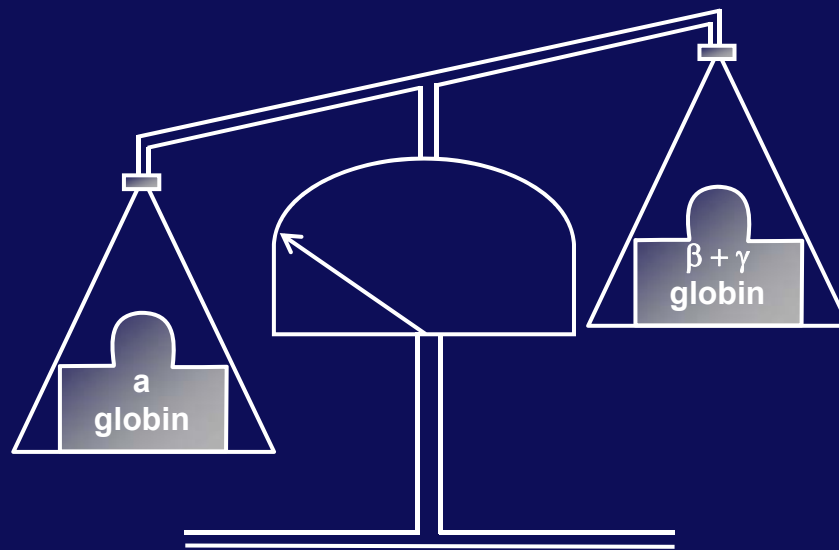
Renzo Galanello* and Raffaella Origa

Relevance of phenotype prediction from genotype

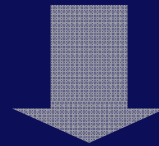
- ✓ diagnosis
- ✓ planning appropriate management:
 - transfusion: starting and regime
 - monitoring of disease, complications and treatment
- ✓ provide appropriate genetic counselling
- ✓ reveal new targets for therapeutic intervention

Pathophysiology of β -thalassemia



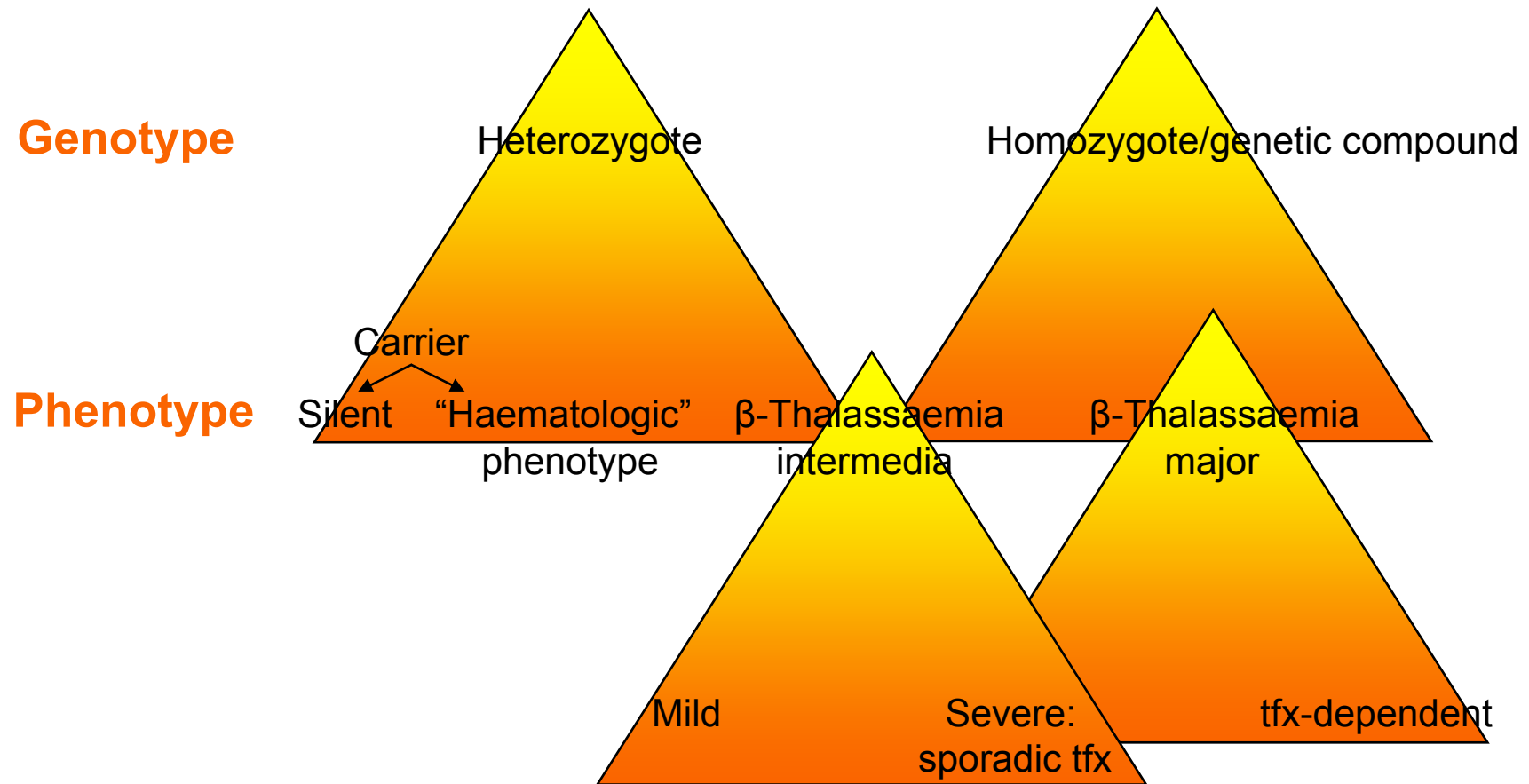


**Imbalance Of Globin Chain Synthesis
In Beta Thalassemia**



Severity Of Clinical Phenotype

β -Thalassaemia: genotypic/phenotypic heterogeneity



tfx = transfusion.

Molecular basis of thalassemia intermedia



Homozygous or compound heterozygous state for β thalassemia

- Inheritance of mild β thalassemia alleles
- Co-inheritance of α thalassemia
- Increased Hb F response
 - Xmn1 G_{γ} polymorphism
 - β globin gene promoter mutations
 - Trans-acting HPFH genetic determinants

Heterozygous state for β thalassemia

- Co-inheritance of excess α globin genes
($\alpha\alpha\alpha/\alpha\alpha$, $\alpha\alpha\alpha/\alpha\alpha\alpha$, $\alpha\alpha\alpha\alpha/\alpha\alpha$)
- Dominantly inherited β thalassemia
(Hyperunstable β globin chain variants)

Compound heterozygotes for β thalassemia and β chain variants

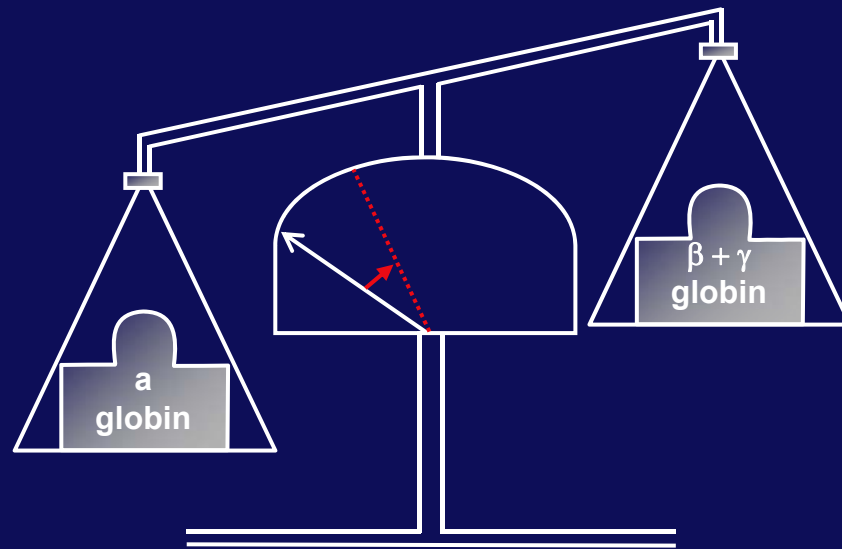
e.g. Hb E/ β thalassemia

Compound heterozygotes for β thalassemia and HPFH or $\delta\beta$ thalassemia

Mechanisms Of β -Thalassemia Intermedia

Severe Phenotype

α thalassemia



Wild/silent β alleles
Increased γ

Genome Wide Association Study

GWAS

- **Definition** (*NIH*)

study of genetic variation across the entire genome designed to identify genetic associations with observable traits or the presence or absence of a disease or condition.

- **Aims**

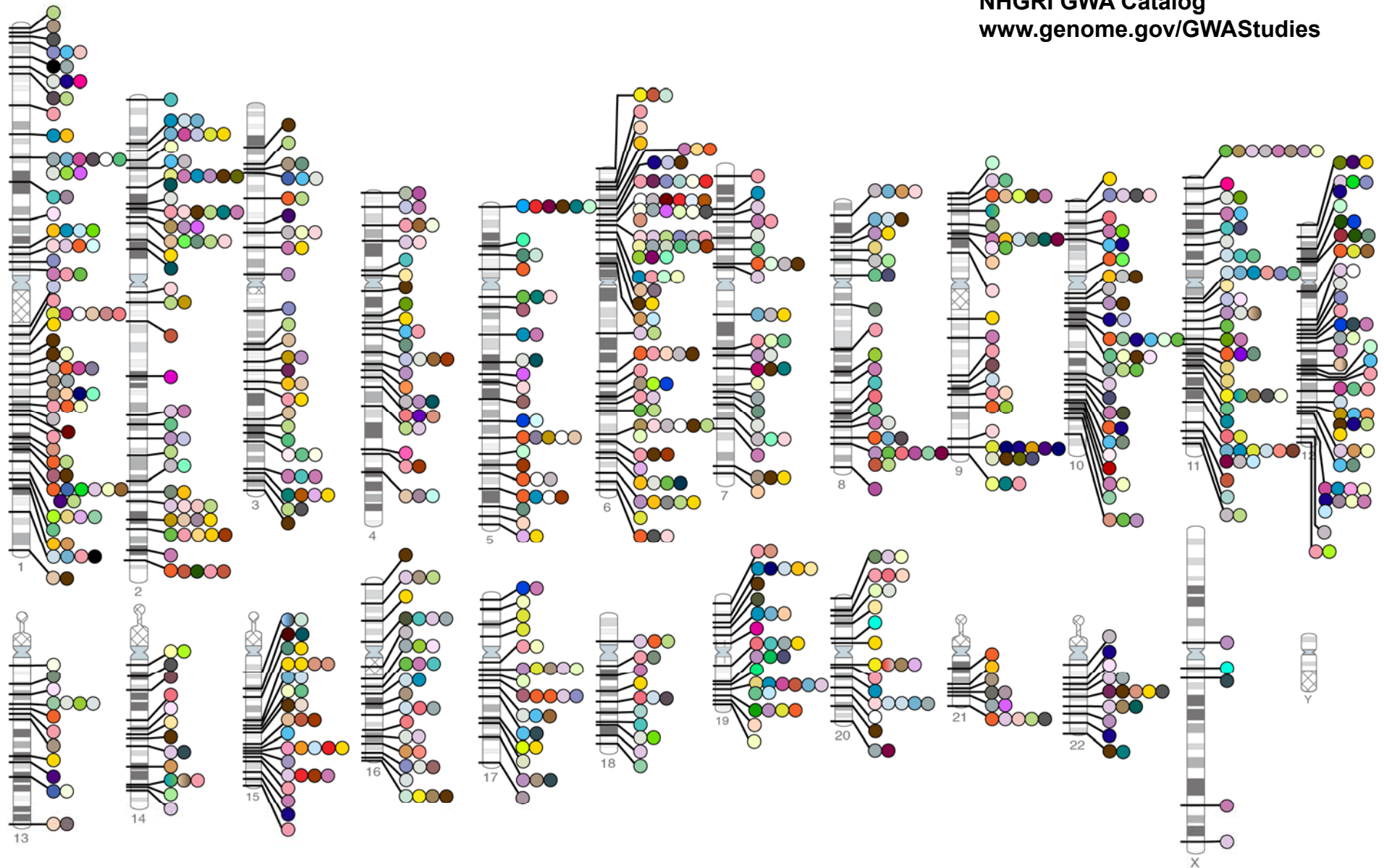
- increased understanding of basic biological processes affecting human health
- improvement in the prediction of disease and patient care
- ultimately the realization of the promise of personalized medicine

- **Research tools**

high-throughput, cost-effective methods for genotyping

**Published Genome-Wide Associations through 6/2010,
904 published GWA at $p \leq 5 \times 10^{-8}$ for 165 traits**

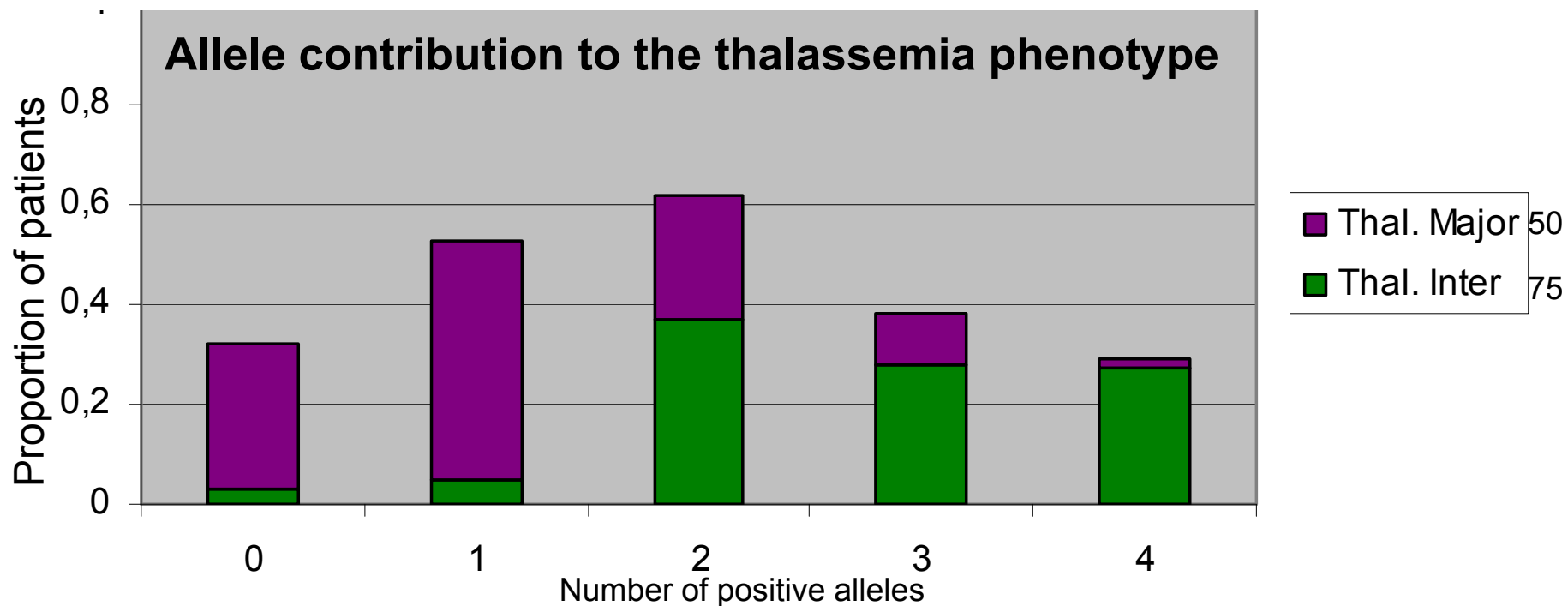
NHGRI GWA Catalog
www.genome.gov/GWASudies



Brief report

Amelioration of Sardinian β^0 thalassemia by genetic modifiers

Renzo Galanello,¹ Serena Sanna,² Lucia Perseu,² Maria Carla Sollaino,¹ Stefania Satta,¹ Maria Eliana Lai,³
Susanna Barella,¹ Manuela Uda,² Gianluca Usala,² Goncalo R. Abecasis,⁴ and Antonio Cao²



Ameliorating alleles:

- BCL11A rs 11886868
- HBS1L-Myb rs 9389268

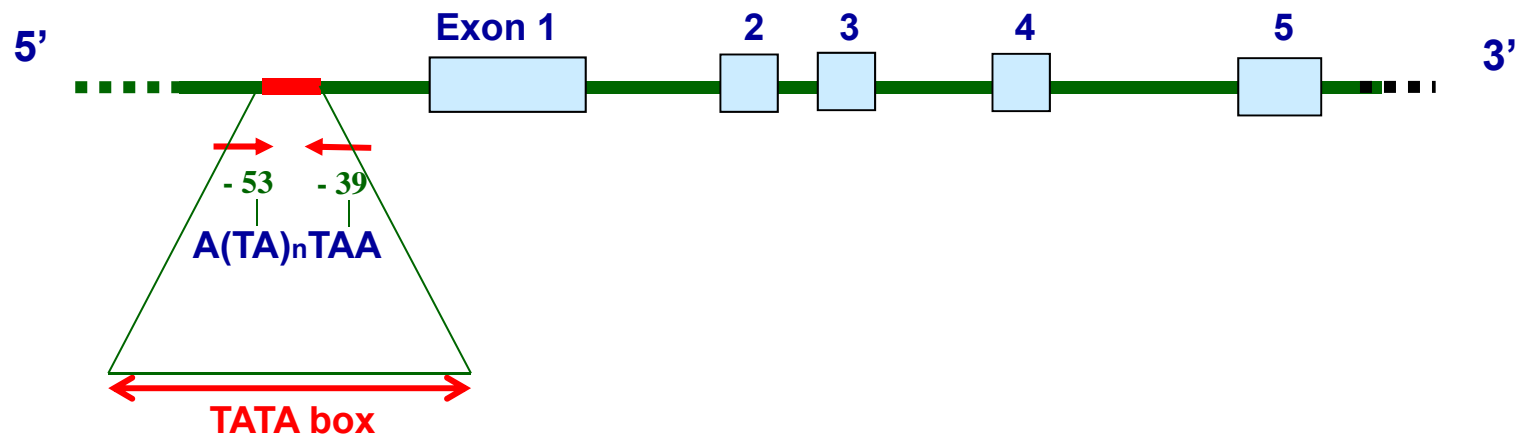
- - alpha/alpha alpha
- -alpha/-alpha

Cholelithiasis and Gilbert's syndrome in homozygous beta thalassemia



	Total patients	Cholelithiasis	Prevalence %
Thalassemia major	261	53	20.3
Thalassemia intermedia	35	20	57.1

Mutation of UGT1A1 gene promoter



Normal subjects

$A(TA)_6TAA$



Normal enzyme activity

Subjects with Gilbert syndrome

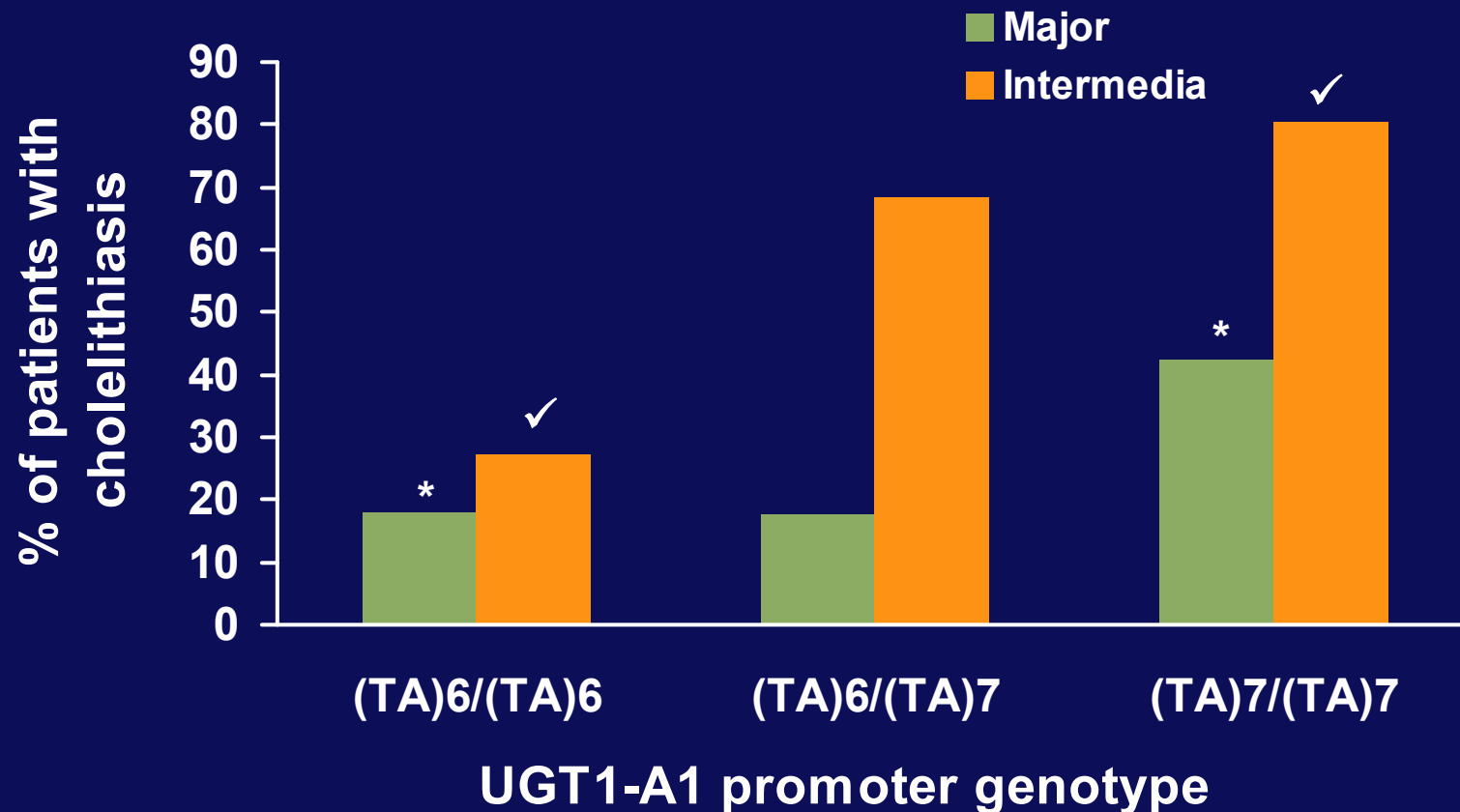
$A(TA)_7TAA$



Enzyme activity :
30% reduction

!

Prevalence of Cholelithiasis And UGT1-A1 Promoter Genotype In Thalassemia Major And Intermedia



* $P < 0.05$

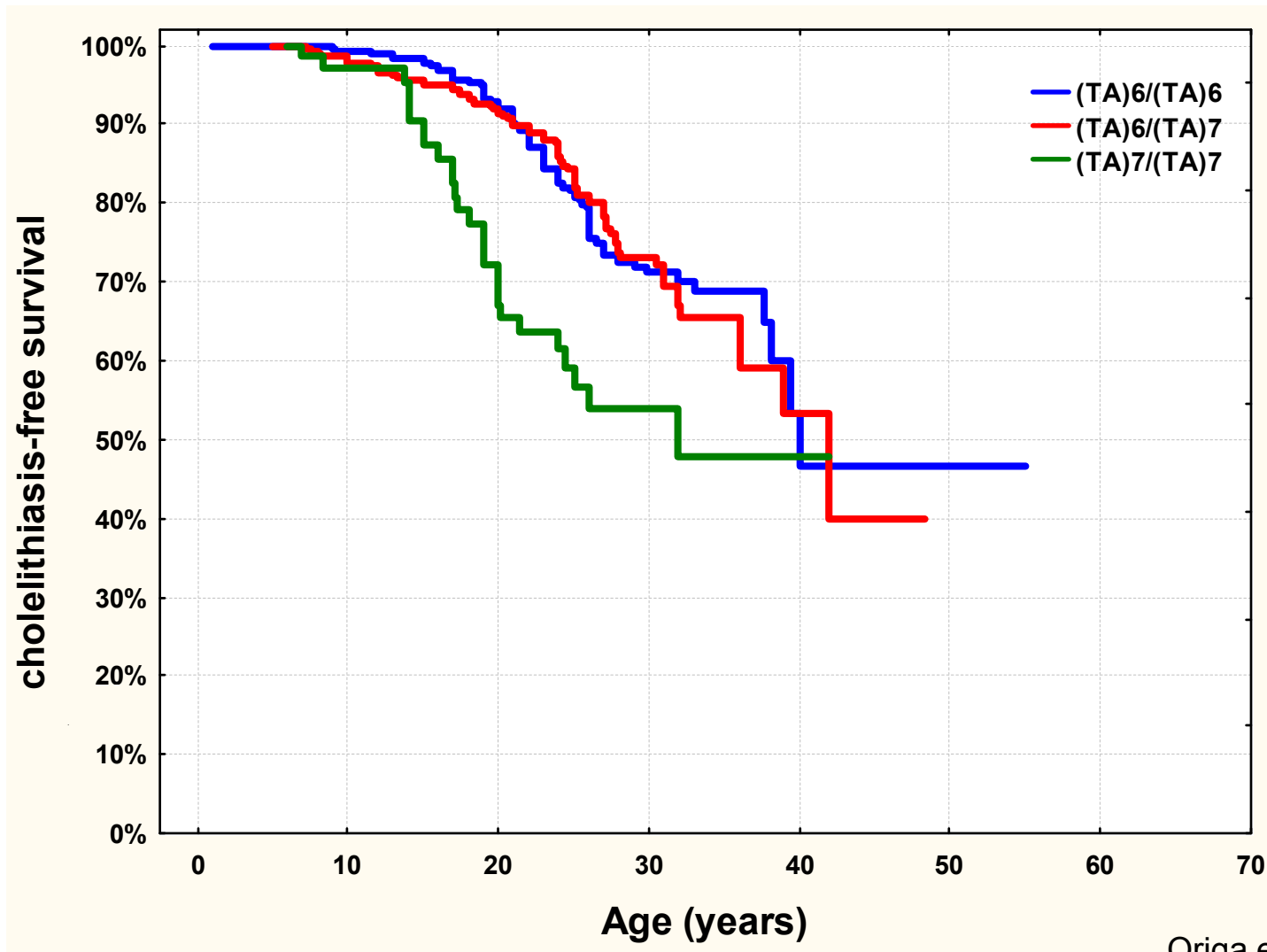
✓ $P < 0.05$

Galanello et al. *BJH*. 2001.

Cumulative proportion of cholelithiasis-free survival in 667 patients with β -thalassaemia major according to the UGT1-A1 genotype



(Webthal study)



Common variants in the *SLCO1B3* locus are associated with bilirubin levels and unconjugated hyperbilirubinemia



Serena Sanna^{1,†}, Fabio Busonero^{1,†}, Andrea Maschio¹, Patrick F. McArdle², Gianluca Usala¹, Mariano Dei¹, Sandra Lai¹, Antonella Mulas¹, Maria Grazia Piras¹, Lucia Perseu¹, Marco Masala¹, Mara Marongiu¹, Laura Crisponi¹, Silvia Naitza¹, Renzo Galanello³, Gonçalo R. Abecasis⁴, Alan R. Shuldiner^{2,5}, David Schlessinger⁶, Antonio Cao¹ and Manuela Uda^{1,*}

2712 *Human Molecular Genetics*, 2009, Vol. 18, No. 14

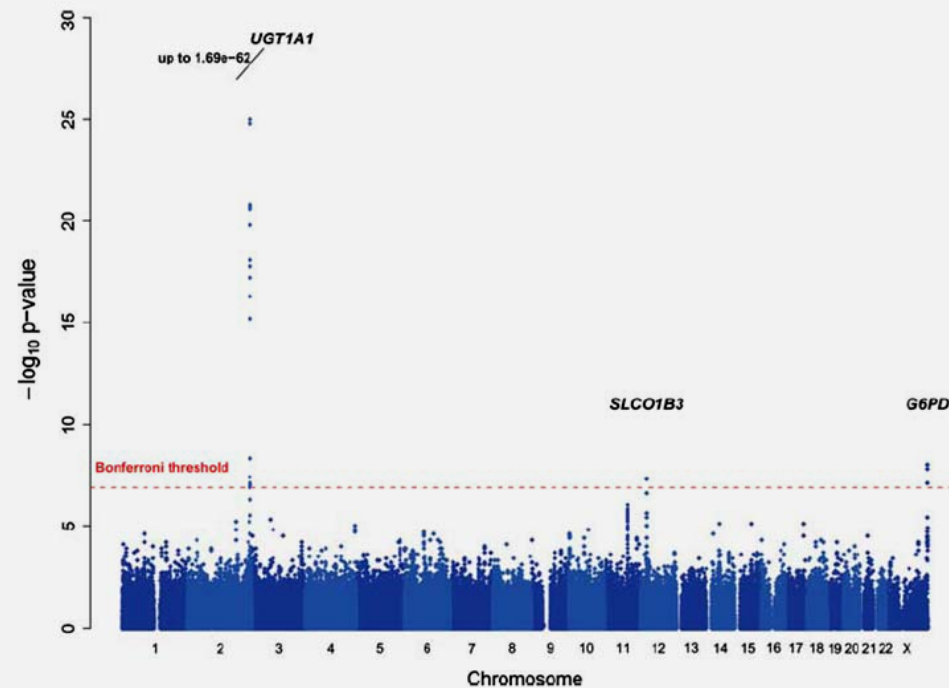


Figure 1. Genome-wide scan of serum total bilirubin. The figure summarizes association *P*-values (additive test) for all SNPs that passed quality control tests ($N = 362,129$). Position of *UGT1A*, *SLCO1B3* and *G6PD* genes are annotated. Red dotted line marks Bonferroni threshold (1.3×10^{-7}).

A Polymorphism Near *IL28B* Is Associated With Spontaneous Clearance of Acute Hepatitis C Virus and Jaundice

Gastroenterology 2010

HANS L. TILLMANN,* ALEX J. THOMPSON,* KEYUR PATEL,* MANFRED WIESE,[†] HANNELORE TENCKHOFF,[§] HANS D. NISCHALKE,[‡] YULIYA LOKHINYGINA,* ULRIKE KULLIG,[¶] UWE GÖBEL,* EMANUELA CAPKA,** JOHANNES WIEGAND,[§] INGOLF SCHIEFKE,^{††} WOLFGANG GÜTHOFF,^{§§} KURT GRÜNGREIFF,^{||} INGRID KÖNIG,^{¶¶} ULRICH SPENGLER,[‡] JEANETTE MCCARTHY,** KEVIN V. SHIANNNA,*** DAVID B. GOLDSTEIN,*** JOHN G. MCHUTCHISON,* JÖRG TIMM,^{†††} and JACOB NATTERMANN[‡] for the German Anti-D Study Group

Genome-wide association of *IL28B* with response to pegylated interferon- α and ribavirin therapy for chronic hepatitis C

nature
genetics

Yasuhito Tanaka^{1,18}, Nao Nishida^{2,18}, Masaya Sugiyama¹, Masayuki Kurosaki³, Kentaro Matsuura¹, Naoya Sakamoto⁴, Mina Nakagawa⁴, Masaaki Korenaga⁵, Keisuke Hino⁵, Shuhei Hige⁶, Yoshito Ito⁷, Eiji Mita⁸, Eiji Tanaka⁹, Satoshi Mochida¹⁰, Yoshikazu Murawaki¹¹, Masao Honda¹², Akito Sakai¹², Yoichi Hiasa¹³, Shuhei Nishiguchi¹⁴, Asako Koike¹⁵, Isao Sakaida¹⁶, Masatoshi Imamura¹⁷, Kiyooki Ito¹⁷, Koji Yano¹⁷, Naohiko Masaki¹⁷, Fuminaka Sugauchi¹, Namiki Izumi³, Katsushi Tokunaga² & Masashi Mizokami^{1,17}

GASTROENTEROLOGY 2010;139:120–129

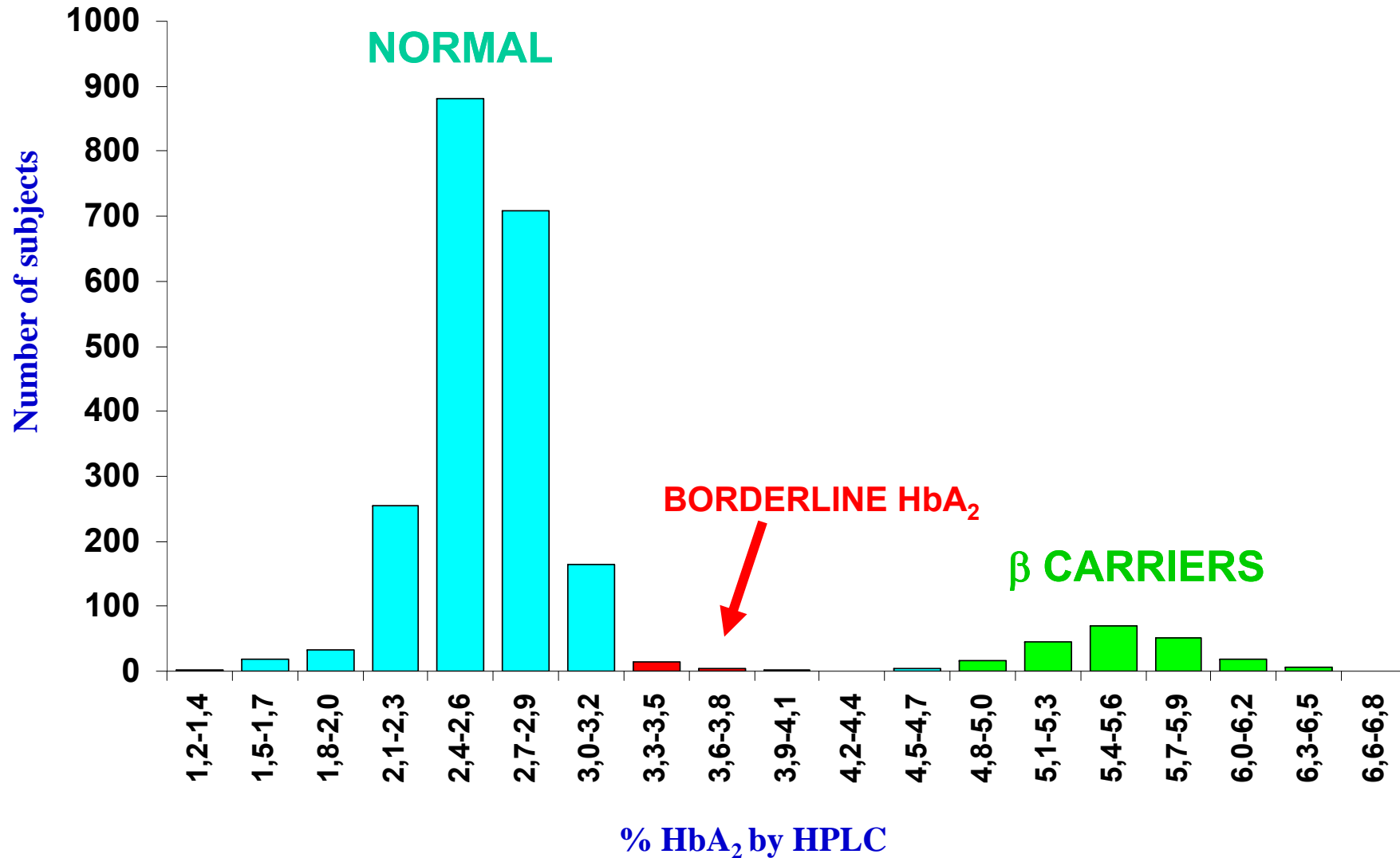
CLINICAL ADVANCES IN LIVER, PANCREAS, AND BILIARY TRACT

Interleukin-28B Polymorphism Improves Viral Kinetics and Is the Strongest Pretreatment Predictor of Sustained Virologic Response in Genotype 1 Hepatitis C Virus

Atypical β -thalassemia carriers

Phenotype	Genotype
Normal MCV and MCH	<ul style="list-style-type: none"> • Co-inheritance of alpha-thalassemia
Borderline HbA ₂ : -low MCV -normal MCV	<ul style="list-style-type: none"> • some mild β-thalassemia alleles • co-inheritance of δ-thalassemia • $\epsilon\gamma\delta\beta$-thalassemia • corfu $\delta\beta$-thalassemia • silent β-thalassemia • triplicated α globin genes • some, Hb variant (<i>Hb Hamilton, Hb City of Hope</i>) • mostly unknown
Increased HbF: -low/normal MCV -normal MCV	<ul style="list-style-type: none"> • $\delta\beta$-thalassemia • HPFH

HbA₂ Distribution in normal and β -thalassemia carriers



Genotype of 53 out of 234 subjects with borderline Hb A2 and normal MCV

$\alpha\alpha/ -\alpha 3.7$	2
IVS 1 nt 6	20
$\beta^{\text{a}}+\delta\text{Cd}27$	7
$\alpha\alpha/\alpha\alpha\alpha^{\text{anti}3.7}$	10
Hb Variants ^b	3
Cap + 1570	1
β promoter mutations (-101; -92)	10

^a β -thal mutations: β 039, IVS I nt 1, IVS I nt110

^b Hb Variants: Hb Acharnes (cd 53 GCT>ACT; Hb Kolcomo (cd 74 GGC>AGC), Hb Emz (cd 123 ACG>AAC)