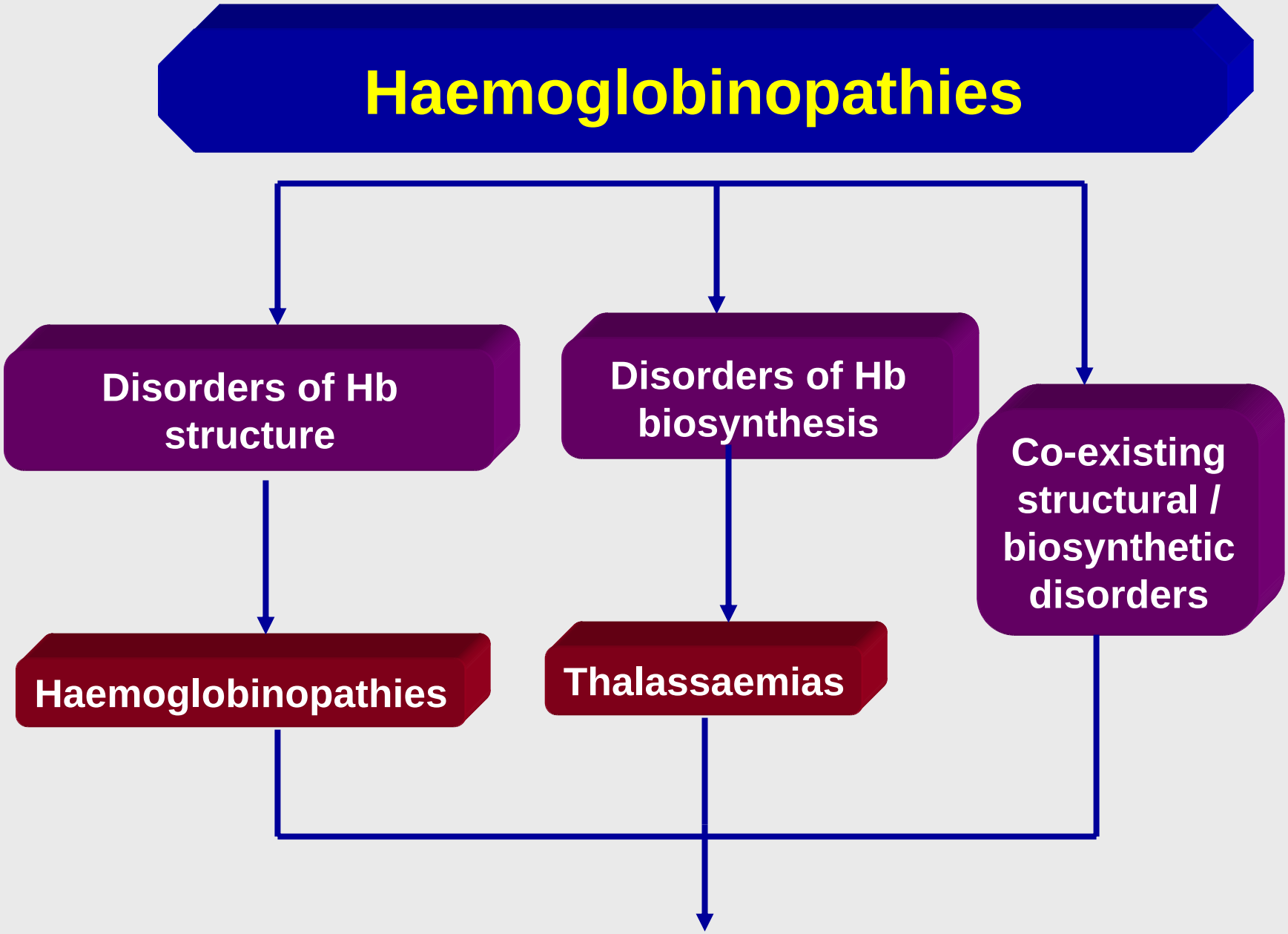
An Overview of Haemoglobinopathies in Saudi Arabia

Arjumand S.Warsy

Haemoglobinopathies

Genetic Disorders affecting Haemoglobin



Constitute a major health problem in several populations of the world

(particularly those in malaria endemic region)

Haemoglobinopathies

- Most frequently encountered genetic disorders in the World.
- Result from mutations in or around the globin genes of haemoglobin.
- Produce haemoglobin variants with altered structure and function or result in decreased amount of Hb.
- Altered functions include:
  - Reduced solubility
  - Altered oxygen affinity- increased or decreased
  - Reduced stability
  - Methaemoglobin formation
- Mostly autosomal recessive inheritance.

Haemoglobinopathies in Saudi Arabia

Presentation Outline

- History
- Haemoglobinopathies identified in Saudi Arabia
- Frequency of different haemoglobinopathies
- Clinical Aspects
- Molecular Studies
- Control and Prevention Programmes

Haemoglobinopathies in Saudi Arabia- Historical

- HbS first reported in Eastern Province by Lehmann et al (1963).
- Gelpi reported a mild SCD in 1965.
- Weatherall et al in 1969 identified α-thalassaemia in Saudi population and related related mild SCD to the presence of associated α-thalassaemia in Eastern Province.
- During 1970's HbS was identified in several areas in Saudi Arabia and three major foci of HbS gene were identified by El-Hazmi et al and other workers. Hb Riyadh discovered in Riyadh family.
- During 1980's Awamy et al initiated new born screening in the EP. Studied natural history of SCD and identified abnormal Hb's.
- During the 1980's HbO-Arab, Hb Setif, Hb F-Dammam & others, the α- and β-thalassaemias were identified in many regions of SA.
- Several screening studies during 1980- 2004 have clarified the picture and have shed light on distribution, molecular defects and the natural history of these genes in Saudis.

  (El-Hazmi et al., Warsy et al; Al Awamy et al., Sejeny et al. Padmos et al.)

Types of Haemoglobin abnormalities in Saudi Arabia

Haemoglobin variants identified in Saudi Arabia

Structural Variants*

- HbS*
- HbC
- HbE
- HbG
- HbD
- HbJ
- Hb Riyadh
- HbO-Arab
- HbF Dammam
- Hb Handsworth
- Hb Setif

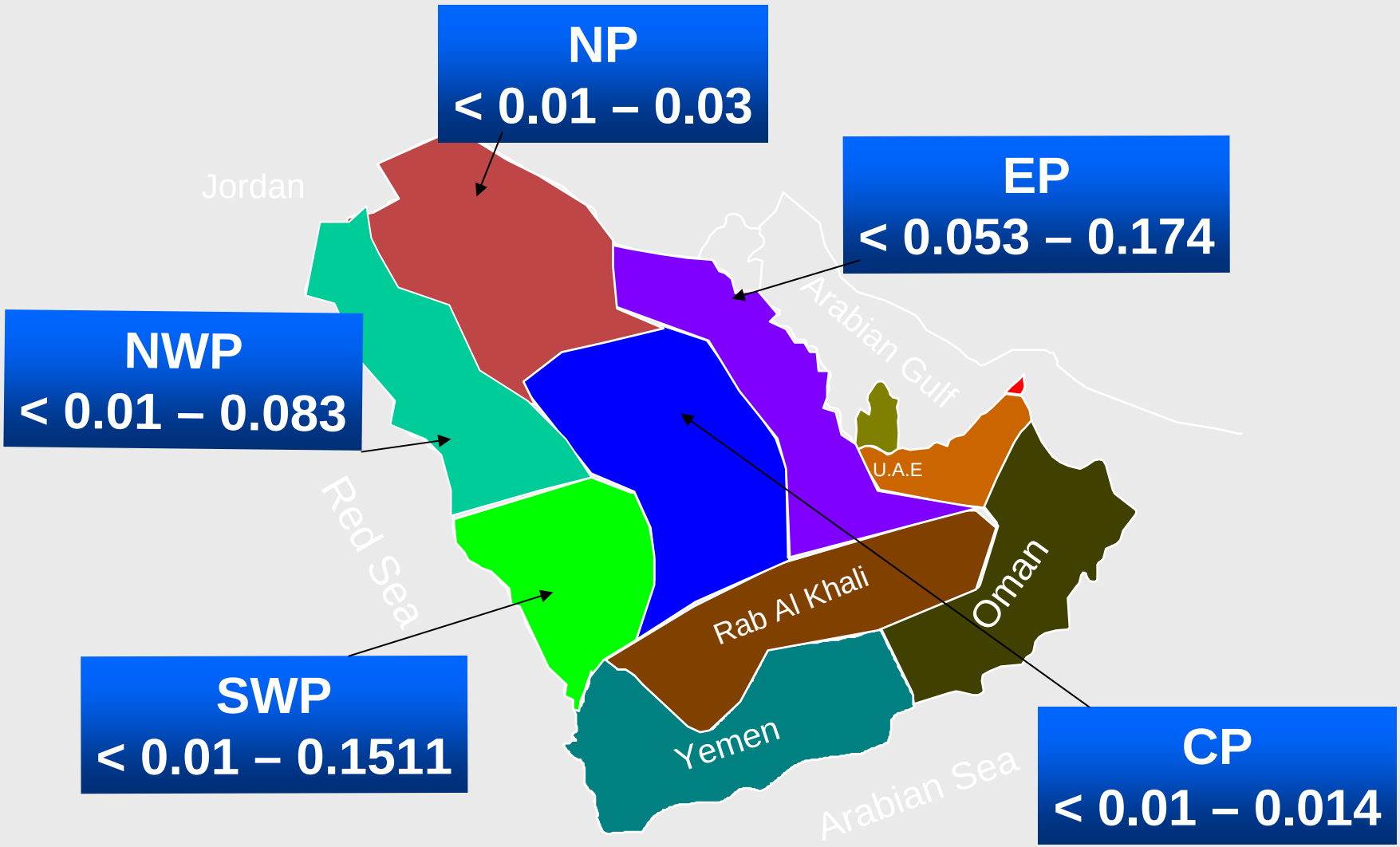
Biosynthetic variants

Causing

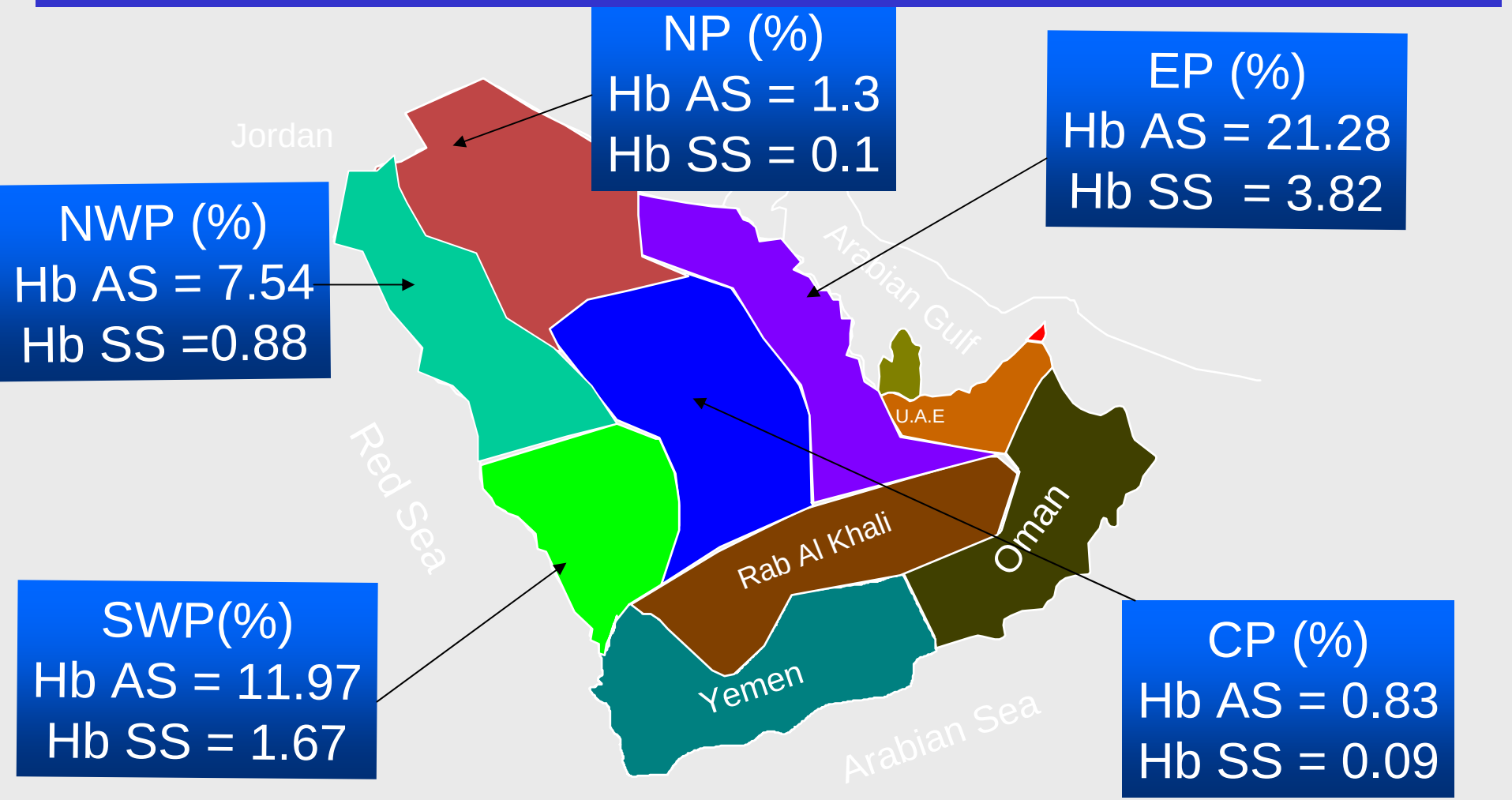
- α-Thalassaemia
- β-Thalassaemia

- * Hb S was identified in all areas at a variable frequency.
- Three main foci in EP, SWP and NWP.
- Other structural variants were sporadic cases.

Hb S Gene Frequency in Saudi Arabia



Prevalence of Hb AS and Hb SS in different Regions of Saudi Arabia



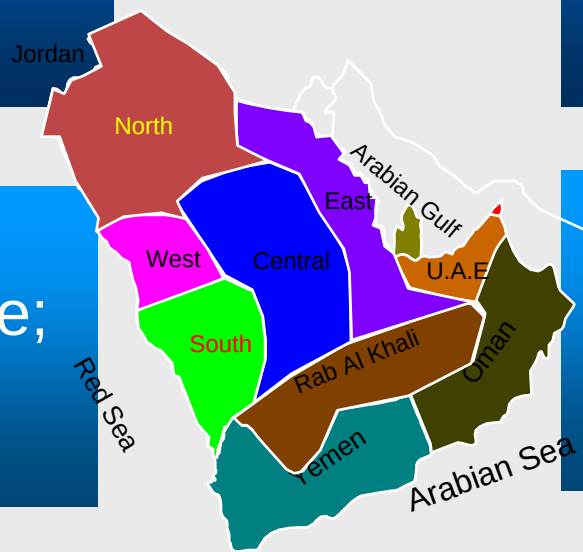
Clinical Presentation of SCD in Saudi Arabia

Variable-Two major forms

Severe Presentation

Mainly in the Western province;

Also some in EP



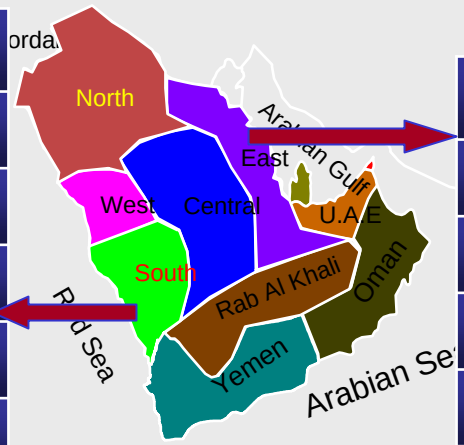
Mild (benign) Presentation

Mainly in the Eastern province

Two forms of SCD in Saudi Arabia - Haematological Parameters

Severe SCD

Parameter	mean±SD
RBC(x10^{12}/l)	2.6 ±0.6*
Hb (g/dl)	8.3 ±1.1*
PCV (l/l)	0.22 ±0.04*
MCV (fl)	87.6 ±7.9*
MCH (pg)	31..7 ±4.8
MCHC (g/dl)	36.9 ±2.81
HbA_2 (%)	3.0 ±0.75*
HbF (%)	9.9 ±6.4



Mild SCD

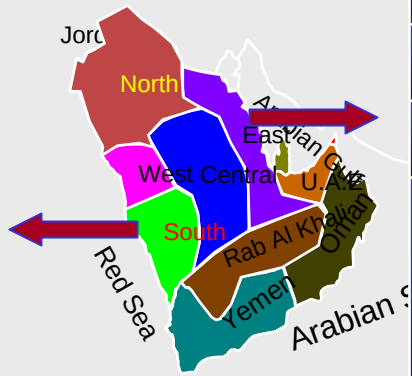
Parameter	mean±SD
RBC(x10^{12}/l)	4.0 ±0.74*
Hb (g/dl)	10.5 ±2.0*
PCV (l/l)	0.3 ±0.05*
MCV (fl)	74.7 ±9.3*
MCH (pg)	26.2 ±4.4
MCHC (g/dl)	34.7 ±3.1
HbA_2 (%)	2.9 ±0.48*
HbF (%)	11.1 ±5.7

(* p< 0.05)

Two forms of SCD in Saudi Arabia – Clinical Presentation

Severe SCD

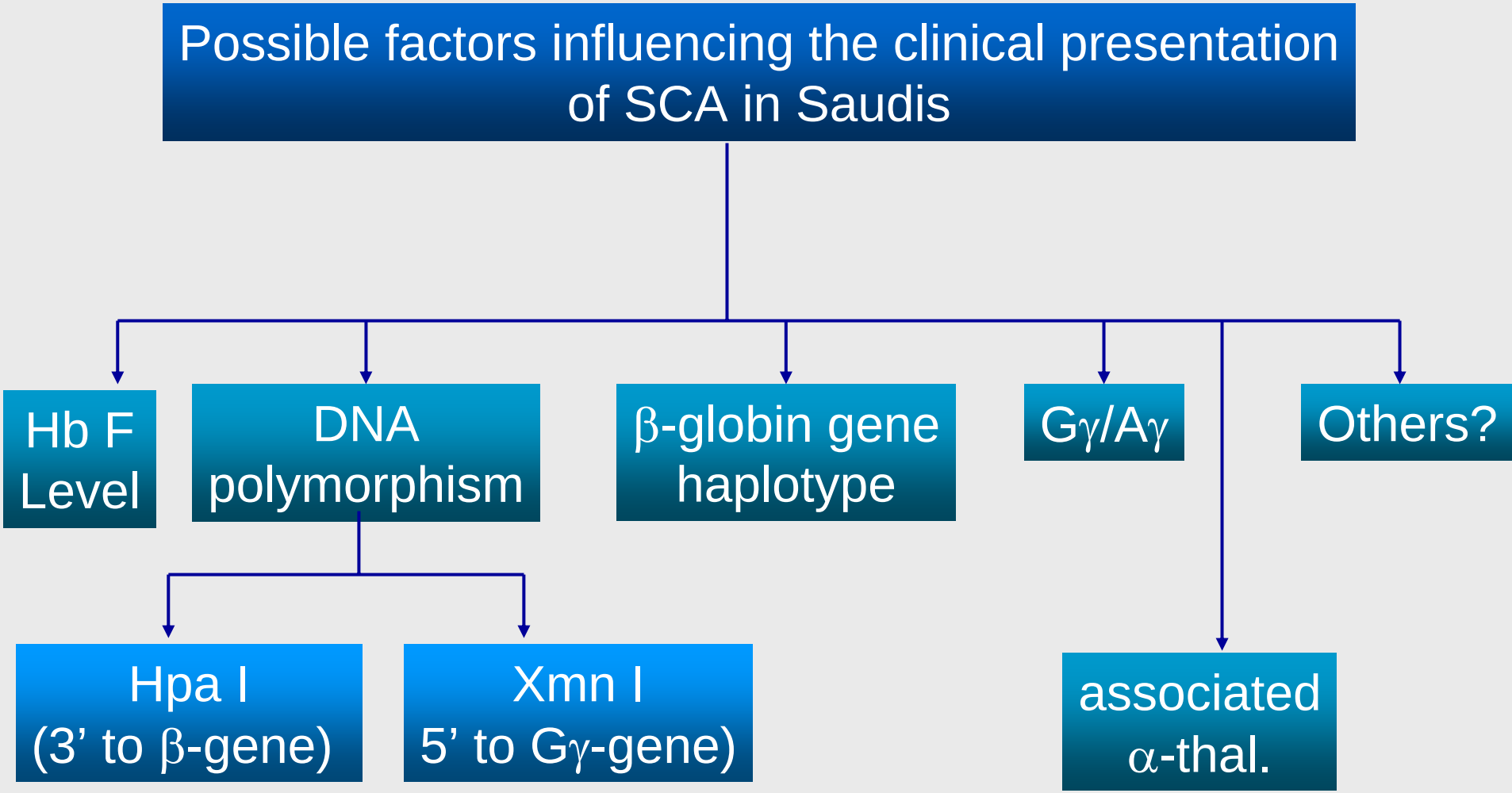
Sign/Symptoms	(%)
Anaemia	100
Jaundice	13.2
Splenomegaly	77.4
Hepatomegaly	66.0
Hand/foot Synd.	33.9
Crises	
-Vasoocclusive	75.5
-Infective	9.4
-Haemolytic	18.9
Hospitalization	96.2
Blood Transfusion	84.9
-2-5 times/year	43.4



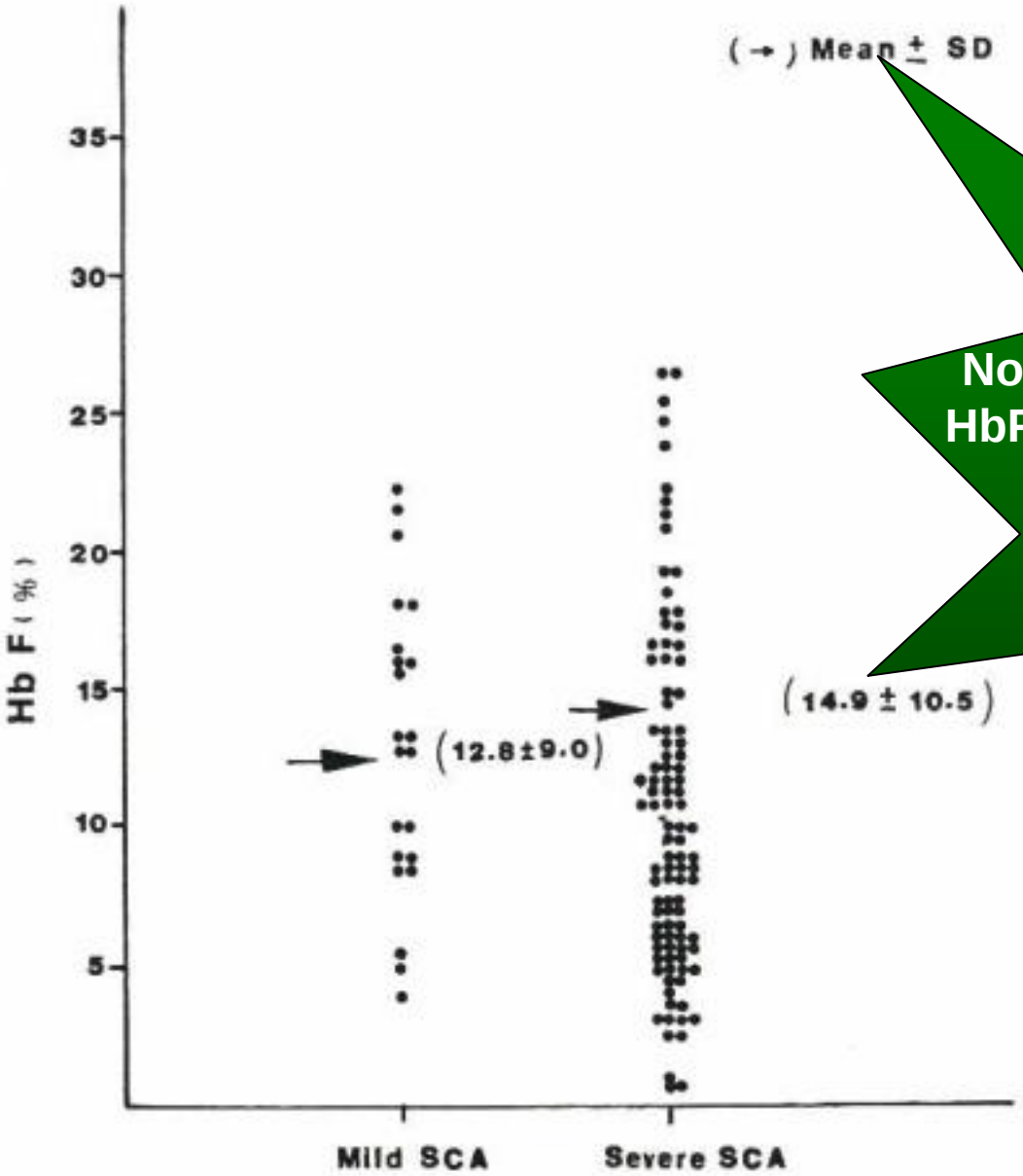
Mild SCD

Sign/Symptoms	(%)
Anaemia	56.1
Jaundice	17.1
Splenomegaly	31.7
Hepatomegaly	36.6
Hand/foot Synd.	Nil
Crises	
-Vasoocclusive	Rare
-Infective	Rare
-Haemolytic	Rare
Hospitalization	41.5
Blood Transfusion	48.8
-2-5 times/year	---

POSSIBLE MODULATING FACTORS OF SCA?

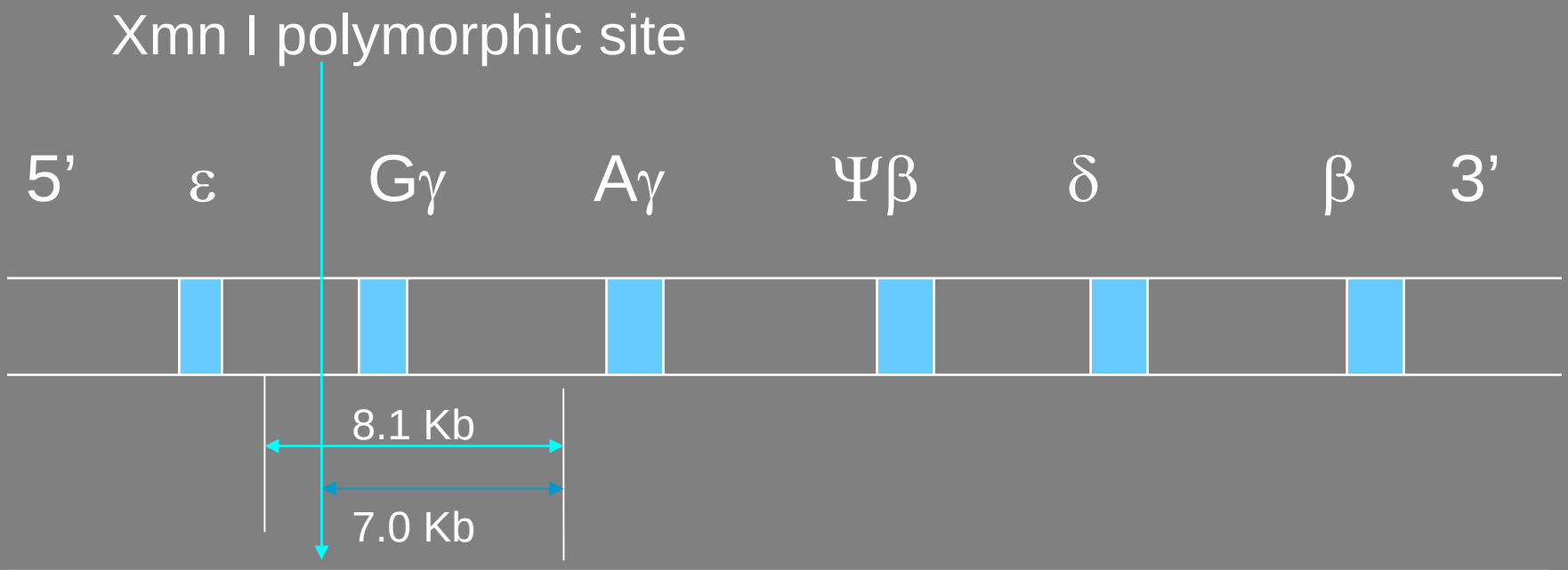


Hb F level in Saudi SCA patients



No major difference seen in the HbF level in patients with mild or severe Disease in Saudi population

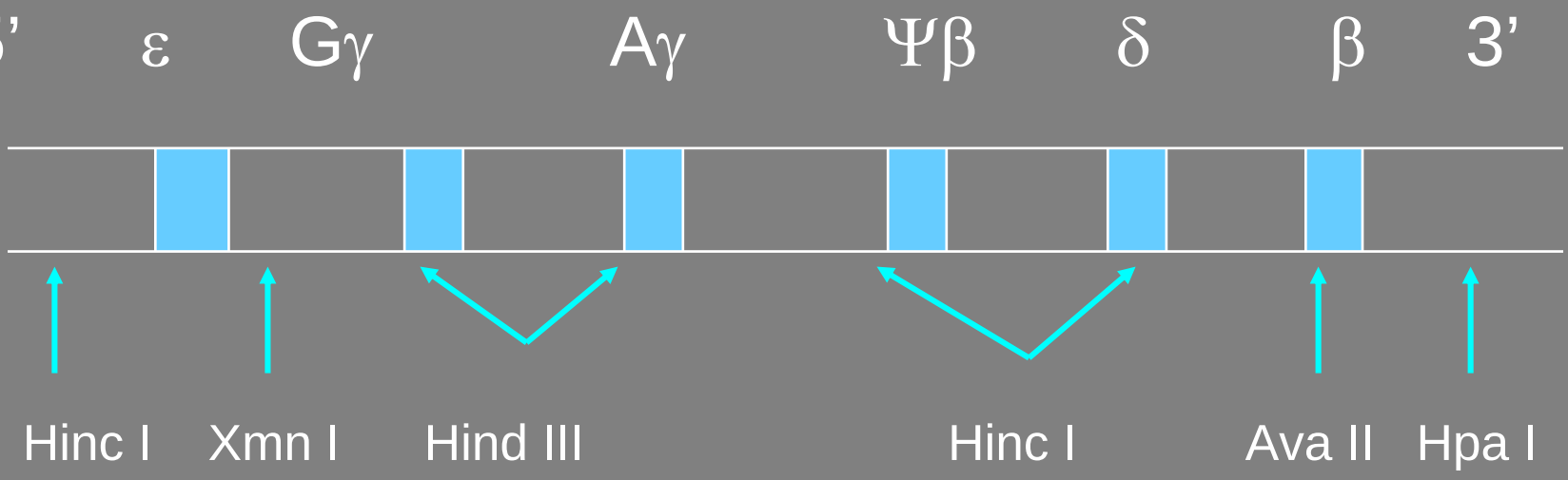
Xmn I polymorphic site in Saudi SCA patients with mild and severe SCA



Xmn I Polymorphic	Fragment size (Kb)	Frequency (%)		P
		Mild SCA	Severe SCA	
Present (+)	7.0	86.54	2.86	<0.0001
Absent (-)	8.1	13.46	97.32	<0.0001

INFLUENCE OF β-GLOBIN GENE HAPLOTYPES ON CLINICAL PRESENTATION OF SCA

- **Two major haplotypes identified in Saudi SCA patients are the Saudi/Indian haplotype and the Benin haplotype.**



Haplotypes								
Saudi	+	+	-	+	+	+	+	+
Indian (31)								
Benin (19)	-	-	-	-	+	+	+	-

FREQUENCY OF THE DIFFERENT HAPLOTYPES IN SAUDI SCD PATIENTS

Frequency			p
Haplotype	Mild SCA	Severe SCA	
Benin	22.7	66.45	< 0.001
Saudi-Indian	72.6	0.75	< 0.001
Others	4.5	32.8	< 0.001

AFFECTS OF ASSOCIATED α-THAL. IN SAUDI SCA PATIENTS (1)

(A) Clinical Presentation

Parameters	SCA (%) (Without α-Thal.)	SCA (%) (With α-Thal.)
Severe anaemia	56	30
Pain in bone and joints	90	70
Abdominal pain	64	29
Hepatomegaly	36	-
General weakness	90	86
Jaundice	18	14
Oedema feet	9	14
Blood Transfusion	73	30
Osteomyelitis	45	30

AFFECTS OF ASSOCIATED α-THAL. IN SAUDI SCA PATIENTS (2)

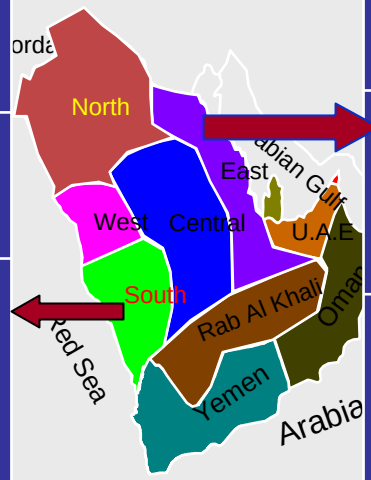
(B) Haematological Presentation

Parameter	SCA (Without α-Thal.)	SCA (-α/αα)	SCA (-α/-α)
RBC ($x10^{12}$/I)	3.3 1.15*	3.84 0.61*	4.35 1.01*
Hb (g/dl)	10.0 3.51	10.84 1.6	10.0 1.9
PCV (I/I)	0.27 0.08*	0.30 0.03*	0.31 0.04*
MCV (fl)	82.8 2.0*	79.8 6.90	72.5 5.4
MCH (pg)	30.3 1.5*	28.3 2.7*	25.0 3.6*
Hb A_2 (%)	2.8 0.13*	2.5 0.26*	3.25 0.6*
Hb F (%)	15.25 2.56	14.14 6.24	7.6 4.2*

Associated α-thal. ameliorates SCA and decreases major complications (*p <0.05)

Genetic differences in the two major forms of Sickle cell Disease in Saudi Arabia

Differences at gene level	Severe SCD
β-globin gene haplotypes	Mainly Benin
Xmn 1 polymorphic site 5’ to γ- globin gene	Absent in > 90 %
Hpa 1 polymorphic site 5’ to β-globin gene	Absent in > 90 %
G γ /A γ Ratio	< 0.8
HbF level	Low to high



Differences at gene level	Mild SCD
β-globin gene haplotypes	Mainly Saudi-Indian
Xmn 1 polymorphic site 5’ to γ- globin gene	Present in > 90 %
Hpa 1 polymorphic site 5’ to β-globin gene	Present in > 90 %
G γ /A γ Ratio	> 1.2
HbF level	Low to high

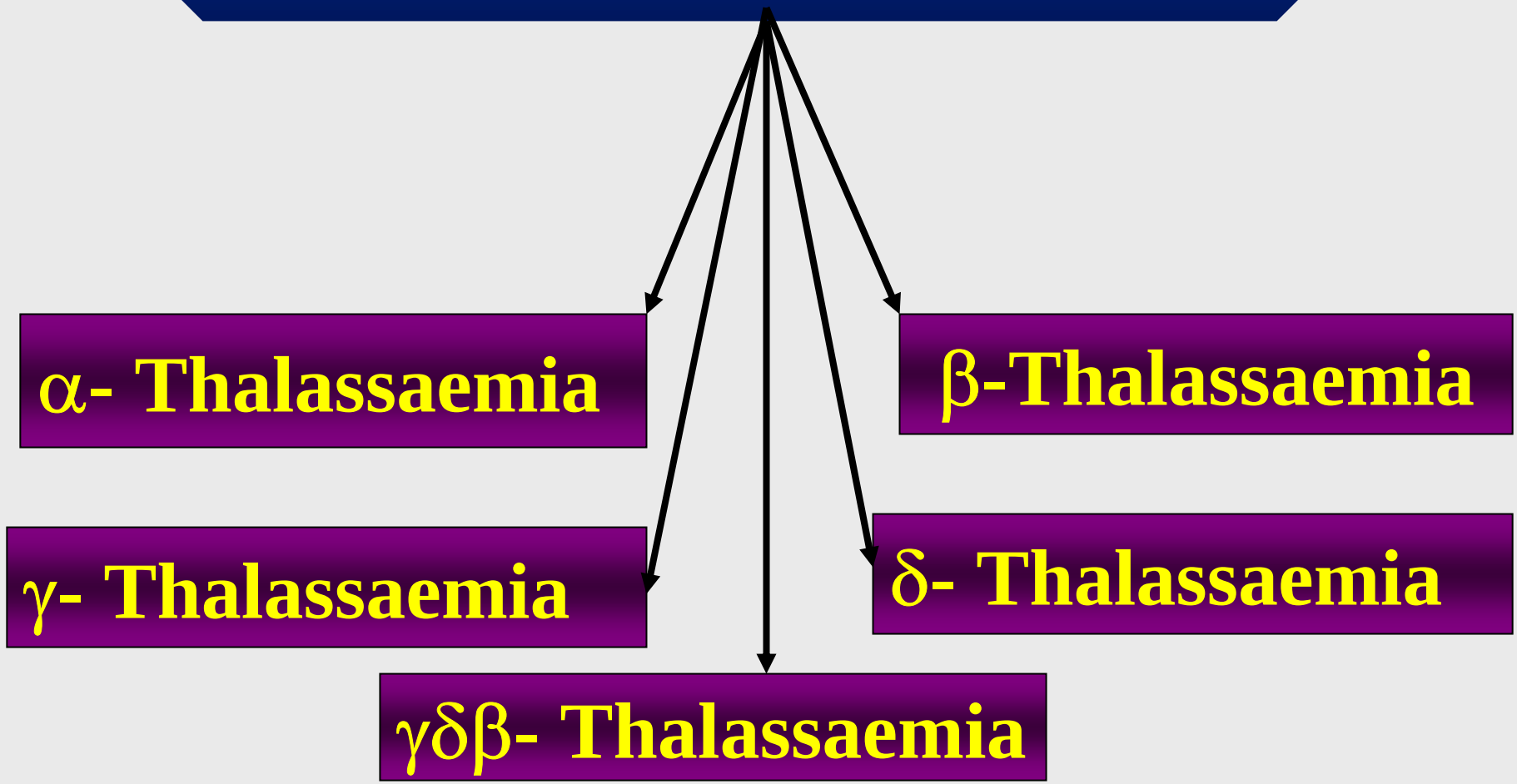
The Thalassaemias

Genetic disorders resulting from decreased synthesis of globin chains of haemoglobin.

The Thalassaemias

- One of the most frequently encountered BGD.
- Mutations in or around the globin genes results in **decreased production** of one or more of the globin chains.
- Thus producing an **imbalance** in the relative amounts of the α- and non α -chains. Hence, an altered α/non- α ratio.
- A few rare Hb variants are effectively synthesized but are highly unstable, and thus cause thalassaemias
- As a consequences of thalassaemias , there is an excess production of the other chains, and a decreased over all haemoglobin synthesis.

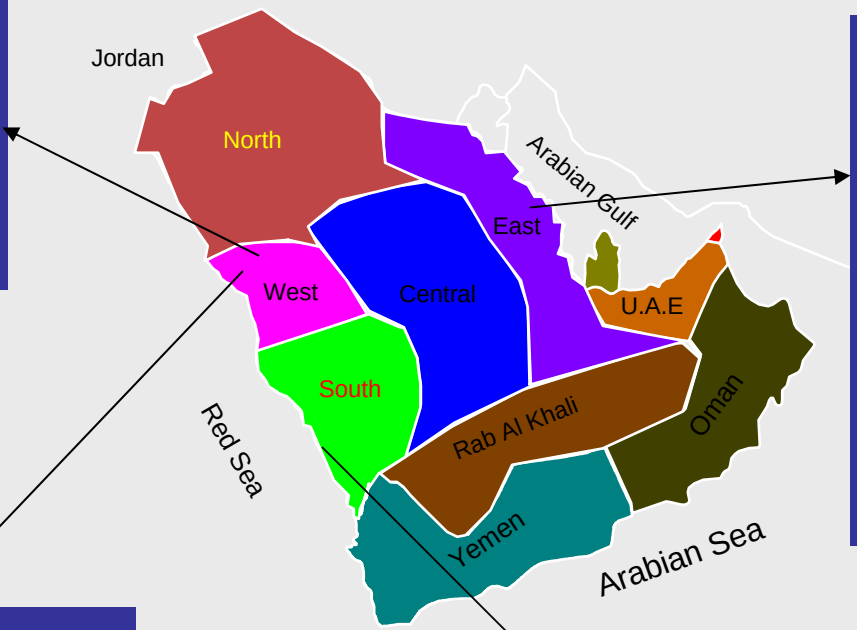
Types of Thalassaemias



Frequency of deletion α–thalassaemia mutations in Saudi Arabia

Al-Ula

–α/αα	12.1
–α/–α	0.5
––/αα	0.1



Al-Hafouf

–α/αα	36.7
–α/–α	19.0
––/αα	2.2
$-\alpha^T/\alpha^T\alpha$	?*
$-\alpha/-\alpha^T$	?*

Khaiber

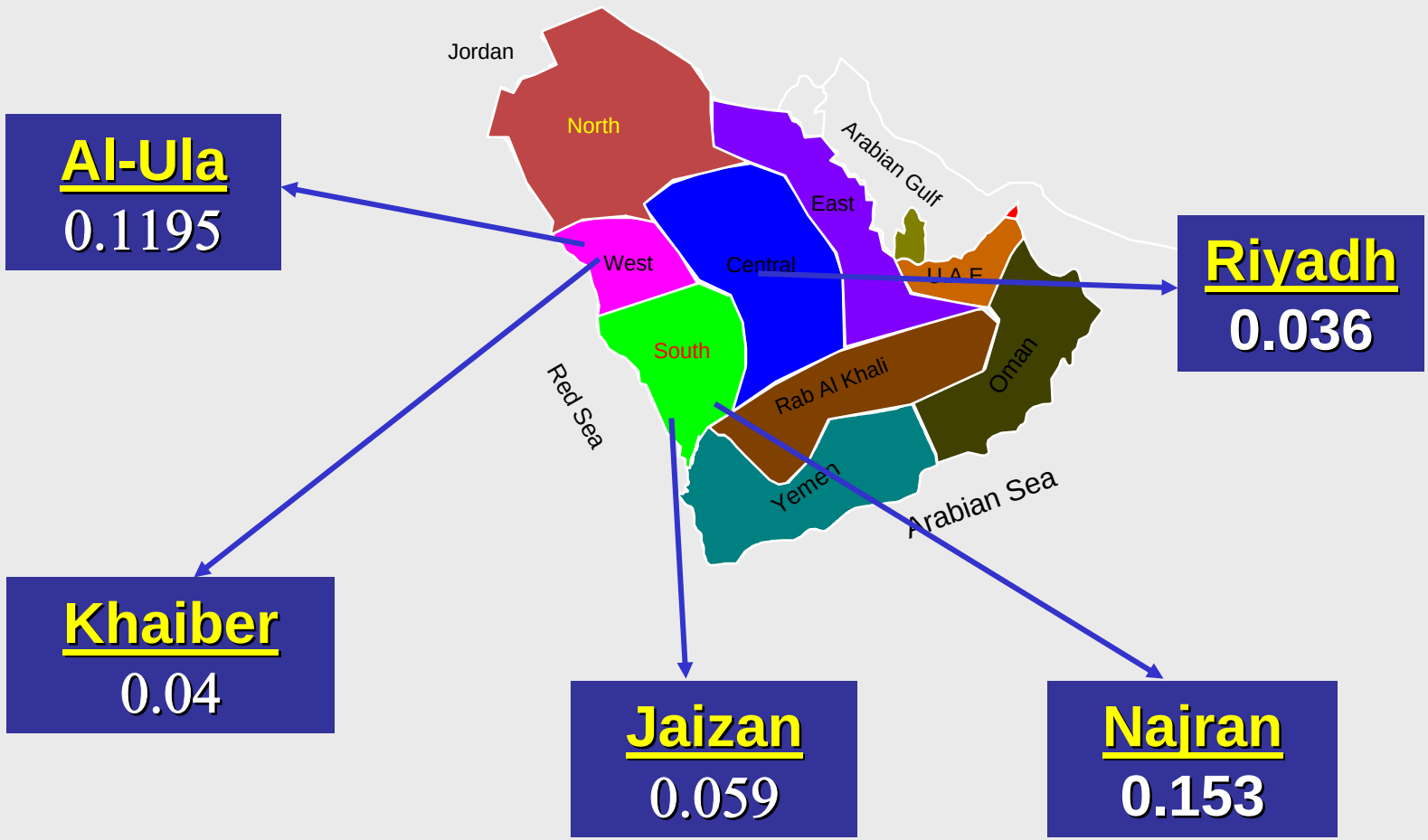
–α/αα	14.7
–α/–α	4.9
––/αα	< 1

Jaizan

–α/αα	41.8
–α/–α	12.4
––/αα	< 1

*Thein et al 1988

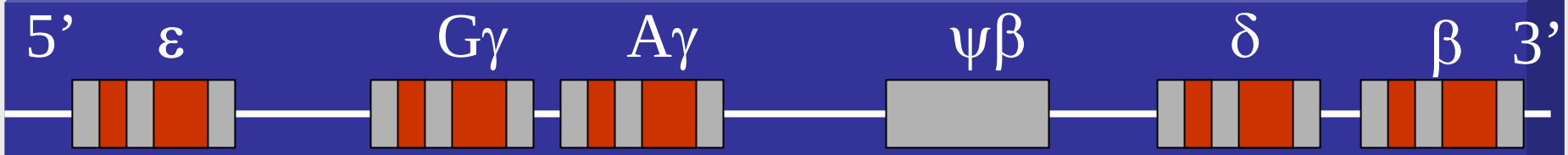
Frequency(%) of β-Thalassaemia in Saudi Arabia



Frequency of the different mutations identified in Saudi β-Thalassaemia patients

Mutations	Number	Percent
IVS-I-110	26	27.4
IVS-I-5	26	27.4
CD-39	27	14.5
IVS-I-3'end	0	12.9
IVS-II-1	30	16.1
CD6	8	4.3
CD 8/9	2	1.07
IVS-I-1	1	0.5
IVS-I-6	1	0.5
CD 44	2	1.07
CD 5	4	2.14
CD 26	1	0.5
Total:	95 %	

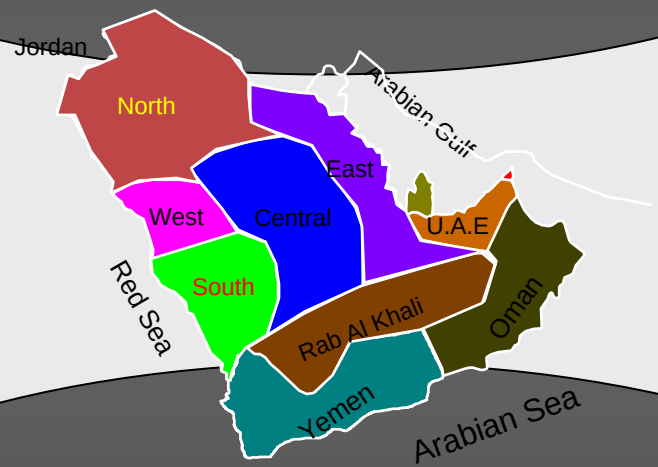
Extensive Polymorphism in β-globin gene in Saudis



- Saudis have extensive Polymorphisms in the β-globin gene and the β-globin gene cluster.
- In a group of β-thalassaemia patients, 23.1% had five polymorphic sites each.
- These were: IVSII 16, IVSII 74, CD2, IVSII 81and IVSII 666.

Control and Prevention Programmes

Provision of Genetic Services



National Working Group for Blood Genetic Disorders

THE NATIONAL WORKING GROUP FOR BLOOD GENETIC DISORDERS

- Conceived in 1990 in collaboration with Ministry of Health, Saudi Arabia
- At College of Medicine, King Saud University, Riyadh, Saudi Arabia.
- Members were drawn from different regions of Saudi Arabia:
  - Ministry of Health hospitals and Health Centres.
  - Other hospitals both governmental and private.

MEMBERS OF NATIONAL WORKING GROUP

- Physicians
- Scientists
- Laboratory Technologists
- Social Workers

  With direct or indirect involvement with patients suffering from blood genetic disorders.

NWG RESPONSIBILITIES

- Multidisciplinary approach to patient care
- Development of awareness and educating the public health care personnels
- Multidisciplinary approach towards control and prevention

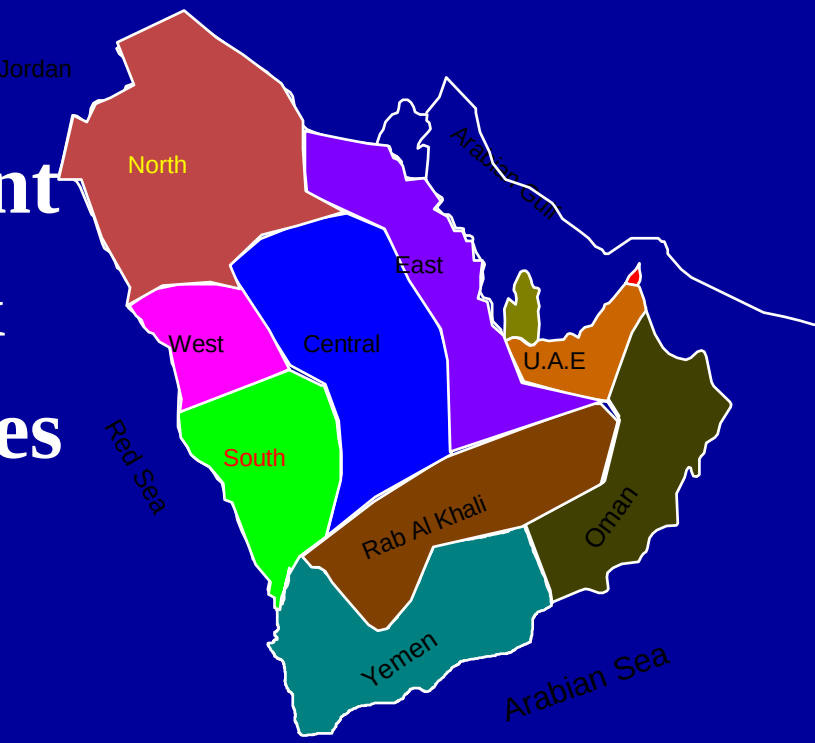
INITIATION OF THE NATIONAL PROGRAM

- ***Formulation of National Committee at the Ministry of Health.***
- ***Responsibilities:***
  - **Assessing the epidemiological situation.**
  - **Evaluating health care.**
  - **Formulating policies.**
  - **Planning a national program for control and prevention. of genetic diseases.**
  - **Adopting a mechanism for coordination.**
  - **Assessment and revision of the plan of work as necessary**
- ***Members of the National Committee***
  - **Expert clinicians from different parts of the country and different medical disciplines.**

Premarital Screening Programmes in Saudi Arabia

- **Approved in 2002 by the Royal Cabinet.**

- **For screening of frequent blood genetic diseases & certain infectious diseases**



Royal Decree About Premarital Examination

The Royal Decree no 3 Issued at 7/11/1424 stated:

"For Screening of genetic diseases , the premarital examination for both couples is recommended. A certificate of examination to be issued before wedding. The results of examination to be explained to the concerned but not to prevent marriage."

Approved Premarital Screening Programme

- Screening of the prospective couples for:

  - **The Thalaessemias**
  - **Sickle cell anaemia**


Thank you for Listening