2nd Sever FH Course
Recognize, Diagnose, and Treat Severe Familial Hypercholesterolemia
Muscat, Oman, December 2-3, 2018

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FAMILIAL HYPERCHOLESTEROLAEMIA IN THE MENA REGION:
DO WE HAVE THE DATA
Familial hypercholesterolemia (FH)

Coronary artery diseases (CAD) inflict heavy economical and social cost on most populations and contribute significantly to their morbidity and mortality rates.

FH is hereditary disease, usually under diagnosed and is a major risk factor for the development of CAD.

Approximately, half of the heterozygous men with FH, if untreated, will develop clinically evident CAD by the age of 55 years.

Affected heterozygous women from the same families typically develop CAD about 9 years later than their affected male relatives.
Epidemiological genetic studies

In the majority of populations, the heterozygote form occurs in less than 1:500 and the homozygous form is one in one million.

However, recent studies have changed this perception and shown that FH is under diagnosed in most populations.

HeFH prevalence according to DLCN criteria may reach 1 in every 200 individuals. Consequently, HoFH may rise to one in every 300,000 individuals.

The highest frequency of heterozygosity with an incidence of less than 1:80 is found in the Afrikaner population in South Africa.

Studies on the French Canadian population where five common mutations are known, show a frequency of 1:270.

This unusual high frequency is due to founder effects and consanguinity.

Because of the AD mode of inheritance the heterozygous are affected and therefore FH is the most frequent Mendelian disorder being more frequent than homozygous CF and sickle cell anaemia.
The incidence of FH is not known in the Middle East

We are not aware of any epidemiological genetic study examining the frequency of FH in MENA population.

The high incidence of consanguinity marriages which exceeding 54% in Saudi population and the occurrence of many cardiovascular centres across the country, suggesting that the incidence might be high.

We estimated that at least 63,485 (this number can be as high as 158,712) Saudis are affected. (http://www.stats.gov.sa/en/node).

Because the disease is asymptomatic, the majority of patients may not be aware of their illness until a severe myocardial infarction, which often leads to sudden death or other cardiovascular events occur in the fourth or fifth decade of life.
Clinical manifestation of FH

Measurement of blood cholesterol levels are NOT sufficient to confirm a diagnosis of FH

The range of blood cholesterol levels in FH overlaps with that of people with non-genetic multifactorial hypercholesterolaemia, which may lead to a false positive or false negative diagnosis

Diagnostic Criteria from
- The Simon Broome Register Group. BMJ. OCT 12 1991
- The Dutch Lipid Clinic Network (The Netherlands). Nordestgaard et al. Eur Heart J. 2013
- The MEDPED criteria (USA).

All suggest that diagnosis can be made on the basis of Laboratory finding, physical signs, family history (a dominant pattern of inheritance for either premature CAD or hypercholesterolaemia) and, where available, genetic confirmation.
Autosomal Dominant FH

**LDLR** (the plasma membrane Low Density Lipoprotein Receptor)

**ApoB** (Apolipoprotein B 100)

**PCSK9** (the neural apoptosis regulated convertase 1)
Autosomal Recessive FH

**LDLRAP1** (the plasma membrane Low Density Lipoprotein Receptor Adaptor Protein 1)
### Classes of LDLR mutations and genotype/phenotype correlation

The **null receptor** phenotype results from non-sense mutation(s) or deletion(s) in the promoter region within the LDLR gene.

The **transport deficient receptors** are synthesised normally in the endoplasmic reticulum but fail to be transported to the Golgi apparatus for further processing.

**Binding deficient LDLR** is transported normally to the cell membrane but binds LDL only partially.

The **internalisation defective receptors** reach the cell surface and bind LDL, but fail to cluster in clathrin coated pits.

<table>
<thead>
<tr>
<th>Protein Domain</th>
<th>Gene</th>
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<tbody>
<tr>
<td>Ligand binding domain 292 AA</td>
<td>Exons 2-6</td>
</tr>
<tr>
<td>EGF precursor homology approx. 400 AA</td>
<td>Exons 7-14</td>
</tr>
<tr>
<td>O-linked sugars 58 AA</td>
<td>Exon 15</td>
</tr>
<tr>
<td>Membrane spanning 22 AA</td>
<td>Exons 16&amp;17</td>
</tr>
<tr>
<td>Cytoplasmic tail 50 AA</td>
<td>Exons 17&amp;18</td>
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</table>
Causative Mutations

- **Loss of Function Mutations**
  
  **LDLR**
  Accounts for 85-90%.
  Over 1000 mutations reported
  No hotspots in some population

- **ApoB**
  Accounts for 1-5%
  Only two mutations reported

- **Gain of Function Mutations**
  
  **PCSK9**
  Account for 5-10%
  Nine mutations are reported

*Other candidate Genes: ABCA1, APOA2, APOC3, PON2, ARH, LDLRAP1, APOC2, APOE, and LPL*
**TUNIS**
c.1477_1479delCTCinsAGAGACA, p.(S493fs*44) (FH-Souassi), Slimane et al., 2001

**ALGERIA**
c.1222G>A, p.(E408K) (FH Algeria-1), Hobbs et al. 1992  
c.1291G>A, p.(A431T) (FH Algeria-2), Hobbs et al. 1990  
c.1301C>A, p.(T434K) (FH Algeria-3), Hobbs et al. 1992

**MOROCCO**
FH-Morocco-1, El Messal et al., 2003  
FH-Morocco-2, El Messal et al., 2003  
c.682G>T, p.(E228*), Hobbs et al., 1992  
c.400T>C, p.(C134R), El Messal et al., 2003  
c.859G>T, p.(G287C), El Messal et al., 2003  
c.1171G>A, p.(A391T), El Messal et al., 2003  
c.2054C>T, p.(P685L), El Messal et al., 2003  
c.2132C>T, p.(C711S), El Messal et al., 2003  
c.138C>T, p.(C46*), Chater et al., 2006  
c.313+5G>T, Chater et al., 2006  
c.1736A>C, p.(D579A), Chater et al., 2006  
c.514G>A, p.(D172N), Chater et al., 2006  
c.1502C>A, p.(A501E), Chater et al., 2006  
c.756_762delCCGGCAC, Chihab et al., 2007

**SYRIA**
c.550T>C, p.(C184R), Hobbs et al. 1992  
c.827G>A, p.(C276Y), Vergopoulos et al. 1998  
c.1027G>A, p.(G343S), Vergopoulos et al. 1998  
c.1172delT, p.(A370fs), Reshef et al., 1996  
c.2043C>A, p.(C681*), Vergopoulos et al. 1998  
c.1999T>C, p.(C667R), Lehrman et al. 1987  
c.89-1G>C, p.(K30T*3), Al-Kateb et al., 2002

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c.406C>T, p.(Q136*), Garcia et al., 2001  
c.605C>A, p.(P202H), Garcia et al., 2001  
748-608G>A, p.(W249ins62*), Wilund et al. 2002  
c.89-1G>C, p.(K30T*3), Lind et al., 2004

**SAUDI ARABIA**
c.2439G>A, p.(W813*), Lehrman et al., 1985

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c.406C>T, p.(Q136*), Garcia et al., 2001  
c.605C>A, p.(P202H), Garcia et al., 2001  
748-608G>A, p.(W249ins62*), Wilund et al. 2002  
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**LDLR = WHITE, ApoB100 = BLUE, PCSK9 = YELLOW, LDLRAP1 = RED**
Points strongly support the need for national genetic screening program and the potential benefits

The vast majority may not be aware of the inherited nature of their illness.

◦ >63,000 (this number can be as high as 158,712) Saudis are affected

Genetic testing using molecular method are the most accurate way of diagnosing FH, especially at the crucial prenatal age

The spectrum of mutations causing FH in Saudis is not known

Once the mutations will be identified, the cost of the genetic diagnosis will also drop an order of magnitude because the testing will be targeted to the defective part of the gene

Genetic counselling can be offered to the affected family members especially for the prevention of the occurrence of homozygotes patients resulting for consanguineous marriages of heterozygote patients
Selection criteria: Simon Broome Criteria

‘Definite’ FH – A+B must be present

‘Possible’ FH – A+C or A+D

A. Total and LDL-Cholesterol

- **16 years+**: Total cholesterol >7.5mmol/l (>290mg/dl) or LDL-C >4.9mmol/l (>190mg/dl)
- **Under 16 years**: Total cholesterol >6.7mmol/l (>260mg/dl) or LDL-C >4.0mmol/l (>155mg/dl)

B. Tendon xanthomas in patient or 1st (parents, sibling, children) or 2nd (grandparents, uncle, aunt) degree relative

C. FH of myocardial infarction (MI) <60 yrs in 1st degree relative or FH of MI <50 yrs in 2nd degree relative

D. FH of total cholesterol >7.5mmol/l (>290mg/dl) in 1st or 2nd degree relative
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C. FH of myocardial infarction (MI) < 60 yrs in 1st degree relative or FH of MI < 50 yrs in 2nd degree relative

D. FH of total cholesterol > 7.5mmol/l (＞290mg/dl) in 1st or 2nd degree relative

Genetic Diversity of FH

- **Homozygous**
- **Heterozygous**
- **Double Heterozygous**
- **Compound Heterozygous**
Familial Hypercholesterolemia mutation detection Algorithm

Clinical suspicion of autosomal dominant hypercholesterolemia according to Simon Broome criteria

**APOB genotype** a is performed for the common APOB 100 mutations R3500Q and R3500W

- **APOB mutation(s) detected** Interpretive report is provided
  - Consider testing at-risk relatives for the familial mutation(s)

- **No APOB mutations detected**
  - **LDLR gene sequencing** b is performed

- **LDLR gene mutation(s) detected by sequencing.** Interprete report is provided
  - Consider testing at-risk relatives for the familial mutation(s)

- **No LDLR gene mutations detected by sequencing.** Interprete report is provided
  - **LDLR large deletion/duplication analysts** c performed using MLPA

- **LDLR large deletion or duplication mutation(s) detected.** Interpretive report provided
  - Consider testing at-risk relatives for the familial mutation(s)

- **No LDLR large deletion or duplication mutations detected.** Interpretive report is provided
  - **PCSK9 mutation analysis** or **NGS analysis using Ion torrent custom made chips**

- **PCSK9 gene mutation(s) detected by capillary sequencing.** Interpretive report is provided
  - Consider testing at-risk relatives for the familial mutation(s)

- **LDLR gene mutation(s) detected by NGS.** Mutation(s) re confirmed by capillary sequencing. Interpretive report is provided
  - Consider testing at-risk relatives for the familial mutation(s)
Identification of Novel nonsense mutation p.D445X in LDLR gene causes familial hypercholesterolemia

We have identified a novel insertion mutation (c.1332_1333insT) at exon 9 of the LDLR gene (alr family)

This insertion mutation results in a premature stop codon at position 445 in exon 9 of the LDLR gene, which results in truncation of the protein.
Development of Next Generation Sequencing chip to Identify Genetic Variants Causative of FH

Ldlr, ApoB, Pcsk9, Abca1, Apoa2, Apoc3, Apon2, Arh, Ldrlrap1, Apoc2, ApoE, and Lpl

LDLR Exon 14 (c.2026delG, p. Gly676Fs), Novel mutation
Glycine – Alanine
Identification of a novel causative frame shift mutation at the LDLR Exon 14 (c.2027delG, p.Gly676fs)
Compound heterozygous LDLR variant in severely affected familial hypercholesterolemia patient

Faisal A. Al-Allaf1,2,3*, Abdullah Alashwaf4*, Zainularifeen Abduljaleel1,2, Mohiuddin M. Taher1,2, Abdellatif Bouzzaouli1,2, Hala Abalkhali5, Ahmad F. Al-Allaf5 and Mohammad Athar1,2,6,7

1Department of Medical Genetics, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia; 2Science and Technology Unit, Umm Al-Qura University, Makkah, Saudi Arabia; 3Molecular Diagnostics Unit, Department of Laboratory and Blood Bank, King Abdullah Medical City, Makkah, Saudi Arabia; 4King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; 5Faculty of Medicine, Alfaisal University, Riyadh, Saudi Arabia.

1 Vol. 64, No 1/2017
75–79
https://doi.org/10.18388/abp.2016_1283
Identification and Treatment of Patients with Homozygous Familial Hypercholesterolaemia: Information and Recommendations from a Middle East Advisory Panel

Abdulhaq Al-Ashtal, Faisal Al-Ahmad, Naseer Al-Shuraim, Abdulla Al-Mohaimeed, Maryam Razzaghi-Alaee, Faisal Al-Allar, Khalid Al-Asadi, and Khalid Al-Rasadi

Table 1: Summary recommendations for the diagnosis of familial hypercholesterolaemia (FH)

<table>
<thead>
<tr>
<th>Ldl cholesterol mg/dl</th>
<th>Clinical diagnosis</th>
<th>Genetic confirmation of two mutant alleles at the LDLR, APOB, PCSK9 or LDLRAP1 gene</th>
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<td>160-190</td>
<td>BPH</td>
<td>Yes, BPH-1, BPH-2, or mutations in the LDLRAP1 gene</td>
</tr>
<tr>
<td>190-200</td>
<td>Pre-FH</td>
<td>Yes, BPH-1, BPH-2, or mutations in the LDLRAP1 gene</td>
</tr>
<tr>
<td>200+</td>
<td>FH</td>
<td>Yes, BPH-1, BPH-2, or mutations in the LDLRAP1 gene</td>
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Identification and treatment of patients with homozygous FH.
In Silico Approach to Investigate the Structural and Functional Attributes of Familial Hypercholesterolemia Variants Reported in the Saudi Population

FATIMA A. MORAD, OM RAN M. RASHIDI, SAIDA S. SADATH, FAISAL A. AL-ALLAF, MOHAMMAD ATHAR, MOHAMED N. ALAMA, SHERIF E. EDRIS, NABEEIL S. BONDAGJI, NOOR A. SHAIK, BABAJAN BANAGANAPALLI, and ZUHIER AWAN
The Spectrum of Familial Hypercholesterolemia (FH) in Saudi Arabia: Prime Time for Patient FH Registry

Faisal Alallaf, Fatima Amanullah H.Nazar, Majed Alnefaie, Adel Almaymuni, Omran Mohammed Rashidi, Khalid Alhabib, Fahad Ainouri, Mohamed-Nabil Alama, Mohammad Athar and Zuhier Awan

![Graph showing expected HeFH and HoFH cases](image-url)
Novel combined variants of LDLR and LDLRAP1 genes causing severe familial hypercholesterolemia

Fahad Alnouri b,*,1, Mohammad Athar b, c, **, 1, Faisal A. Al-Allaf b, c, d, Zainularifeen Abduljaleel b, c, Mohiuddin M. Taher b, c, Abdellatif Bouazzaoui b, c, Dalal Al Ammari d, Hussam Karrar e, Monirah Alabtain a
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c.89-1G>C, p.(K30T*3), Lind et al., 2004

LDLR = WHITE, ApoB100 = BLUE, PCSK9 = YELLOW, LDLRAP1 = RED
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c.1186_1506delAAA, p.(E360_G396del), Jelassi et al., 2008
c.1845_1847delAA (FH-Tunis), Jelassi et al., 2009
c.2670_2671delG, p.(C105W), Jelassi et al., 2009

c.4430_C>T, p.(K1496*) (FH-Tunis), Jelassi et al., 2009

c.7966_A>T, p.(R266N), Jelassi et al., 2009

c.10276_G>T, p.(G343C), Jelassi et al., 2009

c.22446_A>T, p.(R716*), Slimani et al., 2009

c.15457_T>G, p.(F515S), Jelassi et al., 2011
c.20058_A>G, p.(G670E), Jelassi et al., 2011

c.22996delA, p.(M767delAN21), Jelassi et al., 2012

c.12684 bp del (ex2-5), Jelassi et al., 2012
2364 bp del (ex5-6), Jelassi et al., 2012

c.5260 > T, p.(R1745S), Jelassi et al., 2012

**TUNIS**

c.2043C>A, p.(C681Y). Lehrman et al. 1987
c.4866C>T, p.(Q162*) , Garcia et al., 2001
c.6056C>A, p.(P202H), Garcia et al., 2001
478-608G>A, (W249Ins62*), Wiuland et al 2002

**LEBANON**

c.89_101delC, p.(K307*3), Lind et al., 2004

**ALGERIA**

c.1291G>A, p.(A431T) (FH-Algeria-1), Hobbs et al. 1990

c.12226G>T, p.(E408K) (FH-Algeria-1), Hobbs et al. 1992

c.1301C>A, p.(T434K) (FH-Algeria-3), Hobbs et al. 1992

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c.682G>T, p.(E229F), Hobbs et al., 1992

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c.1999T>C, p.(C667R), Lehman et al. 1987

c.550T>C, p.(C184R), Hobbs et al. 1992


c.827G>A, p.(G276Y), Vergopoulos et al. 1998

c.10270G>A, p.(G343S), Vergopoulos et al. 1998

**BAHRAIN**

c.1172del1, p.(A370fsN), Reshef et al., 1996

c.2043C>A, p.(C681Y), Vergopoulos et al. 1998

c.89_101delC, p.(K307*3), Al-Katib et al., 2002

**OMAN**

c.277delG, Al-Himali et al., 2013

**SAUDI ARABIA**

c.2439G>A, p.(W813*) , Lehrman et al., 1985

c.1232dupA, p.(D445S), Al-Alafi et al., 2004

c.2026delc, p.(G676delR), Al-Alafi et al., Gene, 2015

c.2027delG, p.(G676delR*3), Al-Alafi et al., Genomics, 2015

c.313C>T, p.(I105S), Alhathloul et al., 2015

c.1711G>A, p.(A937T), Alhathloul et al., 2015

c.1731G>T, p.(G577C), Al-Alafi et al., ABP, 2017

c.2416dupG, p.(V806Gfs*11), Al-Alafi et al., OCMJ, 2017

c.185C>T, p.(T62M), Al-Alafi et al., OCMJ, 2017

c.6220A>G, p.(E208K), Al-Alafi et al., OCMJ, 2017

c.14740A>G, p.(D492N), Al-Alafi et al., OCMJ, 2017

c.14296G>T, p.(D477N), Al-Alafi et al., OCMJ, 2017

c.1782C>T, p.(R559W), Al-Alafi et al., OCMJ, 2017

c.1706_2A>T in SA site of intron 11, Al-Alafi et al., OCMJ, 2017

c.1255T>G, p.(Y419D), Alnouri et al., Atherosclerosis, 2018

**AL-Alafi et al., 2018 (Submitted)**

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**SAUDI ARABIA**

c.9836A>G, p.(S3279D), Morad et al., JOCB, 2017

c.1985C>T, p.(A53V), Morad et al., JOCB, 2017

c.604_605delTCinsA, p.(S2027ins*2), Alnouri et al., Atherosclerosis, 2018

**AL-Alafi et al., 2018 (Submitted)**
## Lead Investigators

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
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<tbody>
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<td></td>
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<td>Dr. Mohammed Al Jarallah</td>
<td>Head of Sabah Al-Ahmed</td>
<td>Kuwait</td>
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<tr>
<td>Dr. Nidal Asaad</td>
<td>Qatar Heart Hospital, Hamad Medical Corporation</td>
<td>Qatar</td>
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<tr>
<td>Prof. Peter Lansberg</td>
<td>Coordinator Durrer Center for Cardiogenetic Research</td>
<td>Netherland</td>
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## Steering Committee

<table>
<thead>
<tr>
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<tr>
<td>Dr. Hussam Alfaleh</td>
<td>King Fahad cardiac Center, College of Medicine, King Saud University, Riyadh</td>
<td>Saudi Arabia</td>
</tr>
<tr>
<td>Dr. Zuhair Awan</td>
<td>King Abdulaziz University and King Fahad Institute of Research.</td>
<td>Saudi Arabia</td>
</tr>
<tr>
<td>Dr. Abdulhalim Kensara</td>
<td>National Guard Hospital, Jeddah</td>
<td>Saudi Arabia</td>
</tr>
<tr>
<td>Dr. Khalid Al Walli</td>
<td>Biochemistry, Sultan Qaboos University Hospital, Muscat</td>
<td>Oman</td>
</tr>
<tr>
<td>Dr. Fahad Al Zadjali</td>
<td>Biochemistry, College of Medicine &amp; Health Science, Sultan Qaboos University, Muscat</td>
<td>Oman</td>
</tr>
<tr>
<td>Dr. Ibrahim Al Zakwani</td>
<td>Department of Pharmacology &amp; Clinical Pharmacy, College of Medicine &amp; Health Sciences, Sultan Qaboos University, Muscat</td>
<td>Oman</td>
</tr>
<tr>
<td>Dr. Nasreen Al Sayed</td>
<td>Gulf Diabetes Specialist Center, Manama</td>
<td>Bahrain</td>
</tr>
<tr>
<td>Dr. Haitham Amin</td>
<td></td>
<td>Bahrain</td>
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<tr>
<td>Dr. Ahmed Al Sarraf</td>
<td>Laboratory Department, Kuwait Cancer Control Center</td>
<td>Kuwait</td>
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<tr>
<td>Dr. Mohammed Al Jarallah</td>
<td>Head of Sabah Al-Ahmed</td>
<td>Kuwait</td>
</tr>
<tr>
<td>Dr. Nidal Asaad</td>
<td>Qatar Heart Hospital, Hamad Medical Corporation</td>
<td>Qatar</td>
</tr>
<tr>
<td>Prof. Peter Lansberg</td>
<td>Coordinator Durrer Center for Cardiogenetic Research</td>
<td>Netherland</td>
</tr>
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Gulf Registry (eCRF)

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Familial/ Autosomal Dominant Hypercholesterolemia mutation detection Algorithm

Clinical suspicion of autosomal dominant hypercholesterolemia according to Simon Broome criteria

LDLR gene sequencing (Capillary; Sanger) is performed for the common tribes associated mutations panel/hotspot

No LDLR gene mutations detected by sequencing. NGS (Ion torrent) analysis for customized FH associated genes (LDLR, APOB, PCSK9 and LDLRAP1)

Gene mutation(s) detected by NGS. Mutation(s) reconfirmed by capillary sequencing. Interpretive report is provided

Consider testing at-risk relatives for the familial mutation(s)

No gene mutation(s) detected in customized genes by NGS. Whole exome analysis by NGS

Gene mutation(s) detected by NGS. Mutation(s) reconfirmed by capillary sequencing. Interpretive report is provided

Consider testing at-risk relatives for the familial mutation(s)

LDLR gene mutation(s) detected by sequencing. Interpretive report is provided

Consider testing at-risk relatives for the familial mutation(s)
Future work

We need to collaborate with more centers, physicians, and researchers across the Gulf

We need to include other Arab patients from MENA

We need to activate the educational home page and FH registry
Dr Mohammad Athar, UQU, Makkah
Dr Taher Mohiddin, UQU, Makkah
Dr Zainularefeen Abduljaleel, UQU, Makkah
Dr Abdulatif Bouezzi, UQU, Makkah
Dr Iman Abo Mansoor, UQU, Makkah
Dr Zohor Azhar, UQU, Makkah

Mrs Mawaddah Toonsi, UQU, Makkah
Ms Aroob Alhemaidi, UQU, Makkah
Ms Ghaidaa Diari, UQU, Makkah
Mr Faisal Bahammam, UQU, Makkah
Mr Rakan Own, UQU, Makkah
Mr Aiman Al-Shingiti, UQU, Makkah
Mr Moaid Al-Serahi, UQU, Makkah
Mr Rami Bamerdhah, UQU, Makkah

Dr Maisaa Amer, UQU, Makkah
Dr Ahmad Faisal, UQU, Makkah
Dr Mahmood Alsayed, UQU, Makkah

Dr. Abdullah Al-Ashwal, Col, KFSH&RC, Riaydh
Dr. Hala Abalkhail, Col, KFSH&RC, Riaydh
Dr. Fahad Alnoori, Prince Sultan Cardiac Centre, Armed Force Hospital, Riyadh

Dr Zohair Awan, KAU, Jeddah

Mr Ahmad Al-Allaf, AlFaisal University, Riyadh

Khalid F. AlHabib, Khalid Al Rasadi, Dr Wael Almahmeed, Dr Abdullah Shehab, Dr Faisal Al-Allaf, Dr Fahad Al Noori, Dr Hussam Alfaleh, Dr Zuhair Awan, Dr Abdulhalim Kensara, Dr Khalid Al-Waili, Dr Fahad Al-Zadjali, Dr Ibrahim Al-Zakwani, Dr Nasreen AlSayed, Dr Haitham Amin, Dr Ahmed Al-Sarraf, Dr Mohammed Al-Jarallah, Dr Nidal Asaad, Prof Peter Lansberg, Mr Hani Altaradi
Thanks