Final Draft

EVIDENCE REVIEW: Hemoglobin H Disease

Prepared for:
MATERNAL AND CHILD HEALTH BUREAU

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Authors:
Alixandra A. Knapp, Danielle R. Metterville, Alex R. Kemper, James M. Perrin

Evidence Review Group: Chairperson, James M. Perrin, MD
(MGH Center for Child and Adolescent Health Policy)

Committee Members:

Marsha Browning, MD, MPH, MMSc
(Massachusetts General Hospital)

Anne Comeau, PhD
(University of Massachusetts)

Nancy Green, MD
(Columbia University)

Alex R. Kemper, MD, MPH, MS
(Duke University)

Alixandra A. Knapp, MS
(MGH Center for Child and Adolescent Health Policy)

Danielle R. Metterville, MS
(MGH Center for Child and Adolescent Health Policy)

Lisa Prosser, PhD
(University of Michigan)

Denise Queally, JD
(Consumer Representative)

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*Appendices available upon request -

i. Abbreviations used

CHRCO	Children's Hospital & Research Center Oakland
CS	Constant Spring
Hb	Hemoglobin
HPLC	High-performance liquid chromatography
IEF	Isoelectric focusing
PCR	Polymerase Chain Reaction

I. Introduction

Hemoglobin (Hb) H disease belongs to a group of inherited hemoglobinopathies known as the alpha (α)-thalassemias. Individuals with Hb H disease are at risk for developing severe anemia requiring urgent blood transfusions, especially during times of infection, fever, or pregnancy. Other features may include hepatomegaly, splenomegaly, cholelithiasis (gallstones), iron overload in adults, growth retardation in children and, rarely, hydrops fetalis *in utero* (Chui, Fucharoen & Chan 2003). While there is variability in the clinical course, some genotypes are associated with more severe disease course (Chen et al. 2000).

The α-thalassemias are caused by deletions and nondeletional mutations affecting the two adjacent α-globin genes, α1 and α2, on chromosome 16p13.3, resulting in reduced or absent α-globin chain synthesis (Higgs 2001). α-Globin is a subunit essential for both fetal and adult hemoglobin, the molecule that is responsible for oxygen transport in the blood. In adults, the majority of hemoglobin is hemoglobin A (Hb A); a molecule composed of two α-globins and to β-globins (denoted $\alpha_2\beta_2$). Fetal hemoglobin (Hb F) is a molecule composed of two α-globins and two γ-globins ($\alpha_2\gamma_2$) (Forget 2001). Reduced α-globin production disrupts the ratio of globin chains. Specifically in Hb H disease, the relative excess of β chains form a tetramer known as Hb H (β_4), for which the condition is named (Higgs 2001). In the fetal and newborn period, relative excess of γ chains form a tetramer known as Hb Bart's (γ_4).

Typically, an individual has two adjacent α-globin genes on each copy of chromosome 16 (the α1 gene and the α2 gene), for a total of four α-globin genes (αα/αα) (Forget 2001). The severity of hematological findings in the α-thalassemias depends on the number of α-globin genes affected (Table 1) (Chen et al. 2000). Moreover, variable levels of functional α-globin can exist, depending on whether the α1 gene or α2 gene is affected, as the α2 gene expresses more α-globin (Higgs 2001). Absence of one α-globin gene results in somewhat less α-globin chain production from that allele (denoted α^+), but nearly always results in the silent carrier state. Absence of two α-globin genes is termed α-thalassemia trait and can occur in one of two ways: in cis (αα/--) or in trans (α-/α-). An allele with a two α-globin gene deletion in the cis form is also called α^0. Individuals with α-thalassemia trait have mild anemia. The absence of three α-globin genes results in Hb H disease, with moderate to severe anemia. The absence of all four α-globin genes (--/--) results in Hb Bart's hydrops fetalis, which is usually fatal *in utero* or shortly after birth (Higgs & Bowden 2001).

Table 1– α-Thalassemia allele genotypes

Description & Terminology	α1 and α2 Genes	Genotype
Normal	4 functional α-globin genes	αα/αα
Silent carrier	1 deletion	-α/αα
Alpha-thalassemia trait	2 deletions	-α/-α --/αα
Hb H disease (deletional)	3 deletions	--/-α
Hb H disease (nondeletional) Example: Hb H disease with CS	2 deletions + 1 mutation (T) 2 deletions + CS mutation (α2 142 TAA→CAA or Ter→Gln)	--/$\alpha^{T}\alpha$ --/$\alpha^{CS}\alpha$
Hb Bart's hydrops fetalis	4 deletions	--/--

Table 2 – Mutation Specific Designations for α-Thalassemia allele types

α -Thalassemia allele type	Description	Most common alleles
α^{0}-thalassemia allele (-- allele from Table 1)	Deletion of both α-globin genes on a chromosome resulting in absent α-globin chain production	$--^{SEA}$, $--^{MED}$, $--^{FIL}$, $--^{THAI}$
α^{+}-thalassemia allele (-α or $\alpha^{T}\alpha$ allele from Table 1)	Deletion or inactivation of one α-globin gene on a chromosome resulting in decreased α-globin chain production	$\alpha^{CS}\alpha$, $-\alpha^{3.7}$, $-\alpha^{4.2}$

α-Thalassemia is most common among individuals of Southeast Asian, Mediterranean and African descent. Silent carrier frequencies of α^{+}-thalassemia alleles range from 10–20% in parts of sub-Saharan Africa, 40% and greater in some Middle Eastern and Indian populations, and up to 80% in northern Papua New Guinea and isolated groups in northeast India (Weatherall & Clegg 2001). A particular α^{0}-thalassemia allele prevalent in Southeast Asian, ($--^{SEA}$), has a carrier frequency of between 3.5% (Northern Taiwan) and 14% (Northern Thailand) in that region (Chui & Waye 1998).

II. Case definition

For this report, Hb H disease is defined as the presence of deletions or deleterious mutations affecting three of the four α-globin genes, as highlighted in Table 1 (Higgs 2001, Higgs & Bowden, 2001, Higgs & Weatherall 2009).

Hb H disease is classified into two types: deletional and nondeletional (Table 1). In the deletional form, three of the four α-globin genes are absent: there are two deleted α-globin genes on one chromosome (α^{0}) and one deleted α-globin gene on the other chromosome (α^{+}); usually denoted (--/-α). Nondeletional Hb H disease arises if two α-globin genes are deleted, and one of the two remaining α-globin genes is abnormal, usually denoted (--/$\alpha^{T}\alpha$). Nondeletional Hb H disease includes Hb H disease with Constant Spring (CS), caused by a two α-globin gene deletion on one chromosome and a point mutation (142 TAA→CAA) affecting the termination codon of the α2 gene on the other chromosome (Higgs 2001).

Variability in Hb H disease can also be introduced because homozygosity or compound heterozygosity for some mutations on the α2 gene can reduce α-globin chain synthesis to that of one functional α-globin gene (Pressley et al. 1980, Kanavakis et al. 2000, Chui 2005). For example, rare cases of homozygosity or compound heterozygosity for α2 gene mutations such as the polyadenylation (poly A) sequence mutations AATAAA→AATA and AATAAA→AATAAG (known as TSaudi) (Harteveld et al. 1994) and the mutation 104TGC→TAC (known as Sallanches) (Morle et al. 1995, Khan et al. 2000, Waye et al. 2000) may also represent Hb H disease genotypes.

III. Rationale for review

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) has directed the Evidence Review Group (ERG) to produce this report for the nominated condition of Hb H disease. Hb H disease has been nominated for the following reasons:

1. Individuals with Hb H disease may experience significant morbidity.
2. Presymptomatic identification of infants with Hb H disease may improve health outcomes.
3. Newborn screening is possible using current technology for detecting other hemoglobinopathies in dried blood spots. California has been screening for Hb H disease since 1996.
4. Newborn screening permits a window of opportunity for detection of Hb H disease because Hb Bart's is detectable only in the neonatal period.
5. Hb H disease is currently a secondary target (that is, a condition that is detected while screening for another condition) of the uniform screening panel recommended by the ACHDNC.

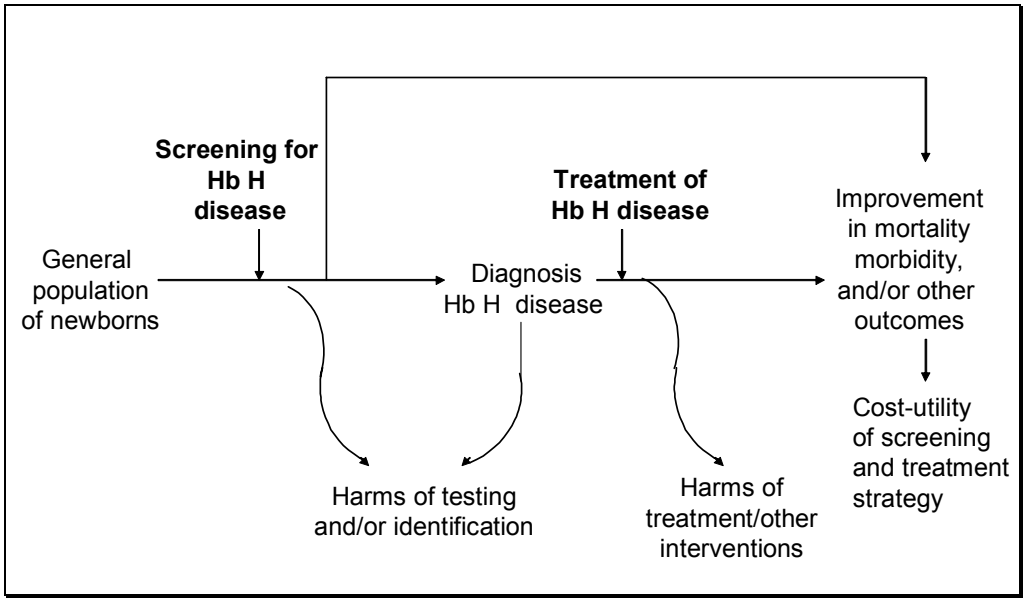
IV. Objectives

The objective of this review is to provide information to the ACHDNC about the potential benefits, harms, and costs of adding Hb H disease to the list of primary conditions for newborn screening, based on published studies and other data available from experts in screening for hemoglobinopathies and the treatment of Hb H disease.

V. Conceptual framework

The conceptual framework below (Figure 1) illustrates our approach to evaluating the evidence regarding the potential benefits and harms of newborn screening for Hb H disease. Our main goals are to assess (1) the potential effectiveness of screening and (2) the potential impact of treatment for those identified through newborn screening compared to those identified later through clinical diagnosis.

Figure 1 - Conceptual framework



VI. Key questions

The following is a list of the key questions for our review:

Condition:

- What is the birth prevalence of deletional and nondeletional Hb H disease?
- What is the natural history, including the spectrum of severity, of deletional and nondeletional Hb H disease during the first five years of life? -

Screening Test: -

- What methods exist and are used by newborn screening programs to screen newborns for Hb H disease? How accurate are those methods and what are the advantages or disadvantages of each method? Do they distinguish between Hb H disease and other types of α-thalassemia (such as carrier states)? What are their sensitivity, specificity and analytic validity?
- Can current screening tests effectively and efficiently identify cases of Hb H disease that may benefit from early identification?
- What is the range of clinical conditions identified in population-based screening?
- What are the potential harms or risks associated with screening? -

Diagnostic Test: -

- What methods exist and are used to diagnose individuals with positive screens?
- Can diagnostic testing discern those children with Hb H disease who are most likely to benefit from early intervention and treatment?
- Are diagnostic testing methods widely available? If diagnostic testing for Hb H disease is not widely available, how feasible is it for other centers to add it to their diagnostic testing repertoire?

Treatment:

- Does early identification improve the health of identified children?

- What treatment methods improve the health of children diagnosed through newborn screening? How do these treatment methods change the natural history of Hb H disease?
- What is the relationship between treatment outcomes and the timing of treatment intervention?
- What harms are associated with delay in diagnosis? How does inappropriate iron supplementation of the anemia associated with Hb H disease affect health outcomes?
- What are the potential harms or risks associated with treatment? -

Economics: -

- What are the costs associated with the screening test? What is the cost-effectiveness of newborn screening for Hb H disease? -
- What are the costs associated with diagnosis, and the failure to diagnose in the presymptomatic period during childhood?
- What is the availability of treatment and what are the costs associated with treatment? -

Other: -

- What critical evidence is lacking that may inform screening recommendations for Hb H disease?

VII. Literature review methods

We searched MEDLINE for all relevant studies published over the 20-year period from 1989 to March 2010 using the National Library of Medicine Medical Subject Heading (MeSH) "alpha-Thalassemia" and the keywords "Hemoglobin H Disease" and "alpha thalassemia." In order to capture articles that have not yet been assigned MeSH terms, we also searched the following keywords within the OVID In-Process and Other Non-Indexed Citations database: "Alpha-Thalassemia," "Hemoglobin H Disease," and "alpha thalassemia." The searches were limited to human studies and English language publications. This search strategy yielded 1485 articles, and captured all published references included on the nomination form submitted to the ACHDNC.

Three investigators (AAK, ARK, and DRM) reviewed all abstracts to select articles for inclusion in the review. Articles were eliminated if they were: not human studies; did not focus on Hb H disease; did not address at least one key question; reviews or editorials that did not include new data; case reports or case-series of four or fewer subjects. 165 abstracts were considered for possible inclusion but upon further review were excluded because the sole focus of the reports were either: a) gene distribution in or outside U.S. with no report of outcomes; b) red blood cell morphology and/or circulating markers of inflammation with no patient outcome data; c) the prenatal period; or the reports lacked a distinct outcome. After abstract review, 90 articles were reviewed in full. All full length articles were subjected to the exclusion criteria above and, in addition, were excluded if the article focused on adult subjects. After this process, 21 articles met all inclusion criteria and were included in this evidence review.

The three investigators each independently abstracted one-third of the articles. All investigators reviewed a subset (16%) to validate the process. Each article was evaluated, using standardized tools, for the quality of the study design (NHS Center for Reviews and Dissemination March 2001, Accessed: October 17, 2008) and the quality of the evidence, as it relates to the category of evidence (Pandor et al. 2004, Pollitt et al. 1997). A given article received only one rating per reader for study design, but may have received multiple quality evaluations for the type of evidence. For example, a study that discusses prevalence and natural history would be evaluated for the quality of the evidence in each of those domains. There were no significant differences in the data extracted by the reviewers.

Table 3 – Study design for abstracted articles

Study Design	Number of Articles
Experimental intervention	0
Cohort study	0
Case-control study	1
Case series	14
Sample size ≤ 10	0
Sample size 11 to 50	3
Sample size 51 to 100	2
Sample size ≥ 101	9
Economic Evaluation	0
Cross-Sectional study	6
Total studies	21

To assure completeness and clarity of the report, a draft of the report was sent to an independent external review panel (see Appendix A for sample conflict of interest form). The report was revised based on their suggestions.

VIII. Methods for interviews with experts

The ERG and the ACHDNC recognize that there may be important but unpublished data regarding Hb H disease. We identified experts, including researchers and Hb H disease newborn screening advocates, to help us identify this information. These individuals were identified as authors of key papers included in the literature review, through discussions with content experts, and through recommendations from the ERG. These individuals are listed in Table 4.

Experts were sent a letter via e-mail (Appendix B for researchers, Appendix C for newborn screening laboratories and Appendix D for advocates) explaining the purpose of the review, a conflict of interest form (Appendix A) and an open-ended survey. Experts had two weeks to respond, and extensions were granted when requested. The project coordinator sent at least one reminder e-mail to those who did not reply. In

cases where clarifications were needed regarding the responses, individuals were either sent a follow up e-mail or contacted via telephone by the authors. When experts and advocates provided information regarding the key questions not otherwise available from the selected articles, we include their responses.

Table 4 – Key experts contacted and degree of participation

Name		Title	Replied	Completed written survey	Telephone interview
Eve	Alley	Thalassemia Outreach Coordinator, Children's Hospital & Research Center Oakland, Oakland, California	✓*		
Sylvia	Au, MS, CGC	State Genetics Coordinator, Hawaii Department of Health, Genetics Program, Honolulu, Hawaii	✓	✓	✓
Stanton	Berberich, Ph.D.	Newborn Screening Lab Director, University of Iowa, University Hygienic Laboratory, Iowa City, Iowa	o		
Charles	Brokopp, PhD	Laboratory Director, Wisconsin State Laboratory of Hygiene, Madison, Wisconsin	✓*		
Michele	Caggana, ScD	Research Scientist, Wadsworth Center, New York State Department of Public Health, Albany, New York	✓^		
Vivian	Chan, PhD	Chui Fook-Chuen Professor in Molecular Medicine, University of Honk Kong, Queen Mary Hospital, Hong Kong	o		
David	Chui, MD	Director, Hemoglobin Diagnostic Reference Laboratory, Boston Medical Center, Boston, Massachusetts	o		
Gina	Cioffi, Esq.	National Executive Director, Cooley's Anemia Foundation, New York, New York	o		
Thomas	Coates, MD	Director, Red Cell/Hemoglobinopathy Program, Children's Hospital Los Angeles, Los Angeles, California	✓	✓	✓
Alan	Cohen, MD	Physician-in-chief, Medical director, Thalassemia Program, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania	✓	✓	
Paul	DiLorenzo	President, Thalassemia Support Foundation, Santa Ana, California	✓^		
Roger	Eaton, PhD	Director, New England Regional Newborn Screening Program, University of Massachusetts Medical School, Jamaica Plain, Massachusetts	✓*		
Suthat	Fucharoen, MD	Professor, Thalassemia Research Center, Institute of Science and Technology Research and Development, Mahidol University, Nakornpathom, Thailand	✓^		

Michael	Glass, MS	Director, Office of Newborn Screening, Washington State Department of Health, Shoreline, Washington	✓	✓	
Althea	Grant, PhD	Epidemiology and Surveillance Team Leader, National Center on Birth Defects and Developmental Disabilities, Division of Blood Disorders, Centers for Disease Control and Prevention, Atlanta, Georgia	o		
Patrick	Hopkins	Laboratory Manager, Newborn Screening Laboratory, State of Missouri, Department of Health and Senior Services, Jefferson City, Missouri	✓	✓	
Carolyn	Hoppe, MD	Associate Hematologist; Medical director, Hemoglobinopathy Reference Laboratory to the California State Newborn Screening for Hemoglobinopathies Follow up Program, Children's Hospital & Research Center Oakland, California	✓	✓	✓
Ho-Wen	Hsu, MD	Assistant Professor of Pediatrics, New England Regional Newborn Screening Program, University of Massachusetts Medical School, Jamaica Plain, Massachusetts	✓	✓	
David	Jinks, PhD	Newborn Screening Laboratory, Illinois Department of Public Health, Chicago, Illinois	o		
Franz	Kuypers, PhD	Principal Investigator, Children's Hospital Oakland Research Institute, Oakland, California	o		
Fred	Lorey, PhD	Acting Director, Genetic Disease Screening Program, California Department of Public Health, Richmond, California	✓	✓	✓
Bertram	Lubin, MD	President of Children's Hospital Medical Research, Children's Hospital Oakland Research Institute, Oakland, California	✓*		
Jennifer	Marcy, MS, CGC	Hemoglobinopathy Follow up, Iowa Department of Public Health, Des Moines, Iowa	✓	✓	
Robert	Mignacca, MD	Medical Director of Hematology, Acting Medical Director of Oncology, Children's Hospital Central California, Madera, California	o		
Julie	Miller	Program Manager, Newborn Screening in Nebraska, Nebraska Department of Health and Human Services, Lincoln, Nebraska	✓*		

Ellis	Neufeld, MD, PhD	Associate Chief, Division of Hematology/Oncology, Children's Hospital Boston, Boston, Massachusetts	✓	✓	✓
Nancy	Olivieri, BSc, FRCPC, MD	Senior Scientist, Hemoglobinopathy Research Program, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada	o		
Sarah	Scollon, MS, CGC	Genetic counselor, Hawaii Department of Health, Genetics Program, Honolulu, Hawaii	✓		✓
Eileen	Scott	Patient Services Manager, Cooley's Anemia Foundation, New York, New York	o		
Sylvia	Singer, MD	Pediatric hematologist, Children's Hospital & Research Center Oakland, Oakland, California	✓#		
Michael	Skeels, PhD, MPH	Laboratory Director, Northwest Regional Newborn Screening Program, Oregon State Public Health Laboratory, Hillsboro, Oregon	o		
Elliott	Vichinsky, MD	Director of Hematology/Oncology, Children's Hospital & Research Center Oakland, Oakland, California	✓	✓	✓
David	Weatherall, MD, FRCP, FRS	(Retired) Regius Professor of Medicine and Director of the Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom	✓	✓	
Kelley	Woodruff, MD	Pediatrician, Bamberg Health Clinic, Bamberg, Germany, Formerly Founder of the Thalaseemia Clinic, Honolulu, Hawai	✓	✓	

o No response

* Deferred to other experts

^ Unable to contribute due to time constraints -
# Contributed to Dr. Hoppe's response -

IX. Results: evidence findings to address the key questions

This section presents the evidence from the included articles organized by key question. Each subsection includes a summary of findings from the literature review, assessment of the quality of the evidence from each included article, and information from experts.

A. Natural history and diagnosis:

Table 5 – Quality assessment of abstracted literature pertaining to condition

Type of evidence	Number of articles
Total (two articles overlap with screening)	**20**
Incidence (cases per 100,000), average within the U.S.	**3**
Data obtained from whole-population screening or comprehensive national surveys of clinically detected cases.	2
As above,but more limited in geographical coverage or methodology.	1
Extrapolated from class I data for non-U.S. populations.	0
Estimated from number of cases clinically diagnosed in U.S.	0
Genotype-Phenotype correlation	**14**
Data from retrospective screening studies in U.S. or similar population.	0
Data from systematic studies other than whole population screening.	12
Estimated from the known clinical features of the condition as described for individual cases or short series.	2
Other natural history of disease	**3**

Adapted from Pandor et al. 2004, Pollitt et al. 1997

We sought to answer the following questions on the natural history of Hb H disease through a literature review and information provided by experts:

- What is the birth prevalence of deletional and nondeletional Hb H disease?
- What is the natural history, including the spectrum of severity, of deletional and nondeletional Hb H disease during the first five years of life?

Literature review:

The following sections describe the clinical manifestations and complications of Hb H disease within the abstracted literature. While this evidence provides a list of potential consequences of Hb H disease at later ages, it provides little information about onset in infancy and early childhood. Almost all abstracted literature reflects studies from clinically identified populations, and most lack denominators to indicate the overall prevalence of these symptoms or complications among all individuals with Hb H disease. Thus, the literature does not allow determination of the frequency or population prevalence of these complications.

Incidence and prevalence

Hb H disease is most commonly found in Southeast Asian, Middle Eastern, and Mediterranean populations. α-Thalassemias are the most common inherited disorders of hemoglobin synthesis in Southeast Asia (Thailand and Laos in particular) and southern China (Chen et al. 2000), however the Mediterranean area is also affected (Greece and Sardinia in particular) (Kanavakis et al. 2000, Origa et al. 2007, Galanello et al. 1992). Between 14% and 57% of patients with Hb H disease have nondeletional

Hb H disease, caused by a mutation such as Hb H with CS or another nondeletional mutation that affecting the α1 or α2 gene (Table 6). However, this varies by population.

Table 6 – Reported deletional and nondeletional genotypes among different populations

Region	Citation	Deletional Hb H disease	Nondeletional Hb H disease
Northern Thailand^	Charoenkwan et al. 2005	44/102 (43%)	58/102 (57%)
Hong Kong	Chen et al. 2000	87/114 (76%)	27/114 (24%)
Sardinia	Gallanello et al. 1992 (1 subject not counted with two non-deletions)	130/154 (84%)	24/154 (16%)
Greece	Kanavakis et al. 2000 (14 subjects not counted with two non-deletions)	41/61 (67%)	20/61 (33%)
Thailand	Laosombat et al. 2009	83/147 (56%)	64/147 (44%)
California, USA*	Lorey et al. 2001	69/89 (77.5%)	20/89 (22.5%)
Mediterranean area	Origa et al. 2007	216/251 (86%)	36/251 (14%)

*Population-based study, remaining studies are from clinically identified populations

^The authors attributed this skewed proportion discrepancy to selection bias, as patients with more severe symptoms seek medical treatment more often

In the United States, California's newborn screening program found 69 deletional cases and 20 nondeletional cases among the 1.32 million newborns screened between January 1998 and June 2000. Of the 20 nondeletional cases, nine had the CS mutation (Lorey et al. 2001b). An updated report from the screening program from January 1998 to June 2006, reported 25 newborns with Hb H disease with CS (Michlitsch et al. 2009). Therefore, from January 1998 to June 2006, the reported birth prevalence of deletional Hb H disease was 9 per 100,000 (Michlitsch et al. 2009) and 0.6 per 100,000 for Hb H disease with CS (Michlitsch et al. 2009).

Spectrum of severity

Phenotypic and genotypic variations and Hb H disease with CS

Hb H disease has a wide range of phenotypic variability. Affected individuals range from asymptomatic to having various clinical complications. Most cases of nondeletional Hb H disease are due to the CS mutation (George et al. 1989). Compared to deletional Hb H disease, nondeletional Hb H disease has been reported to have more severe clinical and hematological features, including younger age at diagnosis (mean of 10.8 years vs. 22.6 years, $p < 0.001$ (Chen et al. 2000), and 3.1 +/- 2.9 years vs. 5.1 +/- 3.9 years, $p = 0.011$ (Charoenkwan et al. 2005)), a higher proportion of patients requiring transfusion, larger liver and spleen sizes, a trend towards higher requirement for splenectomy, growth deficiency in higher percentages, and a larger proportion were symptomatic at presentation (40% nondeletional cases vs. 23% of deletional cases, $p = 0.07$ (Chen et al. 2000)) (Au et al. 2005, Charoenkwan et al. 2005, Chen et al. 2000, Galanello et al. 1992, George et al. 1989, Laosombat et al. 2009). While the nondeletional genotypes

generally have more severe phenotypes than deletional genotypes, there is mention of some milder, but rare, nondeletional cases (Haider, Adekile 2005).

Hb H disease hydrops fetalis syndrome

Several case reports document the most severe form of Hb H disease, hydrops fetalis syndrome, first described in 1985 (Lorey et al. 2001a, Chan et al. 1985). Few data are available about Hb H disease hydrops fetalis syndrome (Lorey et al. 2001b). From January 1998 through June 2000, two such cases of Hb H hydrops fetalis syndrome were found during newborn screening in California (Lorey et al. 2001b). One of the two newborns died, while the other required repeated transfusions in the first few months after birth (Lorey et al. 2001b).

Growth and development in children

Children with Hb H disease who experience more severe anemia also experience bone changes and growth retardation (Wongchanchailert, Laosombat & Maipang 1992). Case series from Hong Kong and Thailand reported growth retardation and mild dysmorphic facial features in children and infants (Chen et al. 2000, Wongchanchailert, Laosombat & Maipang 1992). One study of 21 children with Hb H disease found that growth retardation was not related to genotype (Chen et al. 2000).

Anemia and Blood Transfusions

Clinical presentation of Hb H disease during the newborn period and first year of life includes anemia, with fever or infection often the precipitating cause (Wongchanchailert, Laosombat & Maipang 1992). Overall, patients with nondeletional Hb H disease were more likely to have transfusions and at younger ages (Chen et al. 2000, Charoenkwan et al. 2005, Origa et al. 2007, Laosombat et al. 2009). One study of 147 individuals with Hb H disease between newborn and 20 years of age found that 39.1% nondeletional vs. 6% deletional ($p < 0.0005$) patients received blood transfusions between 0-4 years of age (Laosombat et al. 2009). Two case series reported very few patients requiring transfusions in infancy, and very few requiring regular transfusions (Chen et al. 2000, Wongchanchailert, Laosombat & Maipang 1992).

Pulmonary and Cardiac function

When studying a mild form of Hb H disease in Thailand, 48% of children had an abnormal pulmonary function test (6-18 years of age) (Isarangkura et al. 1993). In a Sardinian population (64 children), mild heart dilatation was noted in 6.6% of the pediatric Hb H disease patients (Origa et al. 2007).

Splenomegaly and Splenectomy

Nondeletional genotypes from studies in Greece, Thailand and China were associated with a larger spleen sizes and a higher requirement for regular blood transfusions and splenectomy than deletional genotypes (Charoenkwan et al. 2005, Laosombat et al. 2009, Kanavakis et al. 2000). Of 102 patients with Hb H disease between the ages of 1 month and 19.8 years, approximately half were nondeletional genotypes, with the need for splenectomy reported as 0% for the deletional genotypes and 7.8% for the nondeletional genotypes (Charoenkwan et al. 2005). Two case series from Thailand

and Hong Kong reported no need for further transfusions post-splenectomy (Chen et al. 2000, Hathirat et al. 1989).

Hepatomegaly and Jaundice

Clinical presentation of Hb H disease during the newborn period included jaundice (Wongchanchailert, Laosombat & Maipang 1992). Jaundice was present in 20% (deletional cases) and 60% (nondeletional cases) of 66 children with Hb H disease from a Sardinian group (Galanello et al. 1992) and 56% of individuals in a case series of Chinese patients (Au et al. 2005.) Hepatomegaly was found in 60% (deletional) and approximately 100% (nondeletional) of the children with Hb H disease in Sardinia (Galanello et al. 1992). In general, children with Hb H disease with CS more often had jaundice and hepatosplenomegaly (Wongchanchailert, Laosombat & Maipang 1992).

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Iron Overload

The major complications and disability in patients with Hb H disease results from iron overload by adulthood (Chen et al. 2000, Chan et al. 2003). Among those with Hb H disease, serum ferritin levels increase with age. In small series (Chen et al. 2000), most adults had elevated serum ferritin levels. These reports state that ferritin levels are not significantly related to genotype, transfusion history, or history of iron supplementation. Because most subjects had elevated serum ferritin levels and the sample sizes are small, it is difficult to assign attributable risk to these potentially predisposing factors.

Cholelithiasis

The effect of genetic factors on the incidence and severity of cholelithiasis is largely unknown. The youngest age with gallstone presentation reported was in adulthood at 25 years of age in a group of 90 individuals with Hb H disease, age 4 to 83 years. (Au et al. 2005). The risk of gallstones was related to higher bilirubin levels but not α-globin genotype, sex, ferritin, or hemoglobin levels (Au et al. 2005).

Expert Information:

The experts corroborated the literature findings.

B. Screening test:

Table 7 – Quality assessment of abstracted literature pertaining to screening test

Type of evidence	Number of articles
Total (two articles overlap with condition/natural history)	**3**
Overall sensitivity and specificity of screening	**1**
Data obtained from screening programs in U.S. population or similar.	1
Data from systematic studies other than from whole population screening.	0
Estimated from the known biochemistry of the condition.	0
False positive rate	**0**
Data obtained from screening programs in U.S. population or similar.	0
Data from systematic studies other than from whole population screening.	0
Estimated from the known biochemistry of the condition.	0
Repeat specimen rate	**0**
Data obtained from screening programs in U.S. population or similar.	0
Data from systematic studies other than whole population screening.	0
Estimated from the known biochemistry of the condition.	0
Second-tier testing	**2**
Data obtained from screening programs in US population or similar.	1
Data from systematic studies other than whole population screening.	0
Estimated from the known biochemistry of the condition.	1
Other screening test characteristics	**1**

Adapted from Pandor et al. 2004, Pollitt et al. 1997

We sought to answer the following questions on the screening test for Hb H disease through a literature review and information provided by experts:

- What methods exist and are used by newborn screening programs to screen newborns for Hb H disease? How accurate are those methods and what are the advantages or disadvantages of each method? Do they distinguish between Hb H disease and other types of α-thalassemia (such as carrier states)? What are their sensitivity, specificity and analytic validity?
- Can current screening tests effectively and efficiently identify cases of Hb H disease that may benefit from early identification?
- What is the range of clinical conditions identified in population-based screening?
- What are the potential harms or risks associated with screening?

Literature review:

In 1996, California State expanded its hemoglobinopathy newborn screening protocol to include a screening trial for Hb H disease (Lorey et al. 2001b). The screening protocol is based on the detection of Hb Bart's levels, elevated in newborns with α-globin chain deficiency. Blood is collected from newborns between 12-48 hours after birth and

stored on dried blood spot cards. The dried blood spots are analyzed within 1-2 days of blood collection. The California newborn screening lab uses automated high-performance liquid chromatography (HPLC) to measure Hb Bart's (Lorey et al. 2001b). The laboratory selected an initial Hb Bart's cutoff of 14%. During the early trial period, the lowest Hb Bart's level detected in a newborn with confirmed Hb H disease was 27%. In August 1998, the Hb Bart's cutoff level was increased from 14% to 25% (Lorey et al. 2001b). In October 1999, California State mandated Hb H disease newborn screening (Lorey et al. 2001b). The mandated screening program included confirmatory diagnostic testing (hematological studies, α-globin genotyping) for all newborns with 25% or more Hb Bart's (Lorey et al. 2001b).

Of the 1.32 million newborns screened in California between January 1998 and June 2000, 101 were found to have elevated Hb Bart's (that is, levels of 14% or more until August 1998 and 25% or more after this time) (Lorey et al. 2001b). α-Globin genotypes were obtained for all 101 newborns. Of the 101 newborns, genotyping confirmed 89 cases of Hb H disease. Thus, Hb H disease newborn screening program found the approximate birth prevalence in California to be 1 in 15,000 (Lorey et al. 2001b). Hb Bart's levels among deletional cases of Hb H disease ranged from 25-49% with a mean of 35%. Hb Bart's levels among nondeletional cases of Hb H disease with CS ranged from 35-52% with a mean of 41%. Of the remaining 12 newborns with elevated Hb Bart's, one had an Hb Bart's hydrops fetalis genotype (--/--), nine had an α-thalassemia trait genotype (--/αα), one had an α-thalassemia silent carrier genotype (-α/αα) and one had a normal genotype (αα/αα). Because most newborns with Hb Bart's levels below the cutoff value did not have confirmatory testing, an undetected case of Hb H disease in this range could not be ruled out (Lorey et al. 2001b).

In a 2009 updated report on the California State hemoglobinopathy newborn screening program, Michlitsch et al. state that of the 530,000 newborns screened annually in California from January 1998 to June 2006, 406 were confirmed to have deletional Hb H disease (9.0/100,000) and 25 were confirmed to have Hb H disease with CS (0.6/100,000) (Michlitsch et al. 2009).

Expert Information:

Dr. Lorey, acting director of the California State newborn screening program, reported on the Hb H disease screening program's progress since the trial period began in 1996. Dr. Lorey reported most cases are deletional Hb H disease, with $--^{SEA}$, $--^{FIL}$, $-\alpha^{3.7}$, $-\alpha^{4.2}$, accounting for the majority of the cases identified. From 1996-2009, 528 newborns were diagnosed with Hb H disease through screening, 59 with Hb H disease with CS and 4 with Hb H disease with other variant point mutations. Between 2000 and November 2009, the positive predictive value for Hb H disease was 91.59% with this screening test. The screen positive rate between 2003 and 2009 was 10.2/100,000 screened.

Dr. Hoppe of Children's Hospital & Research Center Oakland (CHRCO) explained the California state referral process for newborns who screen positive for Hb H disease.

California has seven Newborn Screening Area Service Centers which are responsible for reporting to primary care physicians and encouraging follow up of screening referrals.

Dr. Hoppe provided information on the patients with Hb H disease identified through newborn screening followed at CHRCO. The center currently follows 46 patients with Hb H disorders who were diagnosed through newborn screening: 38 with deletional Hb H disease, 7 with Hb H disease with CS and 1 with another nondeletional Hb H disease. Only one patient in the deletional Hb H disease group was transfused (just before the second birthday). In the Hb H with CS group, 5 patients were transfused, with the ages at first transfusions being 1 year 8 months, 5 years, 5 years 10 months, 5 years 11 months and just before the sixth birthday. Dr. Hoppe did not provide information regarding the numbers actually referred to CHRCO from the newborn screening program. An additional 38 patients (22 with Hb H disease, 16 with Hb H disease with CS) who were identified outside of newborn screening are also followed in the center.

Sylvia Au, the State Genetics Coordinator for the Hawaii Department of Health, described the newborn screening protocol for Hb H disease that began in Hawaii in July 1997. Newborn screening samples are processed by the Oregon State Public Health Laboratory using isoelectric focusing (IEF) followed by HPLC. Newborns with a ≥25% Hb Bart's are considered screen positive. The total number of children screened from July 1997 to October 2009 is reported in Table 8. No mutations could be found in one of these newborns, thus 48 positives were confirmed to have Hb H disease. Ms. Au had no information on the 162 children who were not referred by their primary care physicians to the hemoglobinopathy clinic.

Table 8 – Hawaii Department of Health Newborn Screening July 1997 to October 2009*

Activity	**Number**
Newborns screened in Hawaii July 1997 October - 2009	222,982
Screen positive for Hb H disease (>25% Hb Bart's)	214
Referral to Hemoglobinopathy clinic	52
Second-tier α-globin genotyping	49
Confirmed Hb H disease	48

*Data provided by Sylvia Au

Newborn screening experts from Iowa, Missouri and Washington also reported on their programs' methods for screening and reporting Hb Bart's (Tables 9 - 12). The Iowa referral process involves referring newborns with elevated Hb Bart's to a comprehensive hemoglobinopathy program, of which there are two in Iowa, to establish care. In Missouri, the screening program sends a sample to CHORI for confirmatory α-globin testing and refers the newborn to a contracted Hemoglobinopathy center for diagnosis and counseling. The Washington State Department of Health sends information to the newborn's primary care physician regarding the screening results, probable implications, and recommendations for diagnostic follow up. The physician is asked to update the newborn screening program on the child's heath in the newborn period and

at one year of age. There was no information on the outcomes of the newborns who have screened positive from any of these state programs.

Table 9 – State Methods of Hb Bart's screening and reporting

State Lab	Starting Year	1st tier	1st tier cutoff	2nd tier	Reporting and confirmatory testing
Iowa	Iowa - 1988 North Dakota - 2003 South Dakota - 2007	IEF	Visually abnormal	HPLC Variant	**10% ≤ Hb Bart's < 25%** - reported **Hb Bart's ≥ 25%** - reported and follow up team is alerted that this infant may have Hb H disease
Missouri	1989	IEF	Two distinct Hb Bart's bands easily visible	HPLC	**3% ≤ Hb Bart's < 13%** - Within Normal Limits + Low Level Bart's Comment **13% ≤ Hb Bart's < 20%** - Abnormal: Slightly Elevated Hb Bart's, DNA DBS testing at CHORI **Hb Bart's ≥ 20%** - Presumptive positive for Hb H disease, referred to Hemoglobinopathy Center and DBS DNA testing at CHORI
Washington	1991	IEF	Hb Bart's bands	HPLC	**6.5% ≤ Hb Bart's ≤ 18%** - reported as possible α-thalassemia trait **Hb Bart's > 18%** - reported as possible Hb H Disease, physician notified and sent information on follow up

Table 10 – Iowa Newborn Screening, 2003 to Present*

Activity	Number
Newborns screened to date	882,350
Confirmed Hb H disease 2007 – March 2010	5, all $--^{SEA}/-\alpha^{3.7}$ genotypes

*Data provided by Jennifer Marcy, includes newborns screened in Iowa, North Dakota and South Dakota

Table 11 – Missouri Newborn Screening, 1989 to Present*

Activity	Number
Newborns screened to date	1,650,000
Newborns with elevated Hb Bart's	21
Confirmed Hb H disease	2 genotypes available: $--^{SEA}/\alpha^{CS}\alpha$ $--^{SEA}/-\alpha^{3.7}$

*Data provided by Patrick Hopkins

Table 12 – Washington Newborn Screening, 1991 to Present* -

Activity	Number
Newborns screened to date	1,243,000
Newborns with elevated Hb Bart's	145

*Data provided by Michael Glass

C. Diagnostic test:

We sought to answer the following question about a diagnostic test for Hb H disease through a literature review and information provided by experts:

- What methods exist and are used to diagnose individuals with positive screens?
- Can diagnostic testing discern those children with Hb H disease who are most likely to benefit from early intervention and treatment?
- Are diagnostic testing methods widely available? If diagnostic testing for Hb H disease is not widely available, how feasible is it for other centers to add it to their diagnostic testing repertoire?

Literature review:

Multiple strategies for diagnosing Hb H disease by α-globin genotyping have been described for both peripheral blood and dried blood spot samples (Waye et al. 1993, Chang et al. 1994a, Eng et al. 2000, Fischel-Ghodsian et al. 1988, Bhardwaj et al. 2002, Chan et al. 2007, Liu et al. 2008, Chen et al. 2009, Chong et al. 2000). Methods include Southern blot analysis and various polymerase chain reaction (PCR)-based assays such as amplification refractory mutation system (ARMS) and multiple ligation-dependent probe amplification (MLPA), in addition to direct nucleotide sequencing.

The California State newborn screening program follows up with newborns with elevated Hb Bart's levels for confirmatory genotyping (Lorey et al. 2001b, Michlitsch et al. 2009). Second-tier confirmatory testing includes analyzing newborn peripheral blood samples. Currently, the California newborn screening program uses a multiplexed gap-PCR assay to detect common deletional and nondeletional α-thalassemia mutations (Michlitsch et al. 2009).

Expert Information:

Dr. Hoppe reported that the gap-PCR assay used by the California program's reference lab detects seven common α-globin gene deletions and the CS point mutation. This panel identifies the majority of cases of Hb H disease in the California newborn population. If a deletion or mutation is not identified by this panel, DNA sequencing is performed to identify other α-globin gene point mutations, where the sensitivity of DNA sequencing is noted as 99%. Additionally, multiplex ligation-dependent probe amplification (MLPA) is used to identify rare or unknown deletions.

The Hawaii State newborn screening program, reported by Ms. Au, responds to a screen positive by providing the newborn's primary care physician with educational

materials on Hb H disease and referral information for the Hawai'i Community Genetics (HCG) Hemoglobinopathy Clinic for diagnostic testing. It is the physician's responsibility to manage the newborn's care and make the appropriate referrals. Families referred to the HCG Hemoglobinopathy Clinic by their physician are offered genetic counseling and α-globin genetic testing. Two years ago, the state of Hawaii agreed to cover the additional costs of the newborn's parents' genetic testing. Ms. Au said that this has led to an increased number of referrals because families are having a much better experience within the program now that they are not responsible for these costs.

D. Treatment:

Table 13 – Quality assessment of abstracted literature pertaining to treatment

Type of evidence	Number of articles
Total	**0**
Effectiveness of treatment	**0**
I. Well-designed RCTs.	0
II-1. Well-designed controlled trials with pseudo randomization or no randomization.	0
II-2. Well-designed cohort studies:	0
A. prospective with concurrent controls	0
B. prospective with historical control	0
C. retrospective with concurrent controls.	0
II-3. Well-designed case-control (retrospective) studies.	0
III. Large differences from comparisons between times and/or places with and without intervention	0
IV. Opinions of respected authorities based on clinical experience, descriptive studies and reports of expert committees.	0
Other treatment characteristics	0

Adapted from Pandor et al. 2004, Pollitt et al. 1997

We sought to answer the following questions on the treatment of Hb H disease through a literature review and information provided by experts:

- Does early identification improve the health of identified children?
- What treatment methods improve the health of children diagnosed through newborn screening? How do these treatment methods change the natural history of Hb H disease?
- What is the relationship between treatment outcomes and the timing of treatment intervention?
- What harms are associated with delay in diagnosis? How does inappropriate iron supplementation of the anemia associated with Hb H disease affect health outcomes?
- What are the potential harms or risks associated with treatment?

Literature review:
No published literature on treatment trials for Hb H disease in the newborn, infant or early childhood period (under 5 years of age) that included information on clinical outcomes was identified.

Expert Information:

Clinical Monitoring
Experts agreed that routine monitoring for Hb H disease includes blood tests for complete blood count (CBC), reticulocyte values, measuring iron stores (dependent on age and transfusion history) and measuring growth parameters. The experts also reported starting their patients on folic acid supplementation.

Education
Families are counseled on complications of infection and avoidance of oxidative or iron-rich medications and foods.

Standards of Care
Dr. Hoppe and Dr. Vichinsky referred to the Standards of Care Guidelines for Thalassemia, published by their team at Children's Hospital and Research Center, Oakland in 2009. This document contains consensus recommendations for the care of Hb H disease.

E. Economic evaluation

Table 14 – Quality assessment of abstracted literature pertaining to economic evidence

Type of evidence	Number of articles
Economic	**0**
I. Evaluation of important alternative interventions comparing all clinically relevant outcomes against appropriate cost measurement and including a clinically sensible sensitivity analysis.	0
II. Evaluation of important alternative interventions comparing a limited number of outcomes against appropriate cost measurement, but including a clinically sensible sensitivity analysis.	0
III. Evaluation of important alternative interventions comparing all clinically relevant outcomes against inappropriate cost measurement, but including a clinically sensible sensitivity analysis.	0
IV. Evaluation without a clinically sensible sensitivity analysis	0
V. Expert opinion with no explicit critical appraisal, based on economic theory	0

Adapted from NHS Centre for Reviews and Dissemination Report 4, March 2001

We sought to answer the following questions on the economic evaluation of newborn screening for Hb H disease through a literature review and information provided by experts:

- What are the costs associated with the screening test? What is the cost-effectiveness of newborn screening for Hb H disease? -
- What are the costs associated with diagnosis, and the failure to diagnose in the presymptomatic period during childhood?
- What is the availability of treatment and what are the costs associated with - treatment? -

Literature review:
No economic analyses of Hb H disease for newborn screening were identified.

Expert Information:
No economic evaluations of Hb H disease for newborn screening were available - through key experts. -

X. Key findings and summary

Hb H disease is a well-studied condition among clinically identified populations. However, the review identified little evidence describing the natural history of Hb H disease during the newborn period and early childhood. The literature suggests that individuals with nondeletional Hb H disease, such as Hb H disease with CS, have a generally more severe presentation than those with the deletional type, as well as more severe clinical and hematological features including younger age at diagnosis, a higher proportion of patients requiring transfusion, larger liver and spleen sizes, a trend towards higher requirement for splenectomy and a larger proportion of patients symptomatic at presentation. Regarding children with Hb H disease, those with Hb H disease with CS more often had jaundice, hepatosplenomegaly, and growth retardation and required blood transfusions. While there is some association of genotypes with severity of the condition among different types of Hb H disease, the strength of the association does not support strong genotype-phenotype correlations. Although several reports describe complications of Hb H disease, they do not provide data on the rates of these complications among all individuals with Hb H disease.

The Hb H disease experts corroborated the findings in the literature review. Specifically, they described the natural history of Hb H disease in the first 5 years of life as presenting with anemia and microcytosis exacerbated by viral illnesses and other infections, and splenomegaly.

The California State newborn screening experience suggests that screening for Hb H disease with HPLC for elevated Hb Bart's is a feasible screening method. Unpublished data from Hawaii suggests that screening with isoelectric focusing is also feasible. Several methods for diagnosis of Hb H disease by confirmatory genotyping have been described. Experts associated with the California, Hawaii, Iowa, Missouri and Washington newborn screening programs provided descriptions of the referral process and follow up for infants who screen positive for Hb H disease. However, no published data describe the clinical follow up or outcomes of infants who have been diagnosed through their newborn screening programs.

We found no published evidence directly addressing benefits of early detection. Some experts emphasized the importance of the education, genetic counseling and surveillance provided to patients and families identified through screening. Some have suggested that the sickle cell disease newborn screening experience may help inform the value of early education for Hb H newborn disease screening. In a brief literature review, no evidence was identified specifically regarding the effect of parental education on the outcomes of newborns with sickle cell disease.

Consensus standards of care for Hb H disease have been established by physicians at the Children's Hospital and Research Center, Oakland. However, no published data describe the methods, effectiveness, costs or availability of presymptomatic treatment for Hb H disease.

The following key questions remain:

- What proportion of children with Hb H disease would benefit from condition-specific treatment?
- Does early identification improve the health of identified children?
- What is the relationship between treatment outcomes and the timing of treatment with regard to health outcomes and economic consequences?
- What harms are associated with delay in diagnosis?
- What is the cost-effectiveness of newborn screening for Hb H disease?

Information on long term follow up of children identified through Hb H disease newborn screening in comparison to those diagnosed later in life is required to fully address these questions. The Registry and Surveillance System in Hemoglobinopathies (RuSH), a new pilot surveillance program through the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health, will gather data on individuals with hemoglobinopathies that may provide this needed follow up data.

XI. References

Adekile, A.D., Gu, L.H., Baysal, E., Haider, M.Z., al-Fuzae, L., Aboobacker, K.C., al-Rashied, A. & Huisman, T.H. 1994, "Molecular characterization of alpha-thalassemia determinants, beta-thalassemia alleles, and beta S haplotypes among Kuwaiti Arabs.", Acta Haematologica, vol. 92, no. 4, pp. 176-181.

Al-Allawi, N.A., Badi, A.I., Imanian, H., Nikzat, N., Jubrael, J.M. & Najmabadi, H. 2009, "Molecular characterization of alpha-thalassemia in the Dohuk region of Iraq.", Hemoglobin, vol. 33, no. 1, pp. 37-44.

al-Salem, A.H., al-Dabbous, I. & Bhamidibati, P. 1998, "The role of partial splenectomy in children with thalassemia.", European Journal of Pediatric Surgery, vol. 8, no. 6, pp. 334-338.

Ankra-Badu, G.A., Al-Jama, A. & Al Kadim, Y. 2001, "Hemoglobin H disease in the Al-Qatif Region of Saudi Arabia.", Annals of Saudi Medicine, vol. 21, no. 5-6, pp. 308-311.

Antonelou, M., Papassideri, I.S., Karababa, F., Gyparaki, M., Loutradi, A. & Margaritis, L.H. 2002, "A novel case of haemoglobin H disease associated with clinical and morphological characteristics of congenital dyserythropoietic anaemia type I.", European journal of haematology, vol. 68, no. 4, pp. 247-252.

Au, W.Y., Cheung, W.C., Hu, W.H., Chan, G.C., Ha, S.Y., Khong, P.L., Ma, S.K. & Liang, R. 2005, - "Hyperbilirubinemia and cholelithiasis in Chinese patients with hemoglobin H disease.", Annals of - Hematology, vol. 84, no. 10, pp. 671-674. -

Au, W.Y., Lam, W.W., Chu, W.W., Tam, S., Wong, W.K., Lau, J., Yeung, Y.M., Liu, H.S. & Liang, R. 2009, "Organ-specific hemosiderosis and functional correlation in Chinese patients with thalassemia intermedia and hemoglobin H disease.", Annals of Hematology, vol. 88, no. 10, pp. 947-950.

Au, W.Y., Ma, E.S. & Kwong, Y.L. 2001, "Acute myeloid leukemia precipitated by dengue virus infection in a patient with hemoglobin H disease.", Haematologica, vol. 86, no. 8, pp. E17.

Ausavarungnirun, R., Winichagoon, P., Fucharoen, S., Epstein, N. & Simkins, R. 1998, "Detection of zeta-globin chains in the cord blood by ELISA (enzyme-linked immunosorbent assay): rapid screening for alpha-thalassemia 1 (Southeast Asian type).", American Journal of Hematology, vol. 57, no. 4, pp. 283-286.

Baysal, E. 2001, "Hemoglobinopathies in the United Arab Emirates.", Hemoglobin, vol. 25, no. 2, pp. 247-253.

Baysal, E., Kleanthous, M., Bozkurt, G., Kyrri, A., Kalogirou, E., Angastiniotis, M., Ioannou, P. & Huisman, T.H. 1995, "alpha-Thalassaemia in the population of Cyprus.", British journal of haematology, vol. 89, no. 3, pp. 496-499.

Bernini, L.F. & Harteveld, C.L. 1998, "Alpha-thalassaemia", Baillieres Clinical Haematology, vol. 11, no. 1, pp. 53-90.

Bhardwaj, U., Zhang, Y.H., Blackburn, W., McCabe, L.L. & McCabe, E.R. 2002, "Rapid confirmation of Southeast Asian and Filipino alpha-thalassemia genotypes from newborn screening specimens.", American Journal of Hematology, vol. 71, no. 1, pp. 56-58.

Bhattacharya, G., Sarkar, A.A., Banerjee, D., Chandra, S., Das, M. & Dasgupta, U.B. 2008, "Polymerase chain reaction-based search for two alpha-globin gene mutations in India.", Hemoglobin, vol. 32, no. 5, pp. 485-490.

Bianco, I., Cappabianca, M.P., Foglietta, E., Lerone, M., Deidda, G., Morlupi, L., Grisanti, P., Ponzini, D., Rinaldi, S. & Graziani, B. 1997, "Silent thalassemias: genotypes and phenotypes", Haematologica, vol. 82, no. 3, pp. 269-280.

Boonsa, S., Sanchaisuriya, K., Fucharoen, G., Wiangnon, S., Jetsrisuparb, A. & Fucharoen, S. 2004, "The diverse molecular basis and hematological features of Hb H and AEBart's diseases in Northeast Thailand.", Acta Haematologica, vol. 111, no. 3, pp. 149-154.

Bowie, L.J., Reddy, P.L. & Beck, K.R. 1997, "Alpha thalassemia and its impact on other clinical conditions", Clinics in laboratory medicine, vol. 17, no. 1, pp. 97-108.

Bowie, L.J., Reddy, P.L., Nagabhushan, M. & Sevigny, P. 1994, "Detection of alpha-thalassemias by multiplex polymerase chain reaction.", Clinical chemistry, vol. 40, no. 12, pp. 2260-2266.

Bunyaratvej, A., Fucharoen, S., Butthep, P., Sae-ung, N., Kamchonwongpaisan, S. & Khuhapinant, A. 1995, "Alterations and pathology of thalassemic red cells: comparison between alpha- and beta-thalassemia.", Southeast Asian Journal of Tropical Medicine & Public Health, vol. 26, no. Suppl 1, pp. 257-260.

Bunyaratvej, A., Fucharoen, S., Greenbaum, A. & Mohandas, N. 1994, "Hydration of red cells in alpha and beta thalassemias differs. A useful approach to distinguish between these red cell phenotypes.", American Journal of Clinical Pathology, vol. 102, no. 2, pp. 217-222.

Bunyaratvej, A., Fucharoen, S. & Tatsumi, N. 1992, "Biophysical changes of red cells with thalassemia-like abnormal hemoglobin.", Southeast Asian Journal of Tropical Medicine & Public Health, vol. 23, no. Suppl 2, pp. 86-90.

Butthep, P., Rummavas, S., Wisedpanichkij, R., Jindadamrongwech, S., Fucharoen, S. & Bunyaratvej, A. 2002, "Increased circulating activated endothelial cells, vascular endothelial growth factor, and tumor necrosis factor in thalassemia.", American Journal of Hematology, vol. 70, no. 2, pp. 100-106.

Cai, R., Liu, J., Wang, L., Liang, X., Xiao, B., Su, L., Zhou, Y. & Pan, L. 2004, "Study on molecular epidemiology of the alpha-thalassemias in Liuzhou City, Guangxi Autonomous Region, China.", Hemoglobin, vol. 28, no. 4, pp. 325-333.

Cao, A., Rosatelli, C., Pirastu, M. & Galanello, R. 1991, "Thalassemias in Sardinia: molecular pathology, phenotype-genotype correlation, and prevention.", American Journal of Pediatric Hematology/Oncology, vol. 13, no. 2, pp. 179-188.

Carnley, B.P., Prior, J.F., Gilbert, A., Lim, E., Devenish, R., Sing, H., Sarin, E., Guhadasan, R., Sullivan, S.G., Wise, C.A., Bittles, A.H., Chan, K., Wong, M.S., Chan, V. & Erber, W.N. 2006, "The prevalence and molecular basis of hemoglobinopathies in Cambodia.", Hemoglobin, vol. 30, no. 4, pp. 463-470.

Chan, A.Y., So, C.C., Ma, E.S. & Chan, L.C. 2007, "A laboratory strategy for genotyping haemoglobin H disease in the Chinese.", Journal of clinical pathology, vol. 60, no. 8, pp. 931-934.

Chan, A.Y., So, C.K. & Chan, L.C. 1996, "Comparison of the HbH inclusion test and a PCR test in routine screening for alpha thalassaemia in Hong Kong.", Journal of clinical pathology, vol. 49, no. 5, pp. 411-413.

Chan, J.C., Chim, C.S., Ooi, C.G., Cheung, B., Liang, R., Chan, T.K. & Chan, V. 2006, "Use of the oral chelator deferiprone in the treatment of iron overload in patients with Hb H disease.", British journal of haematology, vol. 133, no. 2, pp. 198-205.

Chan, K., Wong, M.S., Chan, T.K. & Chan, V. 2004, "A thalassaemia array for Southeast Asia.", British journal of haematology, vol. 124, no. 2, pp. 232-239.

Chan, L.C., So, J.C. & Chui, D.H. 1995, "Comparison of haemoglobin H inclusion bodies with embryonic zeta globin in screening for alpha thalassaemia.", Journal of clinical pathology, vol. 48, no. 9, pp. 861-864.

Chan, V., Chan, T.K., Liang, S.T., Ghosh, A., Kan, Y.W. & Todd, D. 1985, "Hydrops fetalis due to an unusual form of Hb H disease", Blood, vol. 66, no. 1, pp. 224-228.

Chan, V., Wong, M.S., Ooi, C., Chen, F.E., Chim, C.S., Liang, R.H., Todd, D. & Chan, T.K. 2003, "Can defects in transferrin receptor 2 and hereditary hemochromatosis genes account for iron overload in HbH disease?.", Blood Cells Molecules & Diseases, vol. 30, no. 1, pp. 107-111.

Chan, V., Yam, I., Chen, F.E. & Chan, T.K. 1999, "A reverse dot-blot method for rapid detection of non-deletion alpha thalassaemia.", British journal of haematology, vol. 104, no. 3, pp. 513-515.

Chang, J.G., Liu, T.C., Chiou, S.S., Chen, J.T., Chen, T.P. & Lin, C.P. 1994, "Rapid detection of -alpha 4.2 deletion of alpha-thalassemia-2 by polymerase chain reaction.", Annals of Hematology, vol. 69, no. 4, pp. 205-209.

Chang, J.G., Liu, T.C., Perng, L.I., Chiou, S.S., Chen, T.P., Chen, P.H. & Lin, C.P. 1994, "Rapid molecular characterization of Hb H disease in Chinese by polymerase chain reaction.", Annals of Hematology, vol. 68, no. 1, pp. 33-37.

Charoenkwan, P., Sirichotiyakul, S., Chanprapaph, P., Tongprasert, F., Taweephol, R., Sae-Tung, R. & Sanguansermsri, T. 2006, "Anemia and hydrops in a fetus with homozygous hemoglobin constant spring.", Journal of Pediatric Hematology/Oncology, vol. 28, no. 12, pp. 827-830.

Charoenkwan, P., Taweephon, R., Sae-Tung, R., Thanarattanakorn, P. & Sanguansermsri, T. 2005, "Molecular and clinical features of Hb H disease in northern Thailand.", Hemoglobin, vol. 29, no. 2, pp. 133-140.

Chen, F.E., Ooi, C., Ha, S.Y., Cheung, B.M., Todd, D., Liang, R., Chan, T.K. & Chan, V. 2000, "Genetic and clinical features of hemoglobin H disease in Chinese patients", New England Journal of Medicine, vol. 343, no. 8, pp. 544-550.

Chen, T.P., Lin, S.F., Chang, J.G., Tsao, C.J., Liu, T.C., Chiou, S.S. & Liu, H.W. 1993, "Molecular characterization of Hb H disease by polymerase chain reaction.", Acta Haematologica, vol. 90, no. 4, pp. 177-181.

Chen, T.P., Liu, T.C., Chang, C.S., Chang, J.G., Tsai, H.J. & Lin, S.F. 2002, "PCR-based analysis of alpha-thalassemia in Southern Taiwan.", International journal of hematology, vol. 75, no. 3, pp. 277-280.

Chen, Y.L., Shih, C.J., Ferrance, J., Chang, Y.S., Chang, J.G. & Wu, S.M. 2009, "Genotyping of alpha-thalassemia deletions using multiplex polymerase chain reactions and gold nanoparticle-filled capillary electrophoresis.", Journal of Chromatography.A, vol. 1216, no. 7, pp. 1206-1212.

Cheng, I.K., Lu, H.B., Wei, D.C., Cheng, S.W., Chan, C.Y. & Lee, F.C. 1993, "Influence of thalassemia on the response to recombinant human erythropoietin in dialysis patients.", American Journal of Nephrology, vol. 13, no. 2, pp. 142-148.

Cheng, M.L., Ho, H.Y., Tseng, H.C., Lee, C.H., Shih, L.Y. & Chiu, D.T. 2005, "Antioxidant deficit and enhanced susceptibility to oxidative damage in individuals with different forms of alpha-thalassaemia.", British journal of haematology, vol. 128, no. 1, pp. 119-127.

Chim, C.S., Chan, V. & Todd, D. 1998, "Hemosiderosis with diabetes mellitus in untransfused Hemoglobin H disease.", American Journal of Hematology, vol. 57, no. 2, pp. 160-163.

Chinprasertsuk, S., Wanachiwanawin, W. & Piankijagum, A. 1994, "Effect of pyrexia in the formation of intraerythrocytic inclusion bodies and vacuoles in haemolytic crisis of haemoglobin H disease.", European journal of haematology, vol. 52, no. 2, pp. 87-91.

Chong, S.S., Boehm, C.D., Higgs, D.R. & Cutting, G.R. 2000, "Single-tube multiplex-PCR screen for common deletional determinants of alpha-thalassemia.", Blood, vol. 95, no. 1, pp. 360-362.

Choubisa, S.L., Choubisa, D.K. & Khare, S. 2000, "Alpha-thalassaemia (Hb-Bart's) in Rajasthan (India).", Haematologia, vol. 30, no. 3, pp. 209-213.

Chow, M.P., Hsu, H.C., Yung, C.H., Chau, W.K., Peng, H.W., Tsay, S.H., Tse, E. & Lin, C.K. 1990, "Hemoglobin H disease complicated iron overload and HLA expression in Chinese.", Chung-Hua Min Kuo Wei Sheng Wu Chi Mien i Hsueh Tsa Chih - Chinese Journal of Microbiology & Immunology, vol. 23, no. 3, pp. 248-252.

Chui, D.H. 2005, "Alpha-thalassaemia and population health in Southeast Asia", Annals of Human Biology, vol. 32, no. 2, pp. 123-130.

Chui, D.H. 2005, "Alpha-thalassemia: Hb H disease and Hb Barts hydrops fetalis", Annals of the New York Academy of Sciences, vol. 1054, pp. 25-32.

Chui, D.H., Fucharoen, S. & Chan, V. 2003, "Hemoglobin H disease: not necessarily a benign disorder", Blood, vol. 101, no. 3, pp. 791-800.

Chui, D.H., Mentzer, W.C., Patterson, M., Iarocci, T.A., Embury, S.H., Perrine, S.P., Mibashan, R.S. & Higgs, D.R. 1989, "Human embryonic zeta-globin chains in fetal and newborn blood.", Blood, vol. 74, no. 4, pp. 1409-1414.

Chui, D.H. & Waye, J.S. 1998, "Hydrops fetalis caused by alpha-thalassemia: an emerging health care problem", Blood, vol. 91, no. 7, pp. 2213-2222.

Cohen, A.R., Galanello, R., Pennell, D.J., Cunningham, M.J. & Vichinsky, E. 2004, "Thalassemia", Hematology, , pp. 14-34.

Curuk, M.A. 2007, "Hb H (beta4) disease in Cukurova, Southern Turkey.", Hemoglobin, vol. 31, no. 2, pp. 265-271.

Curuk, M.A., Dimovski, A.J., Baysal, E., Gu, L.H., Kutlar, F., Molchanova, T.P., Webber, B.B., Altay, C., Gurgey, A. & Huisman, T.H. 1993, "Hb Adana or alpha 2(59)(E8)Gly-->Asp beta 2, a severely unstable alpha 1-globin variant, observed in combination with the -(alpha)20.5 Kb alpha-thal-1 deletion in two Turkish patients.", American Journal of Hematology, vol. 44, no. 4, pp. 270-275.

Desai, S., Colah, R., Gupte, S. & Mohanty, D. 1997, "Is cellulose acetate electrophoresis a suitable technique for detection of Hb Bart's at birth?.", Human heredity, vol. 47, no. 4, pp. 181-184.

Dore, F., Bonfigli, S., Pardini, S. & Longinotti, M. 1995, "Serum interleukin-8 levels in thalassemia intermedia.", Haematologica, vol. 80, no. 5, pp. 431-433.

Durmaz, A.A., Akin, H., Ekmekci, A.Y., Onay, H., Durmaz, B., Cogulu, O., Aydinok, Y. & Ozkinay, F. 2009, "A severe alpha thalassemia case compound heterozygous for Hb Adana in alpha1 gene and 20.5 kb double gene deletion.", Journal of Pediatric Hematology/Oncology, vol. 31, no. 8, pp. 592-594.

Efremov, G.D. 1992, "Hemoglobinopathies in Yugoslavia: an update.", Hemoglobin, vol. 16, no. 6, pp. 531-544.

El-Kalla, S. & Baysal, E. 1998, "alpha-thalassemia in the United Arab Emirates.", Acta Haematologica, vol. 100, no. 1, pp. 49-53.

Eng, B., Patterson, M., Borys, S., Chui, D.H. & Waye, J.S. 2000, "PCR-based diagnosis of the Filipino (--(FIL)) and Thai (--(THAI)) alpha-thalassemia-1 deletions", American Journal of Hematology, vol. 63, no. 1, pp. 54-56.

Eng, B., Patterson, M., Walker, L., Chui, D.H. & Waye, J.S. 2001, "Detection of severe nondeletional alpha-thalassemia mutations using a single-tube multiplex ARMS assay.", Genetic testing, vol. 5, no. 4, pp. 327-329.

Eng, B., Patterson, M., Walker, L., Hoppe, C., Azimi, M., Lee, H., Giordano, P.C. & Waye, J.S. 2006, "Three new alpha-thalassemia point mutations ascertained through newborn screening.", Hemoglobin, vol. 30, no. 2, pp. 149-153.

Eng, B., Walsh, R., Walker, L., Patterson, M. & Waye, J.S. 2005, "Characterization of a rare single alpha-globin gene deletion in a Chinese woman with Hb H disease.", Hemoglobin, vol. 29, no. 4, pp. 297-299.

Fei, Y.J., Liu, J.C., Jogessar, V.B., Westermeyer, K.R., Bridgemohan, R. & Huisman, T.H. 1992, "Combinations of three different forms of alpha-thalassemia in a large Indian family from Durban, South Africa: hematological observations.", Acta Haematologica, vol. 87, no. 1-2, pp. 11-15.

Fei, Y.J., Liu, J.C., Walker, E.L.,3rd & Huisman, T.H. 1992, "A new gene deletion involving the alpha 2-, alpha 1-, and theta 1-globin genes in a black family with Hb H disease.", American Journal of Hematology, vol. 39, no. 4, pp. 299-300.

Fei, Y.J., Oner, R., Bozkurt, G., Gu, L.H., Altay, C., Gurgey, A., Fattoum, S., Baysal, E. & Huisman, T.H. 1992, "Hb H disease caused by a homozygosity for the AATAAA-->AATAAG mutation in the polyadenylation site of the alpha 2-globin gene: hematological observations.", Acta Haematologica, vol. 88, no. 2-3, pp. 82-85.

Fichera, M., Spalletta, A., Fiorenza, F., Lombardo, T., Schiliro, G., Tamouza, R., Lapoumeroulie, C., Labie, D. & Ragusa, A. 1997, "Molecular basis of alpha-thalassemia in Sicily.", Human genetics, vol. 99, no. 3, pp. 381-386.

Fischel-Ghodsian, N., Vickers, M.A., Seip, M., Winichagoon, P. & Higgs, D.R. 1988, "Characterization of two deletions that remove the entire human zeta-alpha globin gene complex (- -THAI and - -FIL)", British journal of haematology, vol. 70, no. 2, pp. 233-238.

Flake, A.W. & Zanjani, E.D. 1998, "In utero transplantation for thalassemia", Annals of the New York Academy of Sciences, vol. 850, pp. 300-311.

Foglietta, E., Deidda, G., Graziani, B., Modiano, G. & Bianco, I. 1996, "Detection of alpha-globin gene disorders by a simple PCR methodology", Haematologica, vol. 81, no. 5, pp. 387-396.

Forget, B.G. 2001, "Molecular Genetics of the Human Globin Genes" in Disorders of Hemoglobin; Genetics, Pathophysiology, and Clinical Management, eds. M.H. Steinberg, B.G. Forget, D.R. Higgs & R.L. Nagel, Cambridge University Press, Cambridge, United Kingdom, pp. 117-130.

Fortina, P., Parrella, T., Sartore, M., Gottardi, E., Gabutti, V., Delgrosso, K., Mansfield, E., Rappaport, E., Schwartz, E. & Camaschella, C. 1994, "Interaction of rare illegitimate recombination event and a poly A addition site mutation resulting in a severe form of alpha thalassemia.", Blood, vol. 83, no. 11, pp. 3356-3362.

Fucharoen, G., Fucharoen, S., Wanhakit, C. & Srithong, W. 1995, "Molecular basis of alpha (0)-thalassemia in northeast of Thailand.", Southeast Asian Journal of Tropical Medicine & Public Health, vol. 26, no. Suppl 1, pp. 249-251.

Fucharoen, S., Ayukarn, K., Sanchaisuriya, K. & Fucharoen, G. 2001, "Atypical hemoglobin H disease in a Thai patient resulting from a combination of alpha-thalassemia 1 and hemoglobin Constant Spring with hemoglobin J Bangkok heterozygosity.", European journal of haematology, vol. 66, no. 5, pp. 312-316.

Fucharoen, S. & Viprakasit, V. 2009, "Hb H disease: clinical course and disease modifiers.", Hematology, , pp. 26-34.

Fucharoen, S., Winichagoon, P., Wisedpanichkij, R., Sae-Ngow, B., Sriphanich, R., Oncoung, W., Muangsapaya, W., Chowthaworn, J., Kanokpongsakdi, S., Bunyaratvej, A., Piankijagum, A. & Dewaele, C. 1998, "Prenatal and postnatal diagnoses of thalassemias and hemoglobinopathies by HPLC.", Clinical chemistry, vol. 44, no. 4, pp. 740-748.

Galanello, R., Aru, B., Dessi, C., Addis, M., Paglietti, E., Melis, M.A., Cocco, S., Massa, P., Giagu, N. & Barella, S. 1992, "HbH disease in Sardinia: molecular, hematological and clinical aspects.", Acta Haematologica, vol. 88, no. 1, pp. 1-6.

Gan, Y.Y., Lai, C.M., Lee, S.H. & Gan, L.H. 1996, "Production of monoclonal and polyclonal antibodies against various haemoglobins for the detection of thalassaemias", Annals of the Academy of Medicine, Singapore, vol. 25, no. 1, pp. 75-78.

Ganczakowski, M., Bowden, D.K., Maitland, K., Williams, T.N., O'Shaughnessy, D., Viji, J., Lucassen, A., Clegg, J.B. & Weatherall, D.J. 1995, "Thalassaemia in Vanuatu, south-west Pacific: frequency and haematological phenotypes of young children.", British journal of haematology, vol. 89, no. 3, pp. 485-495.

George, E., Ferguson, V., Yakas, J., Kronenberg, H. & Trent, R.J. 1989, "A molecular marker associated with mild hemoglobin H disease.", Pathology, vol. 21, no. 1, pp. 27-30.

George, E., Li, H.J., Fei, Y.J., Reese, A.L., Baysal, E., Cepreganova, B., Wilson, J.B., Gu, L.H., Nechtman, J.F. & Stoming, T.A. 1992, "Types of thalassemia among patients attending a large university clinic in Kuala Lumpur, Malaysia.", Hemoglobin, vol. 16, no. 1-2, pp. 51-66.

George, E., Wong, H.B., Jamaluddin, M. & Huisman, T.H. 1993, "Peripheral haemolysis, lipid peroxidation, iron status, and vitamin E in haemoglobin H syndromes in West Malaysia.", Singapore medical journal, vol. 34, no. 3, pp. 241-244.

Ghosh, K., Shaqalaih, A., Salman, A. & Hassanein, A.A. 1993, "Haemoglobinopathies in a large hospital in Kuwait.", Haematologia, vol. 25, no. 3, pp. 185-190.

Giordano, P.C., Harteveld, C.L., Bok, L.A., van Delft, P., Batelaan, D., Beemer, F.A. & Bernini, L.F. 1999, "A complex haemoglobinopathy diagnosis in a family with both beta zero- and alpha (zero/+)-thalassaemia homozygosity.", European Journal of Human Genetics, vol. 7, no. 2, pp. 163-168.

Giordano, P.C., Harteveld, C.L., Michiels, J.J., Terpstra, W., Batelaan, D., van Delft, P., Plug, R.J., van der Wielen, M.J., Losekoot, M. & Bernini, L.F. 1997, "Atypical HbH disease in a Surinamese patient resulting from a combination of the -SEA and -alpha 3.7 deletions with HbC heterozygosity.", British journal of haematology, vol. 96, no. 4, pp. 801-805.

Gonzalez-Redondo, J.M., Gilsanz, F. & Ricard, P. 1989, "Characterization of a new alpha-thalassemia-1 deletion in a Spanish family.", Hemoglobin, vol. 13, no. 2, pp. 103-116.

Hadavi, V., Jafroodi, M., Hafezi-Nejad, N., Moghadam, S.D., Eskandari, F., Tarashohi, S., Pourfahim, H., Oberkanins, C., Law, H.Y. & Najmabadi, H. 2009, "Alpha-thalassemia mutations in Gilan Province, North Iran.", Hemoglobin, vol. 33, no. 3, pp. 235-241.

Haider, M. & Adekile, A. 2005, "Alpha-2-globin gene polyadenylation (AATAAA-->AATAAG) mutation in hemoglobin H disease among Kuwaitis.", Medical Principles & Practice, vol. 14, no. Suppl 1, pp. 73-76.

Hall, G.W., Thein, S.L., Newland, A.C., Chisholm, M., Traeger-Synodinos, J., Kanavakis, E., Kattamis, C. & Higgs, D.R. 1993, "A base substitution (T-->C) in codon 29 of the alpha 2-globin gene causes alpha thalassaemia.", British journal of haematology, vol. 85, no. 3, pp. 546-552.

Harteveld, C.L., Beijer, C., van Delft, P., Zanardini, R., Bernini, L.F. & Giordano, P.C. 2000, "alpha-thalassaemia as a result of a novel splice donor site mutation of the alpha1-globin gene.", British journal of haematology, vol. 110, no. 3, pp. 694-698.

Harteveld, C.L., Losekoot, M., Haak, H., Heister, G.A., Giordano, P.C. & Bernini, L.F. 1994, "A novel polyadenylation signal mutation in the alpha 2-globin gene causing alpha thalassaemia", British journal of haematology, vol. 87, no. 1, pp. 139-143.

Harteveld, C.L., van Delft, P., Wijermans, P.W., Kappers-Klunne, M.C., Weegenaar, J., Losekoot, M. & Giordano, P.C. 2003, "A novel 7.9 kb deletion causing alpha+-thalassaemia in two independent families of Indian origin.", British journal of haematology, vol. 120, no. 2, pp. 364-366.

Harteveld, C.L., Yavarian, M., Zorai, A., Quakkelaar, E.D., van Delft, P. & Giordano, P.C. 2003, "Molecular spectrum of alpha-thalassemia in the Iranian population of Hormozgan: three novel point mutation defects.", American Journal of Hematology, vol. 74, no. 2, pp. 99-103.

Harteveld, K.L., Heister, A.J., Giordano, P.C., Losekoot, M. & Bernini, L.F. 1996, "Rapid detection of point mutations and polymorphisms of the alpha-globin genes by DGGE and SSCA", Human mutation, vol. 7, no. 2, pp. 114-122.

Harteveld, K.L., Losekoot, M., Heister, A.J., van der Wielen, M., Giordano, P.C. & Bernini, L.F. 1997, "alpha-Thalassemia in The Netherlands: a heterogeneous spectrum of both deletions and point mutations.", Human genetics, vol. 100, no. 3-4, pp. 465-471.

Harthoorn-Lasthuizen, E.J., Lindemans, J. & Langenhuijsen, M.M. 1998, "Combined use of erythrocyte zinc protoporphyrin and mean corpuscular volume in differentiation of thalassemia from iron deficiency anemia.", European journal of haematology, vol. 60, no. 4, pp. 245-251.

Hassall, O.W., Tillyer, M.L. & Old, J.M. 1998, "Prevalence and molecular basis of alpha thalassaemia in British South Asians.", Journal of medical screening, vol. 5, no. 1, pp. 31-33.

Hathirat, P., Isarangkura, P., Numhom, S., Opasathien, P. & Chuansumrit, A. 1989, "Results of the splenectomy in children with thalassemia.", Journal of the Medical Association of Thailand, vol. 72, no. Suppl 1, pp. 133-138.

Hellani, A., Fadel, E., El-Sadadi, S., El-Sweilam, H., El-Dawood, A. & Abu-Amero, K.K. 2009, "Molecular spectrum of alpha-thalassemia mutations in microcytic hypochromic anemia patients from Saudi Arabia.", Genetic Testing & Molecular Biomarkers, vol. 13, no. 2, pp. 219-221.

Higgs, D.R. 2001, "Molecular Mechanisms of α Thalassemia" in Disorders of Hemoglobin; Genetics, Pathophysiology, and Clinical Management, eds. M.H. Steinberg, B.G. Forget, D.R. Higgs & R.L. Nagel, Cambridge University Press, Cambridge, United Kingdom, pp. 405-430.

Higgs, D.R., Bowden, D. K. 2001, "Clinical and Laboratory Features of the a-Thalassemia Syndromes" in Disorders of Hemoglobin; Genetics, Pathophysiology, and Clinical Management, eds. M.H. Steinberg, B.G. Forget, D.R. Higgs & R.L. Nagel, Cambridge University Press, Cambridge, United Kingdom, pp. 431-469.

Higgs, D.R. & Weatherall, D.J. 2009, "The alpha thalassaemias", Cellular & Molecular Life Sciences, vol. 66, no. 7, pp. 1154-1162.

Hofgartner, W.T., West Keefe, S.F. & Tait, J.F. 1997, "Frequency of deletional alpha-thalassemia genotypes in a predominantly Asian-American population.", American Journal of Clinical Pathology, vol. 107, no. 5, pp. 576-581.

Hsu, H.C., Lin, C.K., Tsay, S.H., Tse, E., Ho, C.H., Chow, M.P., Yung, C.H. & Peng, H.W. 1990, "Iron overload in Chinese patients with hemoglobin H disease.", American Journal of Hematology, vol. 34, no. 4, pp. 287-290.

Hsu, H.C., Wang, C.C., Peng, H.W., Ho, C.H. & Lin, C.K. 1990, "Hemoglobin H disease--ten years' experience.", Chung Hua i Hsueh Tsa Chih - Chinese Medical Journal, vol. 45, no. 1, pp. 34-38.

Huisman, T.H., Gu, L.H., Liu, J.C., Fei, Y.J. & Walker, E.L.,3rd 1993, "Black alpha-thalassemia-1: partial characterization of an approximately 80 kb deletion which includes the zeta- and alpha-globin genes.", Hemoglobin, vol. 17, no. 4, pp. 345-353.

Hung, C.C., Lee, C.N., Chen, C.P., Jong, Y.J., Hsieh, W.S., Lin, W.L., Su, Y.N. & Hsu, S.M. 2007, "Molecular assay of -alpha(3.7) and -alpha(4.2) deletions causing alpha-thalassemia by denaturing high-performance liquid chromatography.", Clinical biochemistry, vol. 40, no. 11, pp. 817-821.

Igbokwe, E.C. 1989, "Molecular genetics of alpha thalassemia.", Medical hypotheses, vol. 30, no. 2, pp. 75-79.

Isarangkura, P., Chantarojanasiri, T., Hathirat, P., Pintadit, P. & Suwanjutha, S. 1993, "Pulmonary and platelet function in mild form of Hb H disease.", Southeast Asian Journal of Tropical Medicine & Public Health, vol. 24, no. Suppl 1, pp. 210-212.

Jaovisidha, A., Ajjimarkorn, S., Panburana, P., Somboonsub, O., Herabutya, Y. & Rungsiprakarn, R. 2000, "Prevention and control of thalassemia in Ramathibodi Hospital, Thailand.", Southeast Asian Journal of Tropical Medicine & Public Health, vol. 31, no. 3, pp. 561-565.

Jay, G.D. & Renzi, F.P. 1992, "Evaluation of pulse oximetry in anemia from hemoglobin-H disease", Annals of Emergency Medicine, vol. 21, no. 5, pp. 572-574.

Jetsrisuparb, A., Sanchaisuriya, K., Fucharoen, G., Fucharoen, S., Wiangnon, S., Jetsrisuparb, C., Sirijirachai, J. & Chansoong, K. 2006, "Development of severe anemia during fever episodes in patients with hemoglobin E trait and hemoglobin H disease combinations.", Journal of Pediatric Hematology/Oncology, vol. 28, no. 4, pp. 249-253.

Jindadamrongwech, S., Wisedpanichkij, R., Bunyaratvej, A. & Hathirat, P. 1997, "Red cell parameters in alpha-thalassemia with and without beta-thalassemia trait or hemoglobin E trait.", Southeast Asian Journal of Tropical Medicine & Public Health, vol. 28, no. Suppl 3, pp. 97-99.

Jolobe, O.M. 1993, "Haemoglobin-H disease presenting with microcytic hypochromic anaemia in an 81 year old woman.", Postgraduate medical journal, vol. 69, no. 818, pp. 930-931.

Kajanachumpol, S., Tatu, T., Sasanakul, W., Chuansumrit, A. & Hathirat, P. 1997, "Zinc and copper status of thalassemic children.", Southeast Asian Journal of Tropical Medicine & Public Health, vol. 28, no. 4, pp. 877-880.

Kanavakis, E., Papassotiriou, I., Karagiorga, M., Vrettou, C., Metaxotou-Mavrommati, A., Stamoulakatou, A., Kattamis, C. & Traeger-Synodinos, J. 2000, "Phenotypic and molecular diversity of haemoglobin H disease: a Greek experience.", British journal of haematology, vol. 111, no. 3, pp. 915-923.

Kanavakis, E., Traeger-Synodinos, J., Papasotiriou, I., Vrettou, C., Metaxotou-Mavromati, A., Stamoulakatou, A., Lagona, E. & Kattamis, C. 1996, "The interaction of alpha zero thalassaemia with Hb

Icaria: three unusual cases of haemoglobinopathy H.", British journal of haematology, vol. 92, no. 2, pp. 332-335.

Keclard, L., Romana, M., Lavocat, E., Saint-Martin, C., Berchel, C. & Merault, G. 1997, "Sickle cell disorder, - beta-globin gene cluster haplotypes and alpha-thalassemia in neonates and adults from Guadeloupe.", - American Journal of Hematology, vol. 55, no. 1, pp. 24-27. -

Kham, S.K., Quah, T.C., Loong, A.M., Tan, P.L., Fraser, A., Chong, S.S. & Yeoh, A.E. 2004, "A molecular - epidemiologic study of thalassemia using newborns' cord blood in a multiracial Asian population in - Singapore: results and recommendations for a population screening program", Journal of Pediatric - Hematology/Oncology, vol. 26, no. 12, pp. 817-819. -

Khan, S.N., Butt, F.I., Riazuddin, S. & Galanello, R. 2000, "Hb Sallanches [alpha104(G11)Cys-->Tyr]: a rare - alpha2-globin chain variant found in the homozygous state in three members of a Pakistani family.", - Hemoglobin, vol. 24, no. 1, pp. 31-35. -

Ko, T.M., Hsieh, F.J., Hsu, P.M. & Lee, T.Y. 1991, "Molecular characterization of severe alpha-thalassemias - causing hydrops fetalis in Taiwan.", American Journal of Medical Genetics, vol. 39, no. 3, pp. 317-320. -

Ko, T.M., Hwa, H.L., Liu, C.W., Li, S.F., Chu, J.Y. & Cheung, Y.P. 1999, "Prevalence study and molecular - characterization of alpha-thalassemia in Filipinos.", Annals of Hematology, vol. 78, no. 8, pp. 355-357. -

Ko, T.M., Hwang, W.J., Chen, S.H., Lee, T.Y., Hsieh, G.Y. & Lee, C.Y. 1990, "Alpha-thalassemia minor and - neonatal hyperbilirubinemia.", Journal of the Formosan Medical Association, vol. 89, no. 5, pp. 378-382. -

Ko, T.M., Tseng, L.H., Cheng, T.A., Hwa, H.L., Chang, Y.K., Chuang, S.M. & Lee, T.Y. 1994, "Prevalence - and molecular studies of thalassemia in five aboriginal groups in Taiwan.", Journal of the Formosan Medical - Association, vol. 93, no. 5, pp. 379-382. -

Ko, T.M., Tseng, L.H., Kao, C.H., Lin, Y.W., Hwa, H.L., Hsu, P.M., Li, S.F. & Chuang, S.M. 1998, - "Molecular characterization and PCR diagnosis of Thailand deletion of alpha-globin gene cluster", American - Journal of Hematology, vol. 57, no. 2, pp. 124-130. -

Kyriacou, K., Kyrri, A., Kalogirou, E., Vasiliades, P., Angastiniotis, M., Ioannou, P.A. & Kleanthous, M. 2000, - "Hb Bart's levels in cord blood and alpha-thalassemia mutations in Cyprus.", Hemoglobin, vol. 24, no. 3, pp. - 171-180. -

Lafferty, J., Ali, M.A., Carstairs, K. & Crawford, L. 1997, "Proficiency testing of hemoglobinopathy - techniques in Ontario laboratories", American Journal of Clinical Pathology, vol. 107, no. 5, pp. 567-575. -

Lamchiagdhase, P., Nitipongwanich, R., Rattanapong, C., Noulsri, E., Lerdwana, S. & Pattanapanyasat, K. - 2004, "Red blood cell vesicles in thalassemia.", Journal of the Medical Association of Thailand, vol. 87, no. - 3, pp. 233-238. -

Laosombat, V., Fucharoen, S. & Wiriyasateinkul, A. 2001, "Interaction of the alpha2 polyadenylation signal - mutation (AATAAA-->AATA--) and alpha0-thalassemia (--SEA), resulting in Hb H disease in a Thai - patient.", Hemoglobin, vol. 25, no. 4, pp. 383-389. -

Laosombat, V., Pornpatkul, M., Wongchanchailert, M., Worachat, K. & Wiriyasatienku, A. 1997, "The - prevalence of hepatitis C virus antibodies in thalassemic patients in the south of Thailand.", Southeast - Asian Journal of Tropical Medicine & Public Health, vol. 28, no. 1, pp. 149-153. -

Laosombat, V., Viprakasit, V., Chotsampancharoen, T., Wongchanchailert, M., Khodchawan, S., - Chinchang, W. & Sattayasevana, B. 2009, "Clinical features and molecular analysis in Thai patients with - HbH disease.", Annals of Hematology, vol. 88, no. 12, pp. 1185-1192. -

Laosombat, V., Wongchanchailert, M., Kenpitak, K. & Wisitpongpon, C. 1992, "Spontaneous platelet aggregation in thalassemic children and adolescents.", Southeast Asian Journal of Tropical Medicine & Public Health, vol. 23, no. Suppl 2, pp. 42-46.

Lemmens-Zygulska, M., Eigel, A., Helbig, B., Sanguansermsri, T., Horst, J. & Flatz, G. 1996, "Prevalence of alpha-thalassemias in northern Thailand.", Human genetics, vol. 98, no. 3, pp. 345-347.

Leung, K.Y., Lee, C.P., Tang, M.H., Lau, E.T., Ng, L.K., Lee, Y.P., Chan, H.Y., Ma, E.S. & Chan, V. 2004, "Cost-effectiveness of prenatal screening for thalassaemia in Hong Kong.", Prenatal diagnosis, vol. 24, no. 11, pp. 899-907.

Li, D., Liao, C. & Li, J. 2007, "Misdiagnosis of Hb constant spring (alpha142, Term-->Gln, TAA-->CAA in alpha2) in a Hb H (beta4) disease child.", Hemoglobin, vol. 31, no. 1, pp. 105-108.

Li, D., Liao, C., Xie, X., Zhong, H. & Li, J. 2007, "Four cases of Hb Q-H disease found in Southern China.", Hemoglobin, vol. 31, no. 1, pp. 109-111.

Li, Z., Cai, S., Rong, K., Song, G., Li, Y. & Guo, R. 2007, "The first compound heterozygosity for HKalpha alpha allele and Southeast Asian deletion allele.", Clinical biochemistry, vol. 40, no. 5-6, pp. 407-410.

Liang, R., Liang, S., Jiang, N.H., Wen, X.J., Zhao, J.B., Nechtman, J.F., Stoming, T.A. & Huisman, T.H. 1994, "Alpha and beta thalassaemia among Chinese children in Guangxi Province, P.R. China: molecular and haematological characterization.", British journal of haematology, vol. 86, no. 2, pp. 351-354.

Liebhaber, S.A. 1989, "Alpha thalassemia", Hemoglobin, vol. 13, no. 7-8, pp. 685-731.

Lin, C.K., Peng, H.W., Ho, C.H. & Yung, C.H. 1990, "Iron overload in untransfused patients with hemoglobin H disease.", Acta Haematologica, vol. 83, no. 3, pp. 137-139.

Lin, S.F., Liu, T.C., Chen, T.P., Chiou, S.S., Liu, H.W. & Chang, J.G. 1994, "Diagnosis of thalassaemia by non-isotope detection of alpha/beta and zeta/alpha mRNA ratios.", British journal of haematology, vol. 87, no. 1, pp. 133-138.

Lin, T.M., Eng, H.L., Kuo, P.L. & Wu, H.L. 1992, "Neonatal screening for alpha-thalassemia in southern Taiwan.", Journal of the Formosan Medical Association, vol. 91, no. 12, pp. 1213-1215.

Liu, J., Yan, M., Wang, Z., Wang, L., Zhou, Y. & Xiao, B. 2006, "Molecular diagnosis of alpha-thalassemia by combining real-time PCR with SYBR Green1 and dissociation curve analysis.", Translational Research: The Journal Of Laboratory & Clinical Medicine, vol. 148, no. 1, pp. 6-12.

Liu, J.Z., Han, H., Schouten, J.P., Wang, L.R., Fan, X.P., Duarte, H.B., Zhu, C.J., Cai, R., Xiao, B. & Wang, Q.T. 2008, "Detection of alpha-thalassemia in China by using multiplex ligation-dependent probe amplification.", Hemoglobin, vol. 32, no. 6, pp. 561-571.

Liu, T.C., Chiou, S.S., Lin, S.F., Chen, T.P., Tseng, W.P., Chen, P.H. & Chang, J.G. 1994, "Molecular basis and hematological characterization of Hb H disease in southeast Asia.", American Journal of Hematology, vol. 45, no. 4, pp. 293-297.

Lobel, J.S., Cameron, B.F., Johnson, E., Smith, D. & Kalinyak, K. 1989, "Value of screening umbilical cord blood for hemoglobinopathy.", Pediatrics, vol. 83, no. 5 Pt 2, pp. 823-826.

Lorey, F. 2005, "Diagnosis and management of alpha thalassemia disorders.", Annals of the New York Academy of Sciences, vol. 1054, pp. 514-515.

Lorey, F., Charoenkwan, P., Witkowska, H.E., Lafferty, J., Patterson, M., Eng, B., Waye, J.S., Finklestein, J.Z. & Chui, D.H. 2001, "Hb H hydrops foetalis syndrome: a case report and review of literature", British journal of haematology, vol. 115, no. 1, pp. 72-78.

Lorey, F., Cunningham, G., Vichinsky, E.P., Lubin, B.H., Witkowska, H.E., Matsunaga, A., Azimi, M., Sherwin, J., Eastman, J., Farina, F., Waye, J.S. & Chui, D.H. 2001, "Universal newborn screening for Hb H disease in California.", Genetic testing, vol. 5, no. 2, pp. 93-100.

Ma, E.S., Chan, A.Y., Au, W.Y., Yeung, Y.M. & Chan, L.C. 2001, "Diagnosis of concurrent hemoglobin H disease and heterozygous beta-thalassemia.", Haematologica, vol. 86, no. 4, pp. 432-433.

Ma, S.K., Chan, A.Y., Chiu, E.K. & Chan, L.C. 2001, "Haemoglobin H disease due to (--SEA) alpha-globin gene deletion and alpha2-codon 30 (DeltaGAG) mutation: a family study.", Clinical & Laboratory Haematology, vol. 23, no. 5, pp. 325-327.

Ma, S.K., Ma, V., Chan, A.Y., Chan, L.C. & Chui, D.H. 2002, "Routine screening of (--(SEA)) alpha-thalassemia deletion by an enzyme-linked immunosorbent assay for embryonic zeta-globin chains.", Acta Haematologica, vol. 108, no. 1, pp. 8-12.

Mallouh, A.A. & Qudah, A. 1995, "An epidemic of aplastic crisis caused by human parvovirus B19.", Pediatric Infectious Disease Journal, vol. 14, no. 1, pp. 31-34.

Mesbah-Amroun, H., Rouabhi, F., Ducrocq, R. & Elion, J. 2008, "Molecular basis of alpha-thalassemia in Algeria.", Hemoglobin, vol. 32, no. 3, pp. 273-278.

Michlitsch, J., Azimi, M., Hoppe, C., Walters, M.C., Lubin, B., Lorey, F. & Vichinsky, E. 2009, "Newborn screening for hemoglobinopathies in California.", Pediatric Blood & Cancer, vol. 52, no. 4, pp. 486-490.

Miller, S.T., Desai, N., Pass, K.A. & Rao, S.P. 1997, "A fast hemoglobin variant on newborn screening is associated with alpha-thalassemia trait.", Clinical pediatrics, vol. 36, no. 2, pp. 75-78.

Mirabile, E., Samperi, P., Di Cataldo, A., Poli, A., La Spina, M. & Schiliro, G. 2000, "Phenotype-genotype correlation in Sicilian patients with Hb H.", European journal of haematology, vol. 65, no. 5, pp. 306-309.

Morle, F., Francina, A., Ducrocq, R., Wajcman, H., Gonnet, C., Philippe, N., Souillet, G. & Godet, J. 1995, "A new alpha chain variant Hb Sallanches [alpha 2 104(G11) Cys-->Tyr] associated with HbH disease in one homozygous patient", British journal of haematology, vol. 91, no. 3, pp. 608-611.

Nadkarni, A., Phanasgaonkar, S., Colah, R., Mohanty, D. & Ghosh, K. 2008, "Prevalence and molecular characterization of alpha-thalassemia syndromes among Indians.", Genetic testing, vol. 12, no. 2, pp. 177-180.

Nadkarni, A.H., Nair, S.B., Italia, K.Y., Warang, P., Dalvi, M., Ghosh, K. & Colah, R.B. 2010, "Molecular diversity of hemoglobin H disease in India.", American Journal of Clinical Pathology, vol. 133, no. 3, pp. 491-494.

NHS Center for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report 4 (2nd Edition). http://www.york.ac.uk/inst/crd/report4.htm: March 2001, Accessed: October 17, 2008.

Nava, M.P., Trejo, J.M., Aguilar-Luna, C., Barros-Nunez, P., Chavez Mde, L., Magana, M.T., Perea, J. & Ibarra, B. 2006, "Molecular characterization of the--SEA alpha thalassemia allele in Mexican patients with HbH disease.", Revista de Investigacion Clinica, vol. 58, no. 4, pp. 313-317.

Ne-Win, Harano, K., Harano, T., Kyaw-Shwe, Aye-Aye-Myint, Khin-Thander-Aye & Okada, S. 2008, "Hb Constant Spring [alpha 142, Term-->Gln (TAA>CAA in alpha2)] in the alpha-thalassemia of anemic patients in Myanmar.", Hemoglobin, vol. 32, no. 5, pp. 454-461.

Ne-Win, Harano, K., Harano, T., Thein-Thein-Myint, Rai-Mra, Aye-Aye-Myint, Shimono, K. & Okada, S. 2006, "Common alpha-thalassemia deletions in transfusion-dependent thalassemia patients in the Southeast Asia region of Myanmar.", Laboratory Hematology, vol. 12, no. 3, pp. 139-142.

Noguera, N.I., Gonzalez, F.A., Davoli, R.A., Milani, A.C. & Villegas, A. 2001, "A novel splice acceptor site mutation of the alpha2-globin gene causing alpha-thalassemia.", Hemoglobin, vol. 25, no. 3, pp. 311-315.

Novelletto, A., Hafez, M., Di Rienzo, A., Felicetti, L., Deidda, G., el Morsi, Z., al-Tonbary, Y., el-Ziny, M., Abd-el-Gelil, N. & Terrenato, L. 1989, "Frequency and molecular types of deletional alpha-thalassemia in Egypt.", Human genetics, vol. 81, no. 3, pp. 211-213.

Oner, C., Gurgey, A., Oner, R., Balkan, H., Gumruk, F., Baysal, E. & Altay, C. 1997, "The molecular basis of Hb H disease in Turkey.", Hemoglobin, vol. 21, no. 1, pp. 41-51.

Ooi, G.C., Chen, F.E., Chan, K.N., Tsang, K.W., Wong, Y.H., Liang, R., Chan, V. & Ngan, H. 1999, "Qualitative and quantitative magnetic resonance imaging in haemoglobin H disease: screening for iron overload.", Clinical radiology, vol. 54, no. 2, pp. 98-102.

Origa, R., Sollaino, M.C., Giagu, N., Barella, S., Campus, S., Mandas, C., Bina, P., Perseu, L. & Galanello, R. 2007, "Clinical and molecular analysis of haemoglobin H disease in Sardinia: haematological, obstetric and cardiac aspects in patients with different genotypes.", British journal of haematology, vol. 136, no. 2, pp. 326-332.

Ou-Yang, H., Hua, L., Mo, Q.H. & Xu, X.M. 2004, "Rapid, accurate genotyping of the common -alpha(4.2) thalassaemia deletion based on the use of denaturing HPLC.", Journal of clinical pathology, vol. 57, no. 2, pp. 159-163.

Pan, L.L., Eng, H.L., Kuo, C.Y., Chen, W.J. & Huang, H.Y. 2005, "Usefulness of brilliant cresyl blue staining as an auxiliary method of screening for alpha-thalassemia.", Journal of Laboratory & Clinical Medicine, vol. 145, no. 2, pp. 94-97.

Pandor, A., Eastham, J., Beverley, C., Chilcott, J. & Paisley, S. 2004, "Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review", Health technology assessment (Winchester, England), vol. 8, no. 12, pp. iii, 1-121.

Papassotiriou, I., Traeger-Synodinos, J., Kanavakis, E., Karagiorga, M., Stamoulakatou, A. & Kattamis, C. 1998, "Erythroid marrow activity and hemoglobin H levels in hemoglobin H disease.", Journal of Pediatric Hematology/Oncology, vol. 20, no. 6, pp. 539-544.

Papassotiriou, I., Traeger-Synodinos, J., Vlachou, C., Karagiorga, M., Metaxotou, A., Kanavakis, E. & Stamoulakatou, A. 1999, "Rapid and accurate quantitation of Hb Bart's and Hb H using weak cation exchange high performance liquid chromatography: correlation with the alpha-thalassemia genotype.", Hemoglobin, vol. 23, no. 3, pp. 203-211.

Peltier, J.Y., Girault, D., Debre, M., Galacteros, F., Fischer, A. & Girot, R. 1993, "Donor for BMT with haemoglobin H disease.", Bone marrow transplantation, vol. 12, no. 1, pp. 81-84.

Philippon, G., Martinson, J.J., Rugless, M.J., Moulia-Pelat, J.P., Plichart, R., Roux, J.F., Martin, P.M. & Clegg, J.B. 1995, "Alpha-thalassaemia and globin gene rearrangements in French Polynesia.", European journal of haematology, vol. 55, no. 3, pp. 171-177.

Pollitt, R.J., Green, A., McCabe, C.J., Booth, A., Cooper, N.J., Leonard, J.V., Nicholl, J., Nicholson, P., Tunaley, J.R. & Virdi, N.K. 1997, "Neonatal screening for inborn errors of metabolism: cost, yield and outcome", Health technology assessment (Winchester, England), vol. 1, no. 7, pp. i-iv, 1-202.

Pootrakul, P., Sirankapracha, P., Hemsorach, S., Moungsub, W., Kumbunlue, R., Piangitjagum, A., Wasi, P., Ma, L. & Schrier, S.L. 2000, "A correlation of erythrokinetics, ineffective erythropoiesis, and erythroid precursor apoptosis in thai patients with thalassemia.", Blood, vol. 96, no. 7, pp. 2606-2612.

Pressley, L., Higgs, D.R., Clegg, J.B., Perrine, R.P., Pembrey, M.E. & Weatherall, D.J. 1980, "A new genetic basis for hemoglobin-H disease", The New England journal of medicine, vol. 303, no. 24, pp. 1383-1388.

Prior, J.F., Bittles, A.H. & Erber, W.N. 2004, "A community profile of alpha thalassaemia in Western Australia.", Community Genetics, vol. 7, no. 4, pp. 211-215.

Qadri, M.I. & Islam, S.A. 2000, "Hemoglobin H disease in the eastern region of Saudi Arabia.", Saudi medical journal, vol. 21, no. 7, pp. 666-671.

Quadri, M.I., Islam, S.I. & Nasserullah, Z. 2000, "The effect of alpha-thalassemia on cord blood red cell indices and interaction with sickle cell gene.", Annals of Saudi Medicine, vol. 20, no. 5-6, pp. 367-370.

Repapinou, Z., Karababa, P., Boussiou, M., Kafarakis, V., Papadaki, H.A., Mavroudis, D., Eliopoulos, G.D. & Loutradi-Anagnostou, A. 2007, "An improved method for the diagnostic approach of alpha+-thalassaemia.", International Journal of Laboratory Hematology, vol. 29, no. 1, pp. 45-51.

RIGAS, D.A., KOLER, R.D. & OSGOOD, E.E. 1955, "New hemoglobin possessing a higher electrophoretic mobility than normal adult hemoglobin", Science (New York, N.Y.), vol. 121, no. 3141, pp. 372.

Romao, L., Olim, G., Martins, M.C., Rodrigues, V., Coutinho-Gomes, M.P. & Lavinha, J. 1990, "Unusual molecular basis of Hb H disease in the Azores Islands, Portugal.", Hemoglobin, vol. 14, no. 6, pp. 607-616.

Rugless, M.J., Fisher, C.A., Stephens, A.D., Amos, R.J., Mohammed, T. & Old, J.M. 2006, "Hb Bart's in cord blood: an accurate indicator of alpha-thalassemia.", Hemoglobin, vol. 30, no. 1, pp. 57-62.

Sae-ung, N., Fucharoen, G., Sanchaisuriya, K. & Fucharoen, S. 2007, "Alpha(0)-thalassemia and related disorders in northeast Thailand: a molecular and hematological characterization.", Acta Haematologica, vol. 117, no. 2, pp. 78-82.

Safaya, S., Trauber, D.R. & Rieder, R.F. 1992, "Studies on the in vitro and in vivo expression of a dysfunctional alpha-globin gene.", American Journal of Hematology, vol. 39, no. 3, pp. 188-193.

Sardon Estevez, N., Herruer, M.H., Jansen, R., Bergkamp, F.J. & Gorgels, J.P. 2009, "Diagnostic value of zinc protoporphyrin in a screening strategy for alpha-thalassemia.", European journal of haematology, vol. 82, no. 5, pp. 393-397.

Sarnaik, S.A. 2005, "Thalassemia and related hemoglobinopathies", Indian journal of pediatrics, vol. 72, no. 4, pp. 319-324.

Schrier, S.L. & Angelucci, E. 2005, "New strategies in the treatment of the thalassemias", Annual Review of Medicine, vol. 56, pp. 157-171.

Shaji, R.V., Eunice, S.E., Baidya, S., Srivastava, A. & Chandy, M. 2003, "Determination of the breakpoint and molecular diagnosis of a common alpha-thalassaemia-1 deletion in the Indian population.", British journal of haematology, vol. 123, no. 5, pp. 942-947.

Shalmon, L., Kirschmann, C. & Zaizov, R. 1994, "A new deletional alpha-thalassemia detected in Yemenites with hemoglobin H disease.", American Journal of Hematology, vol. 45, no. 3, pp. 201-204.

Shinar, E., Rachmilewitz, E.A. & Lux, S.E. 1989, "Differing erythrocyte membrane skeletal protein defects in alpha and beta thalassemia.", Journal of Clinical Investigation, vol. 83, no. 2, pp. 404-410.

Siala, H., Ouali, F., Messaoud, T., Bibi, A. & Fattoum, S. 2008, "alpha-Thalassaemia in Tunisia: some epidemiological and molecular data.", Journal of Genetics, vol. 87, no. 3, pp. 229-234.

Singer, S.T. 2009, "Variable clinical phenotypes of alpha-thalassemia syndromes", Thescientificworldjournal, vol. 9, pp. 615-625.

Singer, S.T., Kim, H.Y., Olivieri, N.F., Kwiatkowski, J.L., Coates, T.D., Carson, S., Neufeld, E., Cunningham, M.J., Giardina, P.J., Mueller, B.U., Quinn, C.T., Fung, E., Vichinsky, E. & Thalassemia Clinical Research, N. 2009, "Hemoglobin H-constant spring in North America: an alpha thalassemia with frequent complications.", American Journal of Hematology, vol. 84, no. 11, pp. 759-761.

Smetanina, N.S., Leonova, J.Y., Levy, N. & Huisman, T.H. 1996, "The alpha / beta and alpha 2 / alpha 1-globin mRNA ratios in different forms of alpha-thalassemia.", Biochimica et biophysica acta, vol. 1315, no. 3, pp. 188-192.

Smetanina, N.S., Oner, C., Baysal, E., Oner, R., Bozkurt, G., Altay, C., Gurgey, A., Adekile, A.D., Gu, L.H. & Huisman, T.H. 1996, "The relative levels of alpha 2-, alpha 1-, and zeta-mRNA in HB H patients with different deletional and nondeletional alpha-thalassemia determinants.", Biochimica et biophysica acta, vol. 1316, no. 3, pp. 176-182.

Sonakul, D. & Fucharoen, S. 1992, "Pulmonary thromboembolism in thalassemic patients", Southeast Asian Journal of Tropical Medicine & Public Health, vol. 23, no. Suppl 2, pp. 25-28.

Sonati, M.F. & Costa, F.F. 1990, "Hemoglobin Bart's in a Brazilian black population.", Brazilian Journal of Medical & Biological Research, vol. 23, no. 5, pp. 395-396.

Sriroongrueng, W., Pornpatkul, M., Panich, V. & Fucharoen, S. 1997, "Alpha-thalassemia incidence in southern Thailand by restriction endonuclease analysis of globin DNA from placental blood at Songklanagarind Hospital.", Southeast Asian Journal of Tropical Medicine & Public Health, vol. 28, no. Suppl 3, pp. 93-96.

Stanley, P. & Shen, T.C. 1995, "Partial embolization of the spleen in patients with thalassemia.", Journal of Vascular & Interventional Radiology, vol. 6, no. 1, pp. 137-142.

Storti-Melo, L.M., Mangonaro, P.H., Valencio, C.R., Traina Junior, C. & Domingos, C.R. 2009, "Three-dimensional visualization of human hemoglobin phenotypes with HPLC.", Genetics & Molecular Research, vol. 8, no. 1, pp. 354-363.

Sumboonnanonda, A., Malasit, P., Tanphaichitr, V.S., Ong-ajyooth, S., Petrarat, S. & Vongjirad, A. 2003, "Renal tubular dysfunction in alpha-thalassemia.", Pediatric Nephrology, vol. 18, no. 3, pp. 257-260.

Sura, T., Trachoo, O., Viprakasit, V., Vathesatogkit, P., Tunteeratum, A., Busabaratana, M., Wisedpanichkij, R. & Isarangkura, P. 2007, "Hemoglobin H disease induced by the common SEA deletion and the rare hemoglobin Quong Sze in a Thai female: longitudinal clinical course, molecular characterization, and development of a PCR/RFLP-based detection method.", Annals of Hematology, vol. 86, no. 9, pp. 659-663.

Tan, J.A., Kok, J.L., Tan, K.L., Wee, Y.C. & George, E. 2009, "Thalassemia intermedia in HbH-CS disease with compound heterozygosity for beta-thalassemia: challenges in hemoglobin analysis and clinical diagnosis.", Genes & genetic systems, vol. 84, no. 1, pp. 67-71.

Tan, J.R., Li, W.J., Ma, J.Y., Mo, Q.H., Li, L.Y., Jia, S.Q., Lao, X.W., Li, L.Y., He, R.Q. & Xu, X.M. 2003, "Molecular epidemiological study of alpha- and beta-thalassemia in Sihui city.", Di Yi Junyi Daxue Xuebao, vol. 23, no. 7, pp. 716-719.

Tang, D.C., Fucharoen, S., Ding, I. & Rodgers, G.P. 2001, "Rapid differentiation of five common alpha-thalassemia genotypes by polymerase chain reaction.", Journal of Laboratory & Clinical Medicine, vol. 137, no. 4, pp. 290-295.

Tangvarasittichai, O., Jeenapongsa, R., Sitthiworanan, C. & Sanguansermsri, T. 2005, "Laboratory investigations of Hb Constant Spring.", Clinical & Laboratory Haematology, vol. 27, no. 1, pp. 47-49.

Tanphaichitr, V.S., Mahasandana, C., Suvatte, V., Yodthong, S., Pung-amritt, P. & Seeloem, J. 1995, "Prevalence of hemoglobin E, alpha-thalassemia and glucose-6-phosphate dehydrogenase deficiency in 1,000 cord bloods studied in Bangkok.", Southeast Asian Journal of Tropical Medicine & Public Health, vol. 26, no. Suppl 1, pp. 271-274.

Tatsumi, N., Tsuda, I., Funahara, Y., Matsumoto, H., Bunyaratvej, A., Siritanakul, N. & Fucharoen, S. 1992, "Size distribution curves of blood cells in thalassemias and hemoglobin H diseases.", Southeast Asian Journal of Tropical Medicine & Public Health, vol. 23, no. Suppl 2, pp. 79-85.

Tayapiwatana, C., Kuntaruk, S., Tatu, T., Chiampanichayakul, S., Munkongdee, T., Winichagoon, P., Fuchareon, S. & Kasinrerk, W. 2009, "Simple method for screening of alpha-thalassaemia 1 carriers.", International journal of hematology, vol. 89, no. 5, pp. 559-567.

Thakerngpol, K., Fucharoen, S., Boonyaphipat, P., Srisook, K., Sahaphong, S., Vathanophas, V. & Stitnimankarn, T. 1996, "Liver injury due to iron overload in thalassemia: histopathologic and ultrastructural studies.", BioMetals, vol. 9, no. 2, pp. 177-183.

Thompson, C.C., Ali, M.A., Boyadjian, S. & Vacovsky, M. 1989, "Positional effect of cis/trans alpha globin gene deletions on the formation of "H" bodies.", American Journal of Hematology, vol. 31, no. 4, pp. 242-247.

Thonglairuam, V., Winichagoon, P., Fucharoen, S. & Wasi, P. 1989, "The molecular basis of AE-Bart's disease.", Hemoglobin, vol. 13, no. 2, pp. 117-124.

Traeger-Synodinos, J., Harteveld, C.L., Kanavakis, E., Giordano, P.C., Kattamis, C. & Bernini, L.F. 1999, "Hb Aghia Sophia [alpha62(E11)Val-->0 (alpha1)], an "in-frame" deletion causing alpha-thalassemia.", Hemoglobin, vol. 23, no. 4, pp. 317-324.

Traeger-Synodinos, J., Papassotiriou, I., Vrettou, C., Skarmoutsou, C., Stamoulakatou, A. & Kanavakis, E. 2001, "Erythroid marrow activity and functional anemia in patients with the rare interaction of a single functional a-globin and beta-globin gene.", Haematologica, vol. 86, no. 4, pp. 363-367.

van der Dijs, F.P., van den Berg, G.A., Schermer, J.G., Muskiet, F.D., Landman, H. & Muskiet, F.A. 1992, "Screening cord blood for hemoglobinopathies and thalassemia by HPLC.", Clinical chemistry, vol. 38, no. 9, pp. 1864-1869.

Vichinsky, E.P., MacKlin, E.A., Waye, J.S., Lorey, F. & Olivieri, N.F. 2005, "Changes in the epidemiology of thalassemia in North America: a new minority disease.", Pediatrics, vol. 116, no. 6, pp. e818-25.

Villegas, A., Porres, A., Sanchez, J., Gonzalez, F.A., Perez-Clausell, C., Martinez, M., Murga, M.J., Cacha, J., Lozano, M., Fernandez-Fuertes, I., Del Arco, A., Arrizabalaga, B., Perez de Mendiguren, B., San Juan, I., Saavedra, R., Ricart, P., Sainz, C., Guerra, J.L., Munoz, J.A., Lago, C. & Anso, V.M. 1998, "Red blood cell phenotypes in alpha-thalassemias in the Spanish population.", Haematologica, vol. 83, no. 2, pp. 99-103.

Villegas, A., Ropero, P., Gonzalez, F.A., Anguita, E. & Espinos, D. 2001, "The thalassemia syndromes: molecular characterization in the Spanish population.", Hemoglobin, vol. 25, no. 3, pp. 273-283.

Viprakasit, V., Chinchang, W., Glomglao, W. & Tanphaichitr, V.S. 2005, "A rare association of alphaO-thalassemia (--SEA) and an initiation codon mutation (ATG-->A-G) of the alpha2 gene causes Hb H disease in Thailand.", Hemoglobin, vol. 29, no. 3, pp. 235-240.

Viprakasit, V., Green, S., Height, S., Ayyub, H. & Higgs, D.R. 2002, "Hb H hydrops fetalis syndrome associated with the interaction of two common determinants of alpha thalassaemia (--MED/(alpha)TSaudi(alpha)).", British journal of haematology, vol. 117, no. 3, pp. 759-762.

Viprakasit, V. & Tanphaichitr, V.S. 2004, "Unusual phenotype of hemoglobin EE with hemoglobin H disease: a pitfall in clinical diagnosis and genetic counseling.", Journal of Pediatrics, vol. 144, no. 3, pp. 391-393.

Viprakasit, V. & Tanphaichitr, V.S. 2002, "Compound heterozygosity for alpha0-thalassemia (- -THAI) and Hb constant spring causes severe Hb H disease.", Hemoglobin, vol. 26, no. 2, pp. 155-162.

Viprakasit, V., Tanphaichitr, V.S., Pung-Amritt, P., Petrarat, S., Suwantol, L., Fisher, C. & Higgs, D.R. 2002, "Clinical phenotypes and molecular characterization of Hb H-Pakse disease.", Haematologica, vol. 87, no. 2, pp. 117-125.

Viprakasit, V., Tanphaichitr, V.S., Veerakul, G., Chinchang, W., Petrarat, S., Pung-Amritt, P. & Higgs, D.R. 2004, "Co-inheritance of Hb Pak Num Po, a novel alpha1 gene mutation, and alpha0 thalassemia associated with transfusion-dependent Hb H disease.", American Journal of Hematology, vol. 75, no. 3, pp. 157-163.

Vogiatzi, M.G., Macklin, E.A., Fung, E.B., Vichinsky, E., Olivieri, N., Kwiatkowski, J., Cohen, A., Neufeld, E. & Giardina, P.J. 2006, "Prevalence of fractures among the Thalassemia syndromes in North America.", Bone, vol. 38, no. 4, pp. 571-575.

Wang, J.Y., Liang, J.C. & Peng, H.W. 1989, "Structural analysis of the alpha-globin gene cluster in two Chinese families with alpha-thalassemias.", Chung Hua i Hsueh Tsa Chih - Chinese Medical Journal, vol. 43, no. 4, pp. 233-236.

Wang, L.Y., Liang, D.C., Liu, H.C., Chang, F.C., Wang, C.L., Chan, Y.S. & Lin, M. 2006, "Alloimmunization among patients with transfusion-dependent thalassemia in Taiwan.", Transfusion Medicine, vol. 16, no. 3, pp. 200-203.

Waye, J.S., Eng, B., Cai, S.P., Patterson, M., Smith, J., Tang, W. & Chui, D.H. 1993, "Carrier detection and prenatal diagnosis of hemoglobinopathies in Ontario", Clinical and investigative medicine.Medecine clinique et experimentale, vol. 16, no. 5, pp. 358-371.

Waye, J.S., Eng, B., Patterson, M., Chui, D.H. & Olivieri, N.F. 1994, "Identification of a novel termination codon mutation (TAA-->TAT, Term-->Tyr) in the alpha 2 globin gene of a Laotian girl with hemoglobin H disease.", Blood, vol. 83, no. 11, pp. 3418-3420.

Waye, J.S., Eng, B., Patterson, M., Walker, L., Carcao, M.D., Olivieri, N.F. & Chui, D.H. 2001, "Hemoglobin H (Hb H) disease in Canada: molecular diagnosis and review of 116 cases.", American Journal of Hematology, vol. 68, no. 1, pp. 11-15.

Waye, J.S., Walker, L., Chui, D.H., Lafferty, J. & Kirby, M. 2000, "Homozygous Hb Sallanches [alpha104(G11)Cys-->Tyr] in a Pakistani child with Hb H disease", Hemoglobin, vol. 24, no. 4, pp. 355-357.

Weatherall, D.J. & Clegg, J.B. 2001, "Inherited haemoglobin disorders: an increasing global health problem", Bulletin of the World Health Organization, vol. 79, no. 8, pp. 704-712.

Weiss, I., Cash, F.E., Coleman, M.B., Pressley, A., Adams, J.G., Sanguansermsri, T., Liebhaber, S.A. & Steinberg, M.H. 1990, "Molecular basis for alpha-thalassemia associated with the structural mutant hemoglobin Suan-Dok (alpha 2 109leu----arg)[erratum appears in Blood 1991 Mar 15;77(6):1404].", Blood, vol. 76, no. 12, pp. 2630-2636.

Wenning, M.R., Harteveld, C.L., Giordano, P.C., Kimura, E.M., Saad, S.T., Costa, F.F. & Sonati, M.F. 2002, "Hemoglobin H disease resulting from the association of the - alpha 3.7 rightward deletion and the (alpha alpha)MM deletion in a Brazilian patient.", European journal of haematology, vol. 69, no. 3, pp. 179-181.

Wenning, M.R., Kimura, E.M., Costa, F.F., Saad, S.T., Gervasio, S., de Jorge, S.B., Borges, E., Silva, N.M. & Sonati, M.F. 2000, "alpha-globin genes: thalassemic and structural alterations in a Brazilian population.", Brazilian Journal of Medical & Biological Research, vol. 33, no. 9, pp. 1041-1045.

Wenning, M.R., Mello, M.P., Andrade, T.G., Lanaro, C., Albuquerque, D.M., Saad, S.T., Costa, F.F. & Sonati, M.F. 2009, "PIP4KIIA and beta-globin: transcripts differentially expressed in reticulocytes and associated with high levels of Hb H in two siblings with Hb H disease.", European journal of haematology, vol. 83, no. 5, pp. 490-493.

Wickramasinghe, S.N., Lee, M.J., Furukawa, T., Eguchi, M. & Reid, C.D. 1996, "Composition of the intra-erythroblastic precipitates in thalassaemia and congenital dyserythropoietic anaemia (CDA): identification of a new type of CDA with intra-erythroblastic precipitates not reacting with monoclonal antibodies to alpha- and beta-globin chains.", British journal of haematology, vol. 93, no. 3, pp. 576-585.

Wiener, E., Wanachiwanawin, W., Chinprasertsuk, S., Siripanyaphinyo, U., Mawas, F., Fucharoen, S. & Wickramasinghe, S.N. 1996, "Increased serum levels of macrophage colony-stimulating factor (M-CSF) in alpha- and beta-thalassaemia syndromes: correlation with anaemia and monocyte activation.", European journal of haematology, vol. 57, no. 5, pp. 364-369.

Williams, T.N., Maitland, K., Ganczakowski, M., Peto, T.E., Clegg, J.B., Weatherall, D.J. & Bowden, D.K. 1996, "Red blood cell phenotypes in the alpha + thalassaemias from early childhood to maturity.", British journal of haematology, vol. 95, no. 2, pp. 266-272.

Winichagoon, P., Fucharoen, S. & Wasi, P. 1992, "The molecular basis of alpha-thalassemia in Thailand.", Southeast Asian Journal of Tropical Medicine & Public Health, vol. 23, no. Suppl 2, pp. 7-13.

Wongchanchailert, M., Laosombat, V. & Maipang, M. 1992, "Hemoglobin H disease in children.", Journal of the Medical Association of Thailand, vol. 75, no. 11, pp. 611-618.

Wu, J.H., Shih, L.Y., Kuo, T.T. & Lan, R.S. 1992, "Intrathoracic extramedullary hematopoietic tumor in hemoglobin H disease.", American Journal of Hematology, vol. 41, no. 4, pp. 285-288.

Yorke, D., Mitchell, J., Clow, C., Nuguid, E., Cadogan, R., Sinclair, D., Luscombe, S., Rozen, R., Meredith, P. & Esseltine, D. 1992, "Newborn screening for sickle cell and other hemoglobinopathies: a Canadian pilot study.", Clinical & Investigative Medicine - Medecine Clinique et Experimentale, vol. 15, no. 4, pp. 376-383.

Zago, M.A. & Paco-Larson, M.L. 1989, "Hemoglobin H disease caused by two gene deletions.", Brazilian Journal of Medical & Biological Research, vol. 22, no. 6, pp. 675-681.

Zeng, F.Y., Fucharoen, S., Huang, S.Z. & Rodgers, G.P. 1992, "Hb Q-Thailand [alpha 74(EF3)Asp-->His]: gene organization, molecular structure, and DNA diagnosis.", Hemoglobin, vol. 16, no. 6, pp. 481-491.

Zeng, Y. & Huang, S. 2001, "The studies of hemoglobinopathies and thalassemia in China--the experiences in Shanghai Institute of Medical Genetics.", Clinica Chimica Acta, vol. 313, no. 1-2, pp. 107-111.

Zesong, L., Ruijun, G. & Wen, Z. 2005, "Rapid detection of deletional alpha-thalassemia by an oligonucleotide microarray.", American Journal of Hematology, vol. 80, no. 4, pp. 306-308.

Zhao, J.B., Zhao, L., Fei, Y.J., Liu, J.C. & Huisman, T.H. 1991, "A novel alpha-thalassemia-2 (-2.7-kb) observed in a Chinese patient with Hb H disease.", American Journal of Hematology, vol. 38, no. 3, pp. 248-249.

Zhao, Y., Qu, L. & Xu, X. 2001, "A very rare patient with states for HbH disease and congenital heart disease.", Haematologica, vol. 86, no. 4, pp. E13.

Zhu, M., Wehr, T., Levi, V., Rodriguez, R., Shiffer, K. & Cao, Z.A. 1993, "Capillary electrophoresis of abnormal hemoglobins associated with alpha-thalassemias.", Journal of Chromatography.A, vol. 652, no. 1, pp. 119-129.

Zorai, A., Harteveld, C.L., Bakir, A., Van Delft, P., Falfoul, A., Dellagi, K., Abbes, S. & Giordano, P.C. 2002, "Molecular spectrum of alpha-thalassemia in Tunisia: epidemiology and detection at birth.", Hemoglobin, vol. 26, no. 4, pp. 353-362.

XII. Table of abstracted literature

Authors/Researcher Title of Paper Year	Study goal(s)	Study Population Description	Significant findings:
Au,W. Y.;Cheung,W. C.;Hu,W. H.;Chan,G. C.;Ha,S. Y.;Khong,P. L.;Ma,S. K.;Liang,R. Hyperbilirubinemia and cholelithiasis in Chinese patients with hemoglobin H disease. 2005	Genotype-Phenotype correlation	90 males and females with transfusion-independent Hb H disease (from Chen et al 2000) Age range: 4-83 years, median of42 years	• 70% deletional Hb H disease, 30% nondeletional Hb H disease • 50 cases suffered from clinically significant jaundice (including 14 with severe jaundice) • Bilirubin levels comparable between males and females and between deletional and nondeletional Hb H disease • Gallstones detected in 39/90 cases (43%), at the youngest age of 25 years • Risk of gallstones did not vary significantly with sex or Hb H disease genotype • Ultrasound screening for gallstones may be warranted for all new Hb H disease diagnoses, especially if abnormal liver enzyme levels are present
Boonsa,S.;Sanchaisuriya,K.;Fucharoen,G.;Wiangnon,S.;Jetsrisuparb,A.;Fucharoen,S. The diverse molecular basis and hematological features of Hb H and AEBart's diseases in Northeast Thailand. 2004	Genotype-Phenotype correlation	52 Thai individuals with Hb H disease Age range: 5-21 years	• 14/52 patients deletional Hb H • 35/52 patients Hb H disease with Constant Spring • 3/52 patients Hb H disease with Hb Pakse • Nondeletional cases were more anemic and had relatively higher MCV and more Hb H inclusion bodies than deletional cases
Chan,V.;Wong,M. S.;Ooi,C.;Chen,F. E.;Chim,C. S.;Liang,R. H.;Todd,D.;Chan,T. K. Can defects in transferrin receptor 2 and hereditary hemochromatosis genes account for iron overload in Hb H disease? 2003	Genotype-Phenotype correlation	45 males and females with Hb H disease and elevated serum ferritin (from Chen et al 2000) Age range not stated	• Compared to sex, age and genotyped matched Hb H disease case-controls there was no significant difference in serum ferritin or liver hemosiderosis between those with molecular defects of iron absorption and those without • Ineffective erythropoiesis is a more likely cause of excessive iron absorption than coinheritance of molecular defects of iron regulation in these subjects

Chang,J. G.;Liu,T. C.;Perng,L. I.;Chiou,S. S.;Chen,T. P.;Chen,P. H.;Lin,C. P. Rapid molecular characterization of Hb H disease in Chinese by polymerase chain reaction. 1994	Genotype-Phenotype correlation; Screening	101 individuals with Hb H disease Age range not stated	• Development of a PCR based method to distinguish different types of Hb H disease • 60/101 cases were deletional and 41/101 cases were nondeletional (all Hb Constant Spring) • Individuals with the nondeletional Hb H disease had higher MCV values, higher Hb H levels and lower Hb levels
Charoenkwan,P.;Taweephon,R.;Sae-Tung,R.;Thanarattanakorn,P.;Sanguanserm sri,T. Molecular and clinical features of Hb H disease in northern Thailand. 2005	Genotype-Phenotype correlation	102 males and females with Hb H disease Age range: 1 month-19.8 years	• 54/102 had deletional Hb H disease, 58/102 had nondeletional Hb H disease. • Nondeletional cases were associated with more severe clinical and hematological features, including a younger age at presentation, a higher proportion of patients requiring transfusion, larger liver and spleen sizes and a trend towards higher requirement for splenectomy • A patient with (--THAI/$\alpha^{CS}\alpha$) presented with acute intravascular hemolysis requiring red cell transfusion at 1.5 years of age

Chen,F. E.;Ooi,C.;Ha,S. Y.;Cheung,B. M.;Todd,D.;Liang,R.;Chan,T. K.;Chan,V. Genetic and clinical features of hemoglobin H disease in Chinese patients 2000	Genotype-Phenotype correlation	114 males and females with Hb H disease Age range: newborn-80 years	• 87/114 had deletional Hb H disease; 27/114 had nondeletional Hb H disease • 24% of individuals presented with symptoms directly related to Hb H disease such as jaundice (2%), symptoms of anemia (11%) and gallstones (11%) • Diagnosis of Hb H disease was made incidentally in 76% • 53/114 had been treated with transfusions, only one subject was transfusion-dependent (presented with hydrops fetalis in utero) • Individuals with nondeletional Hb H disease had more severe clinical features, a larger proportion were symptomatic at presentation, were younger at, and were more likely to have transfusions • Among the children in this case series, rate of growth was below the 3rd percentile for age in 13%; Growth retardation was not related to the genotype; A few patients had mild dysmorphic facial features • No significant differences in iron overload between male and female subjects, or between subjects with deletional and nondeletional cases; increase in serum ferritin was correlated to age but not genotype
Fucharoen,S;Viprakasit,V. Hb H disease: clinical course and disease modifiers. 2009	Genotype-Phenotype correlation		• Proposed genetic modifiers: polymorphisms in the ATRX gene downregulating alpha-globin expression, and mechanisms related to altered proteolytic activity, apoptosis, red cell membrane integrity and the alpha hemoglobin specific cytosolic chaperone, alpha hemoglobin stabilizing protein. • Proposed environmental modifiers: Increased risk of hemolytic crisis in young patients because of underdeveloped immunity and increased susceptibility to infection, recurrent infectious episodes may lead ot hyperemic and active splenic function.

Galanello,R.;Aru,B.;Dessi,C.;Addis,M.;Paglietti,E.;Melis,M. A.;Cocco,S.;Massa,P.;Giagu,N.;Barella,S. Hb H disease in Sardinia: molecular, hematological and clinical aspects. 1992	Genotype-Phenotype correlation	153 individuals with Hb H disease Age range not stated (66 children and 87 adults)	• Six different Hb H disease genotypes represented; 130/153 deletional and 23/153 nondeletional • Deletional Hb H disease genotypes twice as frequent in females • Subjects with nondeletional genotypes more frequently showed liver and spleen enlargement, jaundice, bone changes, and a higher percentage of occasional hemotransfusion when compared to subjects with deletional Hb H genotypes • Children with deletional Hb H disease had an earlier presentation compared to children with nondeletional
George,E.;Ferguson,V.;Yakas,J.;Kronenberg,H.;Trent,R. J. A molecular marker associated with mild hemoglobin H disease. 1989	Genotype-Phenotype correlation	13 individuals with Hb H disease Age range: 1.3-72 years	• Patients with Hb H nondeletional genotypes (7/13) had the more severe disorder when comparing clinical parameters (necessity of blood transfusion, thalassemic facies) with the Hb H patients with deletional genotypes
Haider,M.;Adekile,A. Alpha-2-globin gene polyadenylation (AATAAA-->AATAAG) mutation in hemoglobin H disease among Kuwaitis. 2005	Genotype-Phenotype correlation	24 males and females with Hb H disease in Kuwait Age range: 6 month -12 years of age	• Hb H genotype involving the Poly A mutation is a mild phenotype • No serious complications and no need for regular blood transfusions; 8/24 (33.3%) had been transfused at least once; age(s) at transfusion(s) not given • Patients received daily folic acid supplement; otherwise no routine treatment was given
Hathirat,P.;Isarangkura,P.;Numhom,S.;Opasathien,P.;Chuansumrit,A Results of the splenectomy in children with thalassemia. 1989	Other natural history	197 children diagnosed with thalassemia/hemoglobinopathy who had a splenectomy 69/197 were followed for evaluation; 9 of which had Hb H disease Age range 5-9.5 years	• Patients followed at least 2 years before and after splenectomy • 1/9 patients with Hb H disease had an immediate post-operative complication (pneumonia) • Post splenectomy, hematocrit increased in patients with Hb H disease from 21% to 34% • Post splenectomy, no further transfusions were needed in patients with Hb H disease and liver size decreased significantly by the fourth year postoperatively • Within two years postsurgery, growth velocity in height kept up with presurgery levels

Isarangkura,P.;Chantarojanasiri,T.;Hathirat,P.;Pintadit,P.;Suwanjutha,S. Pulmonary and platelet function in mild form of Hb H disease. 1993	Genotype-Phenotype correlation	23 children with mild Hb H disease Age range 6-18 years ,mean of 11 years	• Mild form Hb H disease determined by "good" hematocrit level of 30-40% • Pulmonary function defect was noted in 48% with mild form of Hb H disease early in life • No arterial hypoxemia was observed; 5% mild platelet hyperaggregation • Cardiac and platelet levels were normal in most cases
Jetsrisuparb,A.;Sanchaisuriya,K.;Fucharoen,G.;Fucharoen,S.;Wiangnon,S.;Jetsrisuparb,C.;Sirijirachai,J.;Chansoong,K. Development of severe anemia during fever episodes in patients with hemoglobin E trait and hemoglobin H disease combinations. 2006	Genotype-Phenotype correlation	36 individuals with Hb H disease Hb H genotype -- ^{SEA}/Hb Pakse age range: 2-16 year, median 8 years of age Hb H Constant Spring age range: 1.25-61 years, median 10 years	• 7/36 subjects with Hb H genotype -- ^{SEA}/Hb Pakse and 29/36 with Hb H Constant Spring • Half of the pediatric cases with either genotype had growth retardation, even though most had normal birth weights • Most pediatric patients presented with anemic symptoms because of precipitating infections • Severe anemia occurred when patients had a high fever (39-41.2ºC) during viral infection, measles or urinary tract infection • Both genotypes (Hb Pakse and Hb Constant Spring) of Hb H disease had similar presentations clinically and ranged from mild to severe
Kanavakis,E.;Papassotiriou,I.;Karagiorga,M.;Vrettou,C.;Metaxotou-Mavrommati,A.;Stamoulakatou,A.;Kattamis,C.;Traeger-Synodinos,J. Phenotypic and molecular diversity of haemoglobin H disease: a Greek experience. 2000	Genotype-Phenotype correlation	75 individuals with Hb H disease 70/75 children under 18 years of age 5/75 adults over 18 years of age	• Patients with Hb H disease diagnosed following acute haemolysis or referred as anemic and followed for 5-10 years post diagnosis • 41 patients had a deletional genotype and none had severe clinical expression • Majority of patients with at least one nondeletional determinate had intermediate or severe clinical phenotypes • 4 patients with Hb Icaria mutation were severe with a need for regular blood transfusions from infancy • 3/4 of those patients splenectomized at 6-7 years of age • 1/4 of those patients at 24 years old and still needs monthly blood transfusions •

Laosombat, V. ;Viprakasit, V.; Chotsampancharoen, T.; Wongchanchailert, M.; Khodchawan, S.; Chinchang, W.; Sattayasevana, B. Clinical features and molecular analysis in Thai patients with Hb H disease. 2009	Genotype-Phenotype correlation	147 individuals with Hb H disease 20/147 diagnosed in the newborn period	• 83/147 with deletional Hb H disease and 64/147 with nondeletional • Newborns with nondeletional Hb H disease had more severe clinical features, larger proportion of pallor, higher MCV and MCH, higher proportion of Hb Bart's • Children with nondeletional Hb H disease had more severe anemia, hemolysis, hepatosplenomegaly, thalassemia facies and required more transfusions
Lorey,F.;Cunningham, G.;Vichinsky,E. P.;Lubin,B. H.;Witkowska,H. E.;Matsunaga,A.;Azimi,M.;Sherwin,J.;Eastman,J.;Farina,F.;Waye,J. S.;Chui,D. H. Universal newborn screening for Hb H disease in California. 2001	Screening*	1.32 million newborns screened through a heel prick blood sample in California from January 1998 to June 2000	• 89 newborns found to have Hb H disease confirmed through genotyping from January 1998 to June 2000 • 2/89 of the confirmed cases of Hb H disease were Hb H hydrops fetalis syndrome • Approximate birth prevalence based on this is 1 per 15,000 • Used HPLC and 25% Hb Bart's cut-off (as of August 1998); Hb Bart's range among newborns with deletional Hb H disease was 25-49% and among newborns with nondeletional Hb H disease with CS was 35-52%
Michlitsch,J.;Azimi,M.; Hoppe,C.;Walters,M. C.;Lubin,B.;Lorey,F.;Vichinsky,E. Newborn screening for hemoglobinopathies in California. 2009	Incidence*	530,000/year newborns screened through a heel prick blood sample in California between January 1998 – June 2006	• Incidence of Hb H disease was 9.0/100,000 • Incidence of Hb H with Constant Spring was 0.6/100,000

Origa,R.;Sollaino,M. C.;Giagu,N.;Barella,S. ;Campus,S.;Mandas,C .;Bina,P.;Perseu,L.;Ga lanello,R. Clinical and molecular analysis of haemoglobin H disease in Sardinia: haematological, obstetric and cardiac aspects in patients with different genotypes. 2007	Other natural history	251 Sardinian adults and children with Hb H disease Age range: 0-18 years (187 adults and 64 children)	• 86% had deletional Hb H disease; 14% had nondeletional Hb H disease • Mean age of diagnosis for deletional genotypes was 11+/- 12 years (range 0-73 years) and for other genotypes was 13 +/-17 years (range 0-59 years) • 41% of subjects were symptomatic at diagnosis • 5% of subjects with deletional Hb H disease had thalassemia-like facies vs. 73% with nondeletional ($p<0.01$) • 14.2% of subjects with deletional Hb H disease and 31.4% of the other genotypes had been transfused • Mild heart dilatation was found in 30% of the subjects, with an incidence of 6.6% in childhood and 32% in adulthood
Siala,H.;Ouali,F.;Mess aoud,T.;Bibi,A.;Fattou m,S. alpha-Thalassaemia in Tunisia: some epidemiological and molecular data. 2008	Incidence*	529 newborns' cord blood screened in one hospital in Tunis	• Hb Bart's detection on cord blood by cellulose acetate electrophoresis • 39/529 (7.38%) identified as Hb Bart's carriers at birth
van der Dijs,F. P.;van den Berg,G. A.;Schermer,J. G.;Muskiet,F. D.;Landman,H.;Muski et,F. A. Screening cord blood for hemoglobinopathies and thalassemia by HPLC. 1992	Incidence*	503 newborns' cord blood samples, representing 67.2% of all newborns born in Curacao from June - September 1990	• 64/122 (52.2%) of samples with an abnormal hemoglobin pattern had alpha thalassemia (heterozygous or homozygous)

Wongchanchailert,M.; Laosombat,V.;Maipang,M. Hemoglobin H disease in children. 1992	Other natural history	110 children with Hb H disease presenting to a hematology unit in Thailand	• 55/110 had Hb H disease with CS • 4 patients diagnosed in the newborn period (all four with anemia, one with jaundice); 9 diagnosed between 1 month and 1 year of age; 97 diagnosed between 1 year and 19 years of age • Two infants with Hb H with Constant Spring required blood transfusion • Growth retardation was detected in five of the infants • Approximately half of the children with Hb H disease with CS had their first blood transfusion before the age of five and nearly all before ten years • Approximately half of the populationhad fever or infection as the precipitating cause of anemia • Children with Hb H disease with Constant Spring more often had jaundice, hepatosplenomegaly, growth retardation and required blood transfusions

*Population-based study, remaining studies are from clinically identified populations

XIII. Table of case reports of four or fewer subjects

Authors, Primary	Title	Year	Periodical
Antonelou,M.;Papassideri,I. S.;Karababa,F.;Gyparaki,M.;Loutradi,A.;Margaritis,L. H.	A novel case of haemoglobin H disease associated with clinical and morphological characteristics of congenital dyserythropoietic anaemia type I.	2002	European journal of haematology
Au,W. Y.;Ma,E. S.;Kwong,Y. L.	Acute myeloid leukemia precipitated by dengue virus infection in a patient with hemoglobin H disease.	2001	Haematologica
Charoenkwan,P.;Sirichotiyakul,S.;Chanprapaph,P.;Tongprasert,F.;Taweephol,R.;Sae-Tung,R.;Sanguansermsri,T.	Anemia and hydrops in a fetus with homozygous hemoglobin constant spring.	2006	Journal of Pediatric Hematology/Oncology
Cheng,I. K.;Lu,H. B.;Wei,D. C.;Cheng,S. W.;Chan,C. Y.;Lee,F. C.	Influence of thalassemia on the response to recombinant human erythropoietin in dialysis patients.	1993	American Journal of Nephrology
Chim,C. S.;Chan,V.;Todd,D.	Hemosiderosis with diabetes mellitus in untransfused Hemoglobin H disease.	1998	American Journal of Hematology
Chinprasertsuk,S.;Wanachiwanawin,W.;Piankijagum,A.	Effect of pyrexia in the formation of intraerythrocytic inclusion bodies and vacuoles in haemolytic crisis of haemoglobin H disease.	1994	European journal of haematology
Curuk,M. A.	Hb H (beta4) disease in Cukurova, Southern Turkey.	2007	Hemoglobin
Curuk,M. A.;Dimovski,A. J.;Baysal,E.;Gu,L. H.;Kutlar,F.;Molchanova,T. P.;Webber,B. B.;Altay,C.;Gurgey,A.;Huisman,T. H.	Hb Adana or alpha 2(59)(E8)Gly-->Asp beta 2, a severely unstable alpha 1-globin variant, observed in combination with the -(alpha)20.5 Kb alpha-thal-1 deletion in two Turkish patients.	1993	American Journal of Hematology
Durmaz,A. A.;Akin,H.;Ekmekci,A. Y.;Onay,H.;Durmaz,B.;Cogulu,O.;Aydinok,Y.;Ozkinay,F.	A severe alpha thalassemia case compound heterozygous for Hb Adana in alpha1 gene and 20.5 kb double gene deletion.	2009	Journal of Pediatric Hematology/Oncology
Eng,B.;Patterson,M.;Walker,L.;Hoppe,C.;Azimi,M.;Lee,H.;Giordano,P. C.;Waye,J. S.	Three new alpha-thalassemia point mutations ascertained through newborn screening.	2006	Hemoglobin
Eng,B.;Walsh,R.;Walker,L.;Patterson,M.;Waye,J. S.	Characterization of a rare single alpha-globin gene deletion in a Chinese woman with Hb H disease.	2005	Hemoglobin
Fei,Y. J.;Liu,J. C.;Walker,E. L.,3rd;Huisman,T. H.	A new gene deletion involving the alpha 2-, alpha 1-, and theta 1-globin genes in a black family with Hb H disease.	1992	American Journal of Hematology
Fortina,P.;Parrella,T.;Sartore,M.;Gottardi,E.;Gabutti,V.;Delgrosso,K.;Mansfield,E.;Rappaport,E.;Schwartz,E.;Camaschella,C.	Interaction of rare illegitimate recombination event and a poly A addition site mutation resulting in a severe form of alpha thalassemia.	1994	Blood

Fucharoen,S.;Ayukarn,K.;Sanchaisuriya,K.;Fucharoen,G.	Atypical hemoglobin H disease in a Thai patient resulting from a combination of alpha-thalassemia 1 and hemoglobin Constant Spring with hemoglobin J Bangkok heterozygosity.	2001	European journal of haematology
Giordano,P. C.;Harteveld,C. L.;Bok,L. A.;van Delft,P.;Batelaan,D.;Beemer, F. A.;Bernini,L. F.	A complex haemoglobinopathy diagnosis in a family with both beta zero- and alpha (zero/+)-thalassaemia homozygosity.	1999	European Journal of Human Genetics
Giordano,P. C.;Harteveld,C. L.;Michiels,J. J.;Terpstra,W.;Batelaan,D.;van Delft,P.;Plug,R. J.;van der Wielen,M. J.;Losekoot,M.;Bernini,L. F.	Atypical HbH disease in a Surinamese patient resulting from a combination of the -SEA and -alpha 3.7 deletions with HbC heterozygosity.	1997	British journal of haematology
Gonzalez-Redondo,J. M.;Gilsanz,F.;Ricard,P.	Characterization of a new alpha-thalassemia-1 deletion in a Spanish family.	1989	Hemoglobin
Hall,G. W.;Thein,S. L.;Newland,A. C.;Chisholm,M.;Traeger-Synodinos,J.;Kanavakis,E.;Kattamis,C.;Higgs,D. R.	A base substitution (T-->C) in codon 29 of the alpha 2-globin gene causes alpha thalassaemia.	1993	British journal of haematology
Harteveld,C. L.;Beijer,C.;van Delft,P.;Zanardini,R.;Bernini,L. F.;Giordano,P. C.	alpha-thalassaemia as a result of a novel splice donor site mutation of the alpha1-globin gene.	2000	British journal of haematology
Harteveld,C. L.;Losekoot,M.;Haak,H.;Heister,G. A.;Giordano,P. C.;Bernini,L. F.	A novel polyadenylation signal mutation in the alpha 2-globin gene causing alpha thalassaemia.	1994	British journal of haematology
Harteveld,C. L.;van Delft,P.;Wijermans,P. W.;Kappers-Klunne,M. C.;Weegenaar,J.;Losekoot,M.;Giordano,P. C.	A novel 7.9 kb deletion causing alpha+-thalassaemia in two independent families of Indian origin.	2003	British journal of haematology
Huisman,T. H.;Gu,L. H.;Liu,J. C.;Fei,Y. J.;Walker,E. L.,3rd	Black alpha-thalassemia-1: partial characterization of an approximately 80 kb deletion which includes the zeta- and alpha-globin genes.	1993	Hemoglobin
Jay,G. D.;Renzi,F. P.	Evaluation of pulse oximetry in anemia from hemoglobin-H disease	1992	Annals of Emergency Medicine
Jolobe,O. M.	Haemoglobin-H disease presenting with microcytic hypochromic anaemia in an 81 year old woman.	1993	Postgraduate medical journal
Kanavakis,E.;Traeger-Synodinos,J.;Papasotiriou,I.;Vrettou,C.;Metaxotou-Mavromati,A.;Stamoulakatou,A.;Lagona,E.;Kattamis,C.	The interaction of alpha zero thalassaemia with Hb Icaria: three unusual cases of haemoglobinopathy H.	1996	British journal of haematology
Khan,S. N.;Butt,F. I.;Riazuddin,S.;Galanello,R.	Hb Sallanches [alpha104(G11)Cys-->Tyr]: a rare alpha2-globin chain variant found in the homozygous state in three members of a Pakistani family.	2000	Hemoglobin

Ko,T. M.;Hsieh,F. J.;Hsu,P. M.;Lee,T. Y.	Molecular characterization of severe alpha-thalassemias causing hydrops fetalis in Taiwan.	1991	American Journal of Medical Genetics
Ko,T. M.;Tseng,L. H.;Cheng,T. A.;Hwa,H. L.;Chang,Y. K.;Chuang,S. M.;Lee,T. Y.	Prevalence and molecular studies of thalassemia in five aboriginal groups in Taiwan.	1994	Journal of the Formosan Medical Association
Laosombat,V.;Fucharoen,S.;Wiriyasateinkul,A.	Interaction of the alpha2 polyadenylation signal mutation (AATAAA-->AATA--) and alpha0-thalassemia (--SEA), resulting in Hb H disease in a Thai patient.	2001	Hemoglobin
Laosombat,V.;Pornpatkul,M.;Wongchanchailert,M.;Worachat,K.;Wiriyasatienku,A.	The prevalence of hepatitis C virus antibodies in thalassemic patients in the south of Thailand.	1997	Southeast Asian Journal of Tropical Medicine & Public Health
Li,D.;Liao,C.;Li,J.	Misdiagnosis of Hb constant spring (alpha142, Term-->Gln, TAA-->CAA in alpha2) in a Hb H (beta4) disease child.	2007	Hemoglobin
Li,D.;Liao,C.;Xie,X.;Zhong,H.;Li,J.	Four cases of Hb Q-H disease found in Southern China.	2007	Hemoglobin
Li,Z.;Cai,S.;Rong,K.;Song,G.;Li,Y.;Guo,R.	The first compound heterozygosity for HKalpha alpha allele and Southeast Asian deletion allele.	2007	Clinical biochemistry
Lin,C. K.;Peng,H. W.;Ho,C. H.;Yung,C. H.	Iron overload in untransfused patients with hemoglobin H disease.	1990	Acta Haematologica
Ma,S. K.;Chan,A. Y.;Chiu,E. K.;Chan,L. C.	Haemoglobin H disease due to (--SEA) alpha-globin gene deletion and alpha2-codon 30 (DeltaGAG) mutation: a family study.	2001	Clinical & Laboratory Haematology
Mallouh,A. A.;Qudah,A.	An epidemic of aplastic crisis caused by human parvovirus B19.	1995	Pediatric Infectious Disease Journal
Nava,M. P.;Trejo,J. M.;Aguilar-Luna,C.;Barros-Nunez,P.;Chavez Mde,L.;Magana,M. T.;Perea,J.;Ibarra,B.	Molecular characterization of the--SEA alpha thalassemia allele in Mexican patients with HbH disease.	2006	Revista de Investigacion Clinica
Noguera,N. I.;Gonzalez,F. A.;Davoli,R. A.;Milani,A. C.;Villegas,A.	A novel splice acceptor site mutation of the alpha2-globin gene causing alpha-thalassemia.	2001	Hemoglobin
Peltier,J. Y.;Girault,D.;Debre,M.;Galacteros,F.;Fischer,A.;Girot,R.	Donor for BMT with haemoglobin H disease.	1993	Bone marrow transplantation
Romao,L.;Olim,G.;Martins,M. C.;Rodrigues,V.;Coutinho-Gomes,M. P.;Lavinha,J.	Unusual molecular basis of Hb H disease in the Azores Islands, Portugal.	1990	Hemoglobin
Safaya,S.;Trauber,D. R.;Rieder,R. F.	Studies on the in vitro and in vivo expression of a dysfunctional alpha-globin gene.	1992	American Journal of Hematology
Shalmon,L.;Kirschmann,C.;Zaizov,R.	A new deletional alpha-thalassemia detected in Yemenites with hemoglobin H disease.	1994	American Journal of Hematology

Smetanina,N. S.;Leonova,J. Y.;Levy,N.;Huisman,T. H.	The alpha / beta and alpha 2 / alpha 1-globin mRNA ratios in different forms of alpha-thalassemia.	1996	Biochimica et biophysica acta
Stanley,P.;Shen,T. C.	Partial embolization of the spleen in patients with thalassemia.	1995	Journal of Vascular & Interventional Radiology
Sura,T.;Trachoo,O.;Viprakasit,V.;Vathesatogkit,P.;Tunteeratum,A.;Busabaratana,M.;Wisedpanichkij,R.;Isarangkura,P.	Hemoglobin H disease induced by the common SEA deletion and the rare hemoglobin Quong Sze in a Thai female: longitudinal clinical course, molecular characterization, and development of a PCR/RFLP-based detection method.	2007	Annals of Hematology
Tan,J. A.;Kok,J. L.;Tan,K. L.;Wee,Y. C.;George,E.	Thalassemia intermedia in HbH-CS disease with compound heterozygosity for beta-thalassemia: challenges in hemoglobin analysis and clinical diagnosis.	2009	Genes & genetic systems
Tan,J. R.;Li,W. J.;Ma,J. Y.;Mo,Q. H.;Li,L. Y.;Jia,S. Q.;Lao,X. W.;Li,L. Y.;He,R. Q.;Xu,X. M.	Molecular epidemiological study of alpha- and beta-thalassemia in Sihui city.	2003	Di Yi Junyi Daxue Xuebao
Traeger-Synodinos,J.;Harteveld,C. L.;Kanavakis,E.;Giordano,P. C.;Kattamis,C.;Bernini,L. F.	Hb Aghia Sophia [alpha62(E11)Val-->0 (alpha1)], an "in-frame" deletion causing alpha-thalassemia.	1999	Hemoglobin
Viprakasit,V.;Chinchang,W.;Glomglao,W.;Tanphaichitr,V. S.	A rare association of alphaO-thalassemia (--SEA) and an initiation codon mutation (ATG-->A-G) of the alpha2 gene causes Hb H disease in Thailand.	2005	Hemoglobin
Viprakasit,V.;Green,S.;Height,S.;Ayyub,H.;Higgs,D. R.	Hb H hydrops fetalis syndrome associated with the interaction of two common determinants of alpha thalassaemia (--MED/(alpha)TSaudi(alpha)).	2002	British journal of haematology
Viprakasit,V.;Tanphaichitr,V. S.	Unusual phenotype of hemoglobin EE with hemoglobin H disease: a pitfall in clinical diagnosis and genetic counseling.	2004	Journal of Pediatrics
Viprakasit,V.;Tanphaichitr,V. S.	Compound heterozygosity for alpha0-thalassemia (- -THAI) and Hb constant spring causes severe Hb H disease.	2002	Hemoglobin
Viprakasit,V.;Tanphaichitr,V. S.;Veerakul,G.;Chinchang,W.;Petrarat,S.;Pung-Amritt,P.;Higgs,D. R.	Co-inheritance of Hb Pak Num Po, a novel alpha1 gene mutation, and alpha0 thalassemia associated with transfusion-dependent Hb H disease.	2004	American Journal of Hematology
Wang,J. Y.;Liang,J. C.;Peng,H. W.	Structural analysis of the alpha-globin gene cluster in two Chinese families with alpha-thalassemias.	1989	Chung Hua i Hsueh Tsa Chih - Chinese Medical Journal
Wang,L. Y.;Liang,D. C.;Liu,H. C.;Chang,F. C.;Wang,C. L.;Chan,Y. S.;Lin,M.	Alloimmunization among patients with transfusion-dependent thalassemia in Taiwan.	2006	Transfusion Medicine
Waye,J. S.;Eng,B.;Patterson,M.;Chui,D. H.;Olivieri,N. F.	Identification of a novel termination codon mutation (TAA-->TAT, Term-->Tyr) in the alpha 2 globin gene of a Laotian girl with hemoglobin H disease.	1994	Blood

Wenning,M. R.;Harteveld,C. L.;Giordano,P. C.;Kimura,E. M.;Saad,S. T.;Costa,F. F.;Sonati,M. F.	Hemoglobin H disease resulting from the association of the - alpha 3.7 rightward deletion and the (alpha alpha)MM deletion in a Brazilian patient.	2002	European journal of haematology
Wickramasinghe,S. N.;Lee,M. J.;Furukawa,T.;Eguchi,M.;Reid,C. D.	Composition of the intra-erythroblastic precipitates in thalassaemia and congenital dyserythropoietic anaemia (CDA): identification of a new type of CDA with intra-erythroblastic precipitates not reacting with monoclonal antibodies to alpha- and beta-glob	1996	British journal of haematology
Wu,J. H.;Shih,L. Y.;Kuo,T. T.;Lan,R. S.	Intrathoracic extramedullary hematopoietic tumor in hemoglobin H disease.	1992	American Journal of Hematology
Zago,M. A.;Paco-Larson,M. L.	Hemoglobin H disease caused by two gene deletions.	1989	Brazilian Journal of Medical & Biological Research
Zeng,F. Y.;Fucharoen,S.;Huang,S. Z.;Rodgers,G. P.	Hb Q-Thailand [alpha 74(EF3)Asp-->His]: gene organization, molecular structure, and DNA diagnosis.	1992	Hemoglobin
Zhao,J. B.;Zhao,L.;Fei,Y. J.;Liu,J. C.;Huisman,T. H.	A novel alpha-thalassemia-2 (-2.7-kb) observed in a Chinese patient with Hb H disease.	1991	American Journal of Hematology
Zhao,Y.;Qu,L.;Xu,X.	A very rare patient with states for HbH disease and congenital heart disease.	2001	Haematologica