Phenotypic Variability of SCD in Gulf Arabs

Kunle Adekile
Professor
Department of Pediatrics
Kuwait University

4th Global Congress
Sickle Cell Disease
In-person and on-line Congress
JUNE 16-18 2022
Paris, Novotel Tour Eiffel

Outline

- Introduction
- Kuwait as an example of uniform haplotype distribution
- HbF influence on phenotype
  - Comparison of Kuwait and Oman
- Stroke and TCD across the Gulf
- HbF Modifiers among Kuwaiti patients
- Conclusions

SCD in the Arabian Peninsula

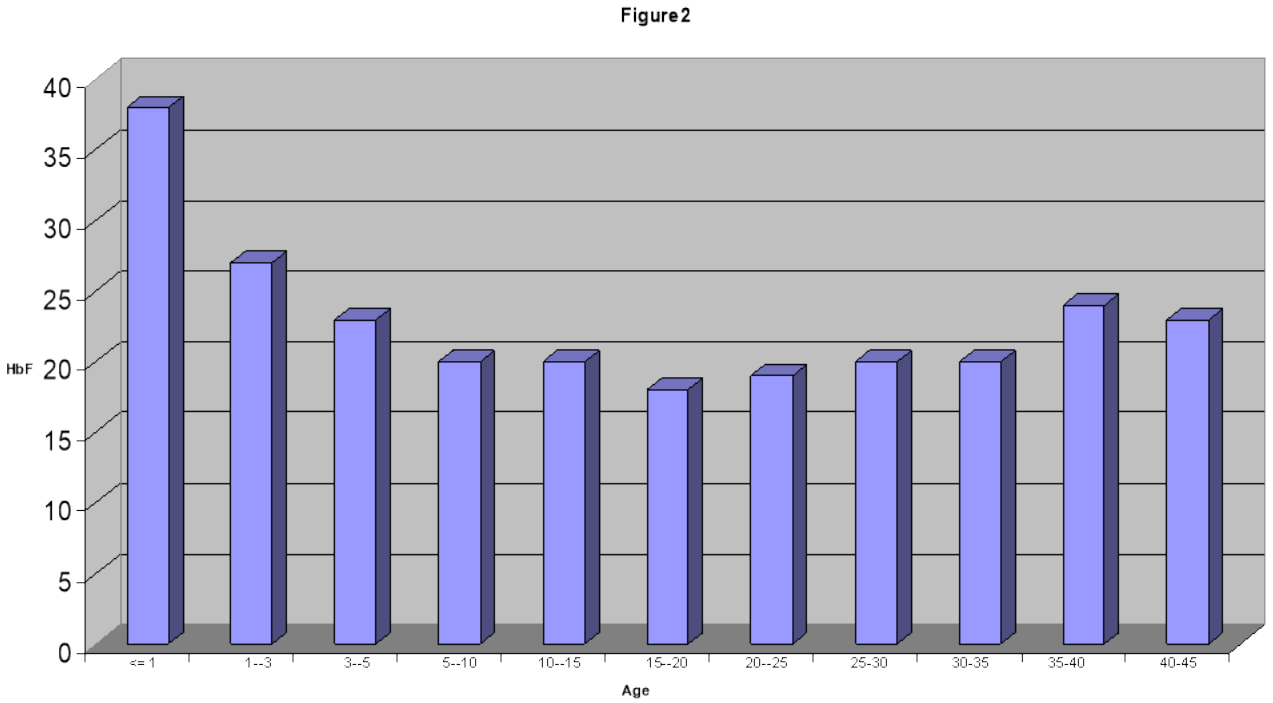
- Most diverse in the world
  - All haplotypes represented
    - Arab/India
    - Benin
    - Bantu
  - HbF Influence
  - Spectrum of phenotypes
    - Severe
    - Mild
  - Many compound heterozygotes
    - Sβ-thal
    - SD
    - SO_{Arab}
    - SE
  - High frequency of α-thal
  - Dominant inheritance
    - HbS_{Oman}
- Many lessons to be learned

Beta S Haplotype Distribution (%) in Kuwait and some other Countries

Haplotype	Nigeria[1]	Lebanon[2]	Kuwait[3]	Oman[4]
BEN	93.0	73.0	12.0	52.1
AI	0	10.0	80.4	26.7
CAR	1.0	15.0	6.5	21.4
CAM	3.4	0	0	0
SEN	0.2	2.0	0	0

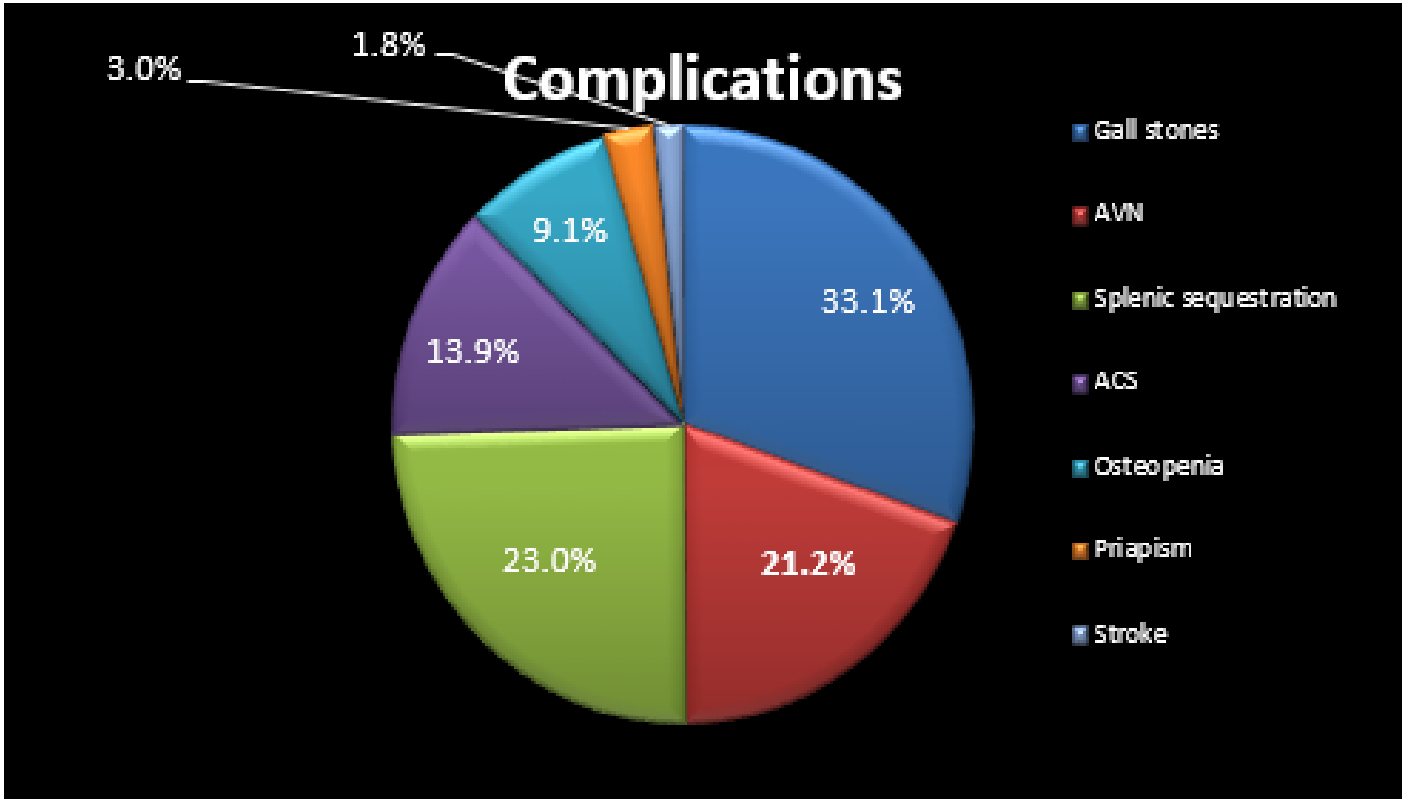
Adekile (1992)[1], Inati et al (2003) [2], Adekile et al (1994)[3], Daar et al (2000)[4]

Hb F Levels in Kuwaiti SCD Patients



Adekile et al Med Princ Pract 2008

Distribution of Complications



Sickle Cell Phenotype in Kuwait

- Uniformly high Hb F levels, varying from about 15 to > 30%
- Patients usually asymptomatic in first 3-4 years
- Bacterial infections are uncommon
- Hemolysis is not intense
- Pain episodes are common
- Stroke and SBI rare
- Priapism and leg ulcers are extremely rare

Hematological Profile of Kuwaiti and Omani SCD Patients

Group	Age (yrs)	Hb (g/dl)	WBC (x10^9/l)	Plt (x10^9/l)	MCV (fl)	MCH (pg)	LDH (iu/l)	Bil (umol/l)	Hb F (%)
All N=144	19.0 ±14.3	9.6 ±1.8	7.9±3.4	321.2 ±173.7	75.6 ±12.4	26.2 ±5.9	435 ±172.3	33.3 ±17.6	18.8 ± 10.1
Kuwait N = 93	17.7 ±14.3	9.6 ±2.0	8.0 ±3.5	300 ±151.2	76.9 ±13.7	26.6 ±6.6	423 ±172.3	35.2 ±18.6	22.4 ±9.6*
Oman N = 51	21.4 ±14.1	9.6 ±1.5	7.7 ±3.2	359 ±201.9	73.6 ± 9.7	25.5 ± 4.4	459 ±171.6	29.7 ±15.2	12.1 ±7.0*
≤ 16 years N = 92	9.7 ±3.4	9.3 ±2.0	8.0 ±3.5	322 ±168.5	73.5 ±11	25.6 ±5.9	461 ±170	32.8 ±17.5	20.0 ±10.0
≥16 years N = 52	35.6 ±11.1	10.0 ±1.5	7.8 ± 3.1	318 ±185.3	79.8 ±14	27.3 ±5.7	371 ±164.5	34.2 ±18	16.7±9.7

Frequencies of Pain Episodes, Transfusion and Acute Chest Syndrome

- Classified:
  - Mild 0 - 1
  - Moderate 2 - 3
  - Severe >3

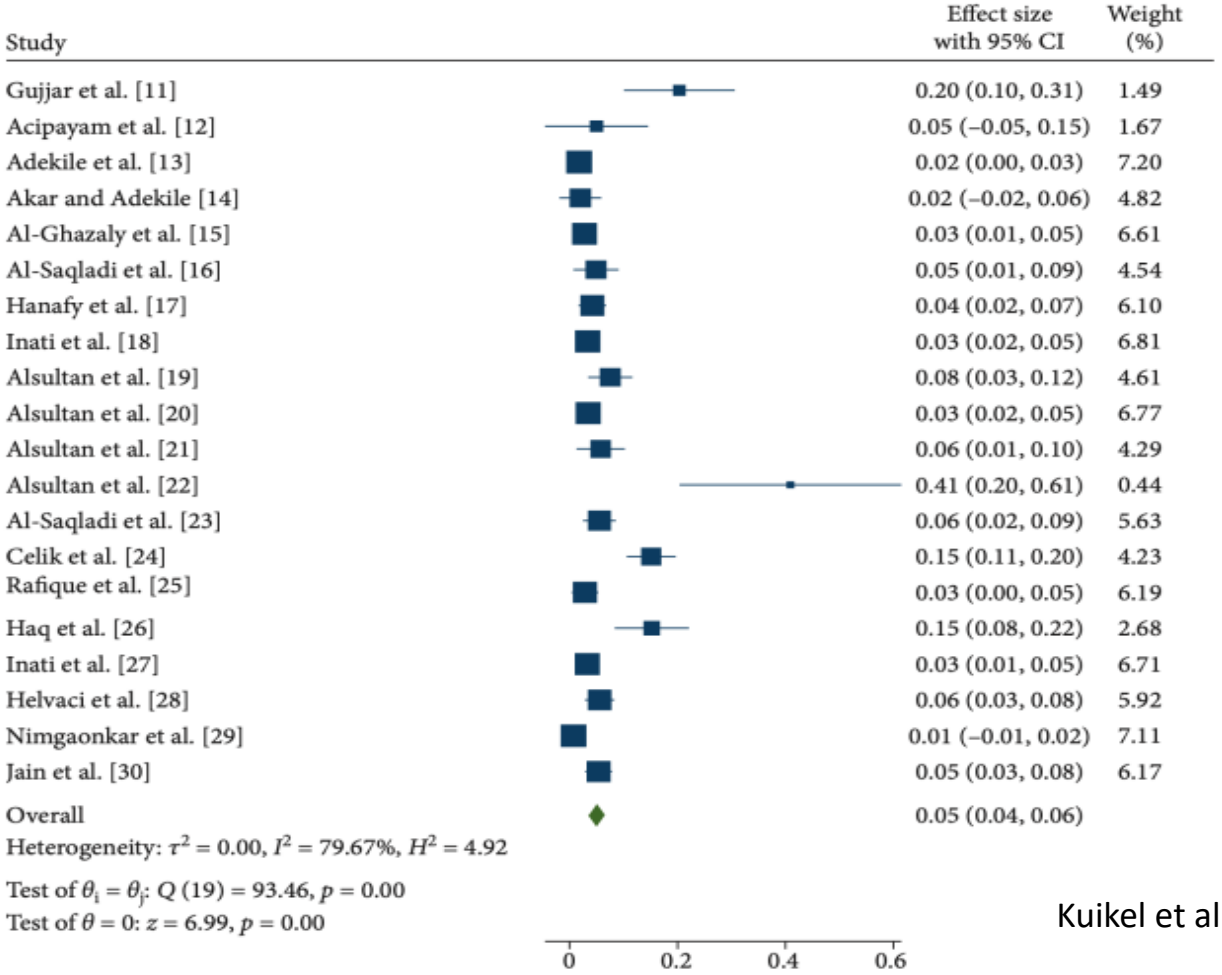
Comparisons

Phenotype	Population	Chi Square	P Value
Pain	All	7.6	0.023*
	<16 years	10.1	0.006*
	≥16 years	0.04	0.978
Transfusion	All	7.92	0.048*
	<16 years	17.6	0.001*
	≥16 years	6.43	0.092
ACS	All	8.4	0.015*
	<16 years	2.47	0.291
	≥16 years	3.8	0.149

Other Phenotypes not seen in the 2 Populations

- Stroke - ~11% in the literature, especially in childhood
- Priapism – up to 35% in the literature, especially in adolescents & adults
- Leg ulcers – 25 – 75% reported historical prevalence

Prevalence of Stroke in Asian Patients with SCD



Kuikel et al Neur Res Int 2021

TABLE 2 Rates of SCD complications among Saudi patients that indicate HSCT

	SW (n=250)				E (n=126)			
SCD indications for HSCT	Overall	<14 years (n=88)	≥14 years (n=162)	*P* value	Overall	<14 years (n=21)	≥14 years (n=105)	*P* value
Severe recurrent pain crisis only	7.6%	10.2%	6.2%	.24	11.1%	9.5%	11.4%	.79
Recurrent ACS only	0.8%	2.3%	0	.05	0	0	0	n/a
Overt stroke only	5.2%	1.1%	7.4%	.03	2.4%	0	2.8%	.43
Severe recurrent pain crisis and ACS	5.6%	4.5%	6.1%	.28	2.4%	0	2.8%	.43
Severe recurrent pain crisis and stroke	3.2%	1.1%	4.3%	.17	1.5%	0	1.9%	.52
Recurrent ACS and stroke	0	0	0	n/a	0	0	0	n/a
All three indications	1.2%	1.1%	1.2%	.94	0	0	0	n/a
Overall	23.6%	20.3%	25.2%	.38	17.4%	9.5%	18.9%	.29

E, Eastern province; n/a, not applicable.

Alsultan et al. Ped Trans, 2016

TCD in Children with SCD and high HbF

TABLE II. TAMV (cm/seconds) Values (Mean, SD, Range) in the Different Arteries in Patients and Controls

Artery	Patients	Controls	*P*
ICA	82.0 ± 11.6 (51.1–144.7)	72.9 ± 22.2 (39.9–137.1)	0.07
ACA	84.9 ± 18.0 (46.8–138.9)	71.3 ± 18.0 (44.4–131.4)	0.004
MCA	99.0 ± 19.2 (64.4–143.2)	87.8 ± 18.1 (58.8–145.0)	0.02
PCA	64.0 ± 13.7 (37.5–98.1)	52.5 ± 14.6 (34.8–107.8)	0.002

Asbeutah et al Ped Blood Canc 2013

J Ultrasound Med. 2019 Jan;38(1):165-172. doi: 10.1002/jum.14680. Epub 2018 May 6.

Transcranial Doppler Ultrasound in Peninsular Arab Patients With Sickle Cell Disease

Adekunle Adekile [1], Meaad Hassan [2], Akram Asbeutah [3], Mohamed Al-Hinai [4], Omar Trad [5], Nayef Farhan [6]

Affiliations + expand

PMID: 29732592 DOI: 10.1002/jum.14680

Data on 415 SCD patients from 4 countries – Kuwait, Iraq, UAE and Oman. No abnormal values and only 3.1%, all Iraqis had conditional values

Inference

- Stroke is relatively uncommon among Gulf Arabs
- TCD is generally normal
- Why??
  - Related to HbF, especially in early life?
  - Is it haplotype independent?
  - Are there other protective ethnic genetic factors?

Table 5. Haplotypes among HbSS patients.

	Haplotype	n (%)	Age (Years)	* Hb (g/dl)	** MCV (fl)	*** MCH (pg)	**** HbF (%)
SS	AI/AI	100 (64.9)	13.2+/−11.8	11.2+/−7.5	81.0+/−13.8	27.5+/−4.3	24.2+/−7.9
	AI/ATP	25 (16.2)	15.0+/−13.2	9.9+/−9.2	76.6+/−12.1	25.9+/−4.6	21.0+/−7.9
	AI/BEN	9 (5.8)	15.3+/−13.7	9.4+/−1.5	86.1+/−15.6	29.0+/−6.8	19.3+/−11.5
	AI/SEN	5 (3.2)	12.1+/−8.3	10.7+/−0.5	65.2+/−4.1	21.1+/−1.4	15.2+/−8.8
	BEN/BEN	4 (2.6)	6.4+/−5.0	8.9+/−1.0	81.9+/−8.5	26.9+/−4.0	16.8+/−9.2
	AI/CAR	4 (2.6)	12.0+/−12.2	10.0+/−0.4	90.2+/−8.6	29.8+/−3.0	19.7+/−5.1
	CAM/CAM	2 (1.3)	14.5+/−4.9	8.9+/−0.1	89.5+/−19.2	29.2+/−7.1	13.2+/−2.0
	SEN/SEN	2 (1.3)	16.0+/−7.1	10.7+/−1.1	85.2+/−21.0	29.2+/−8.5	24.1+/−11.0
	BEN/CAM	1 (0.6)	11	11	78.6	26	34.9
	BEN/ATP	1 (0.6)	7	7.9	76	24	9.3
	AI/CAM	1 (0.6)	2	9.7	68	31.3	22.6

* Hemoglobin. ** Mean corpuscular volume. *** Mean corpuscular hemoglobin. **** Fetal hemoglobin.

Adekile et al J Per Med 2021 11(567)

Journal of *Personalized Medicine* 2021, 11(567)

MDPI

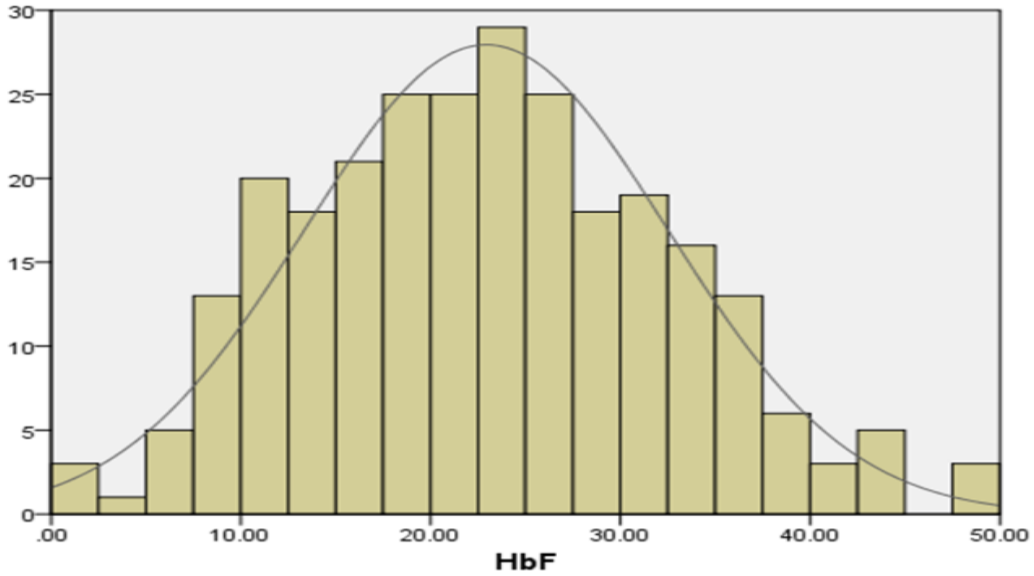
Article

Unique Polymorphisms at *BCL11A*, *HBS1L-MYB* and *HBB* Loci Associated with HbF in Kuwaiti Patients with Sickle Cell Disease

Nagihan Akbulut-Jeradi [1,*], Maria Jinky Fernandez [1], Rasha Al Khaldi [1], Jalaja Sukumaran [2] and Adekunle Adekile [2]

Studied 126 SNPs in 237 patients

HbF Subgroups

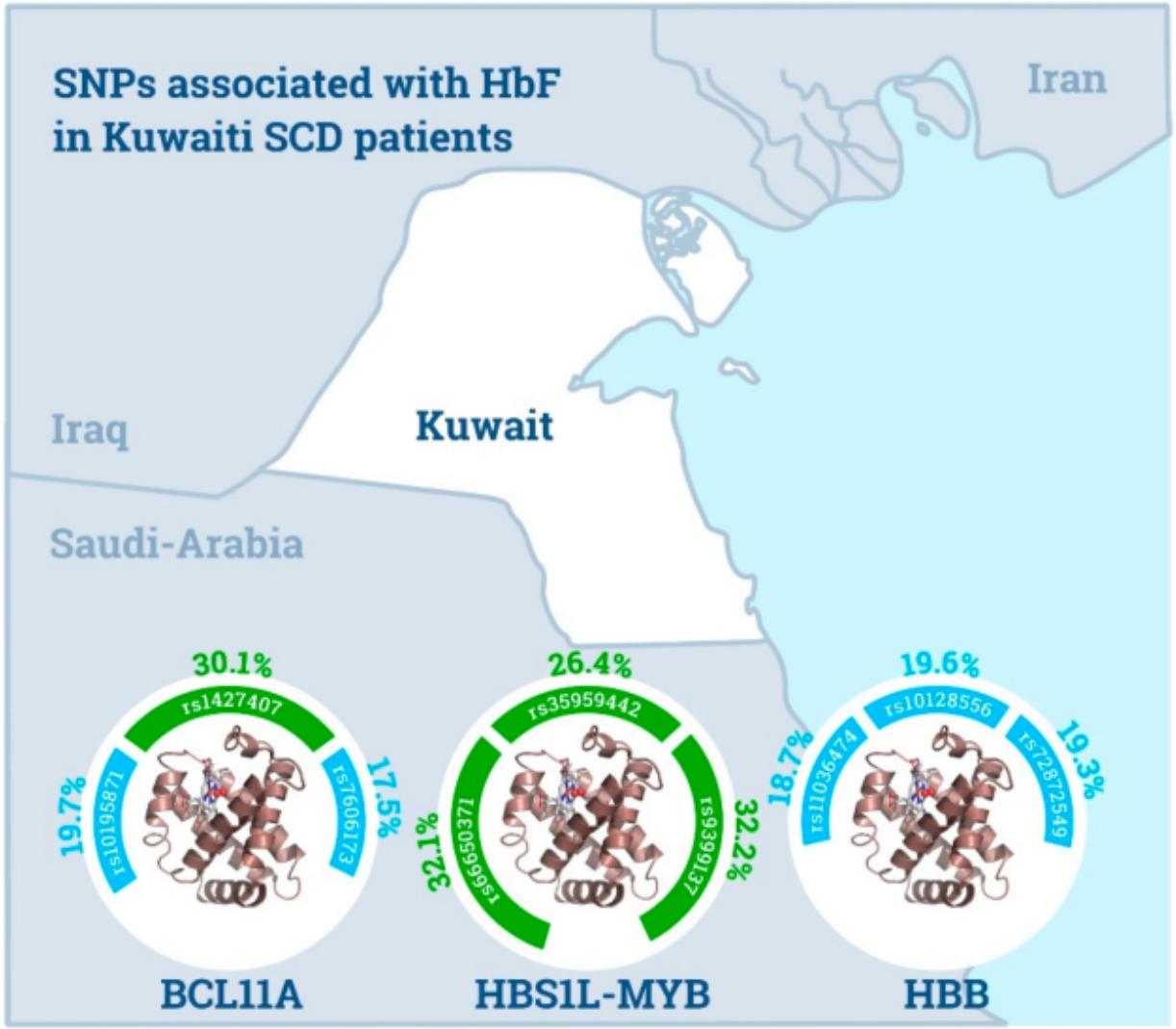


Studied 237 SCD patients divided according to:HbF1 = <20%, HbF2 = 20 – 30% and HbF3 = >30%

Table 1. Variants in *BCL11A*, *HBS1L-MYB* and *HBB* loci showing the most significant association with HbF in Kuwaiti patients with SCD.

Locus	SNP ID	BP	MAF	A1	% R^2	HbF-1		HbF-2		HbF-3		β	*p*
						χ^2	*p*	χ^2	*p*	χ^2	*p*		
BCL11A	rs1427407	60490908	0.2975	T	5.80	14.86	0.0003	17.31	3.32×10^{-5}	9.97	0.0087	1.65	0.0023
	rs7606173	60498316	0.3249	C	1.70	16.46	6.13×10^{-5}	9.99	0.0143	8.53	0.0103	−1.27	9.17×10^{-5}
	rs10195871	60493454	0.4916	G	3.40	15.00	7.95×10^{-5}	10.66	0.0234	6.22	0.0126	−1.21	0.0003
	rs7569946	60460824	0.3207	A	1.80	3.21	0.13169	0.80	0.4420	7.51	0.0061	0.59	0.0073
HBS1L-MYB	rs9399137	135097880	0.1181	C	0.10	3.33	0.1090	4.96	0.0259	9.49	0.0021	0.78	0.0056
	rs66650371	135097495	0.1181	2 *	3.40	3.33	0.1090	5.33	0.0214	9.49	0.0021	0.78	0.0056
	rs35786788	135097904	0.1181	A	0.20	3.33	0.1090	4.96	0.0259	9.17	0.0015	0.76	0.0043
	rs35959442	135103041	0.1983	G	2.70	1.60	0.3053	2.77	0.0960	9.19	0.0025	0.76	0.0026
HBB	rs67385638	5269140	0.2089	C	1.70	19.22	1.65×10^{-5}	19.82	9.96×10^{-6}	3.65	0.1641	−1.13	0.0002
	rs11036474	1253948	0.2131	T	1.50	18.13	2.65×10^{-5}	18.22	2.44×10^{-5}	3.43	0.0963	−1.08	0.0002
	rs10128556	5242453	0.2152	C	1.30	17.61	3.34×10^{-5}	17.47	3.76×10^{-5}	3.11	0.1849	−1.07	0.0003
	rs72872549	5268823	0.2152	C	1.70	16.48	4.95×10^{-5}	15.45	0.0002	3.11	0.1849	−1.07	0.0003
	rs7482144	5254939	0.2574	G	1.20	15.25	0.0002	16.04	9.02×10^{-5}	2.59	0.3364	−1.08	0.0005
	rs3759071	5270302	0.1160	G	0.20	1.45	0.2699	3.72	0.0804	8.55	0.0044	0.70	0.0100

* rs66650371 genotypes codes are (1: TACTA, 2: TA), A1 indicates Minor Allele; β, Beta Coefficient; *BCL11A*, B-cell lymphoma/leukemia 11A; BP, Physical Position; *HBB*, beta globin; *HBS1L-MYB*, intergenic region between GTP-binding elongation factor *HBS1L* and myeloblastosis oncogene MYB; ID, Identification; MAF, Minor Allele Frequency; % R^2, Variance Explained; χ^2, Chi-square.


SNPs associated with HbF
in Kuwaiti SCD patients
Iran
Iraq
Kuwait
Saudi-Arabia
30.1%
rs1427407
19.7%
rs10195871
17.5%
rs7606173
BCL11A
26.4%
rs35959442
32.1%
rs66650371
32.2%
rs9399137
HBS1L-MYB
19.6%
rs10128556
18.7%
rs11036474
19.3%
rs72872549
HBB

Conclusions

- Wide variety of SCD among Gulf Arabs
- Compound heterozygotes are very common
- There are unique HbF modifiers in the region, which may not be haplotype specific
- More work needs to be done in documenting the natural history of the disease in the region
  - Collaboration across different centers

Acknowledgements

- Patients who consented for studies
- In the Dept. of Pediatrics, KU
  - Mohammad Haider
  - Gursev Dhaunsi
  - Mark D'Souza
  - Jalaja Sukumaran
  - Nada Mustafa
  - Diana Thomas
  - Rubina Hussain
- Faculty of Medicine
  - Renu Gupta
  - Raj Raghupathy
- Faculty of Allied Health
  - Akram Asbeutah
- Hematology Unit, Mubarak Hosp
  - Hanan Al-Abboh
  - Akmal Zahra
- Sultan Qaboos Univ. Oman
  - Salam Al-Kindi
  - Yasser Wali
- Advanced Technical Company
  - Ahmad Jeradi
  - Nagihan Akbulut-Jeradi
- Funders
  - Kuwait Univ. Research Sector
  - Kuwait Foundation for Advancement of Science (KFAS)