Journal of Clinical Lipidology (2015) ■, ■–■

Journal of Clinical Lipidology

Review Article

Familial hypercholesterolemia mutations in the Middle Eastern and North African region: A need for a national registry

Mary Aderayo Bamimore, BMSc, MSc, Ahmed Zaid, PhD, Yajnavalka Banerjee, PhD, Ahmad Al-Sarraf, MD, Marianne Abifadel, PhD, PharmD, HDR, Nabil G. Seidah, PhD, Khalid Al-Waili, MD, Khalid Al-Rasadi, MD, Zuhier Awan, MD, PhD, FRCPC*

Department of Clinical Biochemistry, King Abdulaziz University, Abdullah Sulayman, Jeddah, Saudi Arabia (Ms Bamimore and Dr Awan); Department of Biochemistry, Tripoli University, Tripoli, Libya (Dr Zaid); Department of Biochemistry, Sultan Qaboos University, Al Khod, Muscat, Oman (Drs Banerjee, Al-Waili, and Al-Rasadi); Department of Medical Biochemistry, Ministry of Health, Kuwait City, Safat, Kuwait (Dr Al-Sarraf); Department of Pharmacy, Saint Joseph University, Beirut, Lebanon (Dr Abifadel); and Department of Biochemistry and Neuroendocrinology, Clinical Research Institute of Montreal, Montreal, QC, Canada (Dr Seidah)

KEYWORDS:
Familial hypercholesterolemia registry;
Cardiovascular diseases;
Cascade testing;
Mutations;
Genetic screening

BACKGROUND: Familial hypercholesterolemia (FH) is a well-understood Mendelian disorder that increases the risk of cardiovascular disease (CVD), a leading cause of mortality in Middle Eastern and North African (MENA) countries.

OBJECTIVE: Review the reporting status of FH mutations across MENA and propose a systemic and strategic method for building a MENA FH registry.

METHODS: Systematic literature search for statistics pertaining to CVD and comparison of number of FH mutations reported in MENA countries and countries with established FH registries.

RESULTS: Only 57 mutations were reported in 17 MENA countries, whereas more than 500 mutations reported in 3 Western countries. Mortality rates due to CVD were significantly higher in MENA countries compared with Western countries.

CONCLUSIONS: The relatively low reporting of FH mutations in the consanguineous MENA communities with higher prevalence of CVD indicates poor awareness of CVD genetic risk and warrants a registry to prevent premature CVD due to FH. This registry will help in identifying novel and reported FH mutations, all of which will have clinical and research benefits in MENA countries.

Introduction

Cardiovascular disease

Cardiovascular disease (CVD) is the generic term used to describe any disease that adversely affects the cardiovascular system and is the leading cause of mortality in North America [1] and in Middle Eastern and North African

* Corresponding author. Division of Clinical Biochemistry, King Abdulaziz University, Abdullah Sulayman, Jeddah 22254, Saudi Arabia.
E-mail address: zawan@kau.edu.sa
Submitted July 16, 2014. Accepted for publication November 23, 2014.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2014.11.008

(MENA) countries.[2,3] More individuals from developing countries such as Oman, Kuwait, Saudi Arabia, Lebanon, Egypt, and Morocco are now adopting the stereotypical Western lifestyle of low physical activity and fatty diet and have witnessed exponential Westernized urbanization in the past few decades.[3–5] Figure 1 (and Supplementary Tables 1 and 2) compares the mortality rates due to CVD between the MENA countries and Western countries as reported in the World Health Organization.[6,7] The mortality rates due to CVD were greater in the MENA group in 2002 ($P < 0.05$) and 2004 ($P < 0.05$), which is in line with the fact that CVD-related mortality is emerging in developing countries, despite declining in developed countries (Fig. 1).[8,9]

Consanguinity and its role in disease predisposition in MENA

The traditional practice of consanguinity in MENA countries is another reason CVDs are a concern. Consanguinity increases the inbreeding coefficient; it increases the risks of inheriting 2 defective alleles from the related parents through autozygosity[10] and decreases the frequency of protective heterozygosity. There are high rates of consanguinity in MENA region; consanguineous breeding increases the risk of having offspring with various diseases including cancer, diabetes, and heart diseases.[11] These diseases are more frequent and severe among individuals from consanguineous parents compared with individuals from nonconsanguineous parents.[11,12]

Familial hypercholesterolemia in MENA

In familial hypercholesterolemia (FH), hypercholesterolemia occurs due to perturbation of hepatic clearance of low-density lipoprotein (LDL) cholesterol (LDL-C).[13] The patterns of inheritance of FH were first described in Lebanon by Khachadurian.[14] Low-density lipoprotein receptor (*LDLR*),[15] apolipoprotein B-100 (*APOB*),[16] and proprotein convertase subtilisin/kexin type 9 (*PCSK9*)[17] are genes implicated in the autosomal dominant form of FH; low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*) is implicated in the autosomal recessive form of FH.[18] In North America, 1 in 500 individuals has heterozygous FH and 1 in 1,000,000 individuals has homozygous FH.[19] In the MENA region, the prevalence of FH is currently unknown,[20] which also instigates an urgent screening strategy.

Compared with Western countries, FH-related mutations have been inadequately reported in MENA countries[21–23] (Supplementary Table 3). We define the term "FH-related

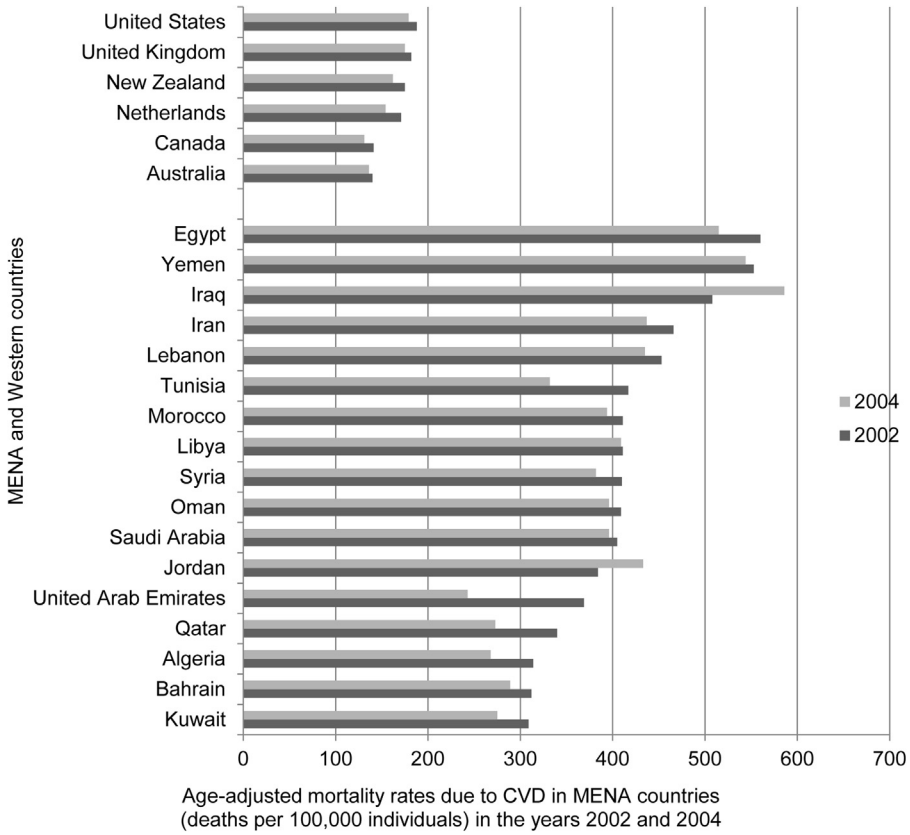

Figure 1 Mortality rates due to CVD in MENA countries and Western countries. This figure is a graph representing the age-standardized mortality rates (deaths per 100,000 individuals) due to CVD in MENA countries and Western countries for the years 2002 and 2004. Data used in creating this figure were taken from data presented by the WHO (http://www.who.int/gho/publications/world_health_statistics/EN_WHS2012_Full.pdf). CVD, cardiovascular disease; MENA, Middle Eastern and North African; WHO, World Health Organization.

mutation" as any variant that is associated with FH; thus, the term is inclusive of variants that are causative, associated or in linkage disequilibrium with causative variants. A systematic review in PubMed was done to identify all FH-related mutations reported in MENA and Western populations throughout the English language literature (till June 2014) using the advanced search term: (((*familial hyperchol*) AND (*mutation* OR *varia*)) AND (*report* OR *identi* OR *discov* OR *found* OR *find*)) AND *country*; respective country replaced 'country'. More than 500 FH-related mutations were reported from Australia, Netherlands, and New Zealand; 57 FH-related mutations were reported from 17 MENA countries (Supplementary Table 3).

The Moroccan, Tunisian, and Lebanese populations each reported 14 FH-related mutations, which was the highest number reported from MENA countries. No FH-related mutations were reported from the Kuwaiti, Qatari, Emirati, Jordanian, Libyan, Yemeni, and Egyptian populations (Supplementary Table 3). *LDLR* c.1706-2A>T,[23] *LDLR* p.E408K,[24] and *LDLR* c.2439G>A[25] were the only FH-related mutations reported from the Bahraini, Algerian, and Saudi Arabian populations, respectively. In MENA, FH-related mutations were only found in *LDLR*, *PCSK9*, and *LDLRAP1*, with majority in *LDLR*. No FH-related mutation was found in *APOB* in MENA. FH-related mutations due to *PCSK9* genes were reported only from the Omani (*PCSK9* p.V474I[21]), Tunisian (*PCSK9* p.F515L,[26] *PCSK9* p.E670G,[26] *PCSK9* p.P174S[27]), and Lebanese (*PCSK9* L21dup[28]) populations. FH-related mutations due to *LDLRAP1* gene were reported from only the Syrian (*LDLRAP1* c.89-1G>C[29]), Lebanese (*LDLRAP1* p.Q136X,[18] *LDLRAP1* c.605C>A,[18] *LDLRAP1* c.89-1G>C[30]), and Iranian (*LDLRAP1* c.71dupG[31]) populations (Supplementary Table 3). Small to large scale deletion mutations were only reported in *LDLR* and from the Omani (*LDLR* c.272delG[32]), Moroccan ("FH Morocco-1,"[33] "FH Morocco-2,"[33] *LDLR* c.756_762delCCGGCAG[34]), Tunisian ("FH-Souassi,"[35] *LDLR* c.2299delA,[27] *LDLR* 12684bp deletion including exons 2–5,[36] *LDLR* 2364bp deletion including exons 5–6[36]), and Iranian ("FH-Yrmeih"[37]) populations.

Nevertheless, some of the 57 reported FH-related mutations from MENA led to further understanding of genetics of FH. For instance, the "Arabic allele" (*LDLR* c.1706-2A>T) was first found among various Arab tribes[23]; it is a splice-site single base-pair substitution mutation that activates a cryptic splice site and results in deletion of bases.[23] The "Lebanese allele" (*LDLR* c.2043C>A) was originally found in the Lebanese population[38] and creates premature termination of LDLR (ie, *LDLR* p.C681X). This particular mutation explains most FH cases in the Lebanese population[38] and is reported in Brazilian, Canadian, Greek, United Kingdom, and French populations because of global Lebanese emigration.[23] Abifadel et al[28] was the first to implicate *PCSK9* as a possible modifier gene in FH by studying the impact of *PCSK9* polymorphisms on LDL-C levels of Lebanese FH patients carrying the Lebanese allele. Al-Hinai et al[32] reported the first Omani family where FH screening resulted in identification of a novel FH-related mutation, namely *LDLR* c.272delG. In Oman, Al-Waili et al[21] was the first to report an FH-related mutation in *PCSK9* in the Arab population, namely *PCSK9* p.V474I. *LDLR* p.G343C and *LDLR* c.2446A>T (a nonsense mutation) were first discovered in the Tunisian population.[39] Thus, a MENA FH registry would be an opportunity to identify more novel and known FH-related mutations from the MENA population.

Management of FH in MENA

Hypercholesterolemia can be reduced by dietary and lifestyle modifications.[40] Statins lower cholesterol by preventing cholesterol biosynthesis[40]; ezetimibe blocks the absorption of cholesterol from the small intestine[40]; and bile acid sequestrants increase the conversion of cholesterol to bile acids.[41] These treatment options are less effective in homozygous FH patients. Surgical intervention such as liver transplantation is the most effective treatment for homozygous FH[42] as it replaces dysfunctional LDLR with functional LDLR, which leads to near-normal LDL metabolism.[42] Khalifeh et al[43] reported a successful liver transplantation case of a homozygous FH patient, who was born to first cousins, in Lebanon. Other forms of surgical intervention for FH treatment were successful in Tunisia.[44] However, Alkhateeb et al[45] used 2 cases of Egyptian female homozygous FH individuals, who were both born to consanguineous parents, to emphasize the existing problem of poor FH diagnosis and management in Egypt. Thus, a MENA FH registry could lead to an efficient and uniform treatment regimen for both forms of FH across MENA.

A preventive measure toward decreasing the prevalence of homozygous FH would be for both consanguineous and nonconsanguineous individuals to be involved in genetic counseling and genetic testing before planning to have offspring. Although homozygous FH can result from consanguineous breeding due to autozygosity, homozygous FH can also result from breeding between nonrelated FH heterozygous individuals.

Materials and methods

Details can be found in Data Supplement file.

The need for a regional FH registry

A "patient registry" is defined as the uniform collection of patients through a systematic and comprehensive approach for clinical, research, and policy purposes.[46]

FH puts an individual at a 20-fold risk for CVD if untreated; a significant proportion of CVD patients have FH.[47] In the European Union, CVD costs its economy €169 billion per year; CVD costs the US economy $394 billion

per year.[48] Health care costs, which include inpatient, outpatient, and emergency care, accounted for most of the CVD economic burden; productivity loss (ie, working years lost because of CVD mortality) accounted for the remaining economic burden.[48] It is reasonable to assume that a similar cost is draining MENA economies. The relatively low reporting of FH with the higher prevalence of CVD in MENA (Fig. 1) instigates establishing an FH registry as a preventive measure toward reducing CVD burden, more so FH patients have 20-fold risk for CVD.

Hegele[49] excellently emphasized the contribution of genetic or genomic studies in unraveling lipoprotein metabolism and lipidology-related clinical practice. FH is underdiagnosed in most of the individuals due to its insidious progression.[20,50–52] Thus, identification of more FH patients, through an FH registry, would enable better statistically powered studies, scientific collaborations, meta-analytical studies, and international clinical trials. It also makes sense to have a regional registry, more so many researchers and bodies in the lipid field have recommended having regional registries.[46,52]

Many countries are establishing FH registries: United States, Canada,[52] and Australia[46] are catching up with European countries. Hitherto, the Netherlands FH registry is a prime model.[20,52–54] With the growing economy and medical expertise in the Gulf, MENA FH registry is projected to be successful as there could not be a better time for local intelligence to collaborate.

A proposed systemic and strategic method for building a regional FH registry

Because establishing an FH registry is relatively new, there is no "standard" rule in building one. The International FH foundation recently produced a very comprehensive, well-structured, consensus-based guidance for FH management from an international perspective by Watts et al[55]; it is an appropriate guide for all stages in the establishment of the MENA FH registry.[55]

Detection and diagnosis

Targeted, universal, and opportunistic screening strategies will be used to identify index FH cases in MENA populations[55]; individuals suspected to have FH would be recommended to lipid specialists if feasible. Figure 2 represents an acceptable criterion for FH screening and is to be evaluated after a 5-year period for efficiency. Watts et al[55] did not suggest any specific diagnostic criteria. Genotypic and phenotypic tests are ideal in FH diagnosis, but phenotypic testing can be used if genotypic testing is not feasible.[55]

Cascade screening and genetic testing

Cascade screening (or cascade testing) is the name given to the procedure where FH is diagnosed in relatives of an

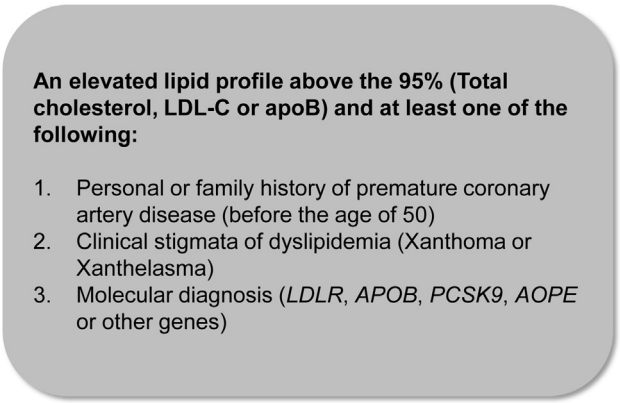

Figure 2 Suggested criteria to include individuals in the FH registry (MENA criteria for FH). APOB, apolipoprotein B-100; APOE, apolipoprotein E; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; MENA, Middle Eastern and North African; PCSK9, proprotein convertase subtilisin/kexin type 9.

FH individual starting with the index case (ie, the first individual with the clinical presentation of a disease in a pedigree) and then "cascading" throughout the extended family.[56] Figure 3 is modeled after the United Kingdom–based National Institute for Health and Care Excellence guidelines[57–60] (http://pathways.nice.org.uk/pathways/familial-hypercholesterolaemia#path=view%3A/pathways/

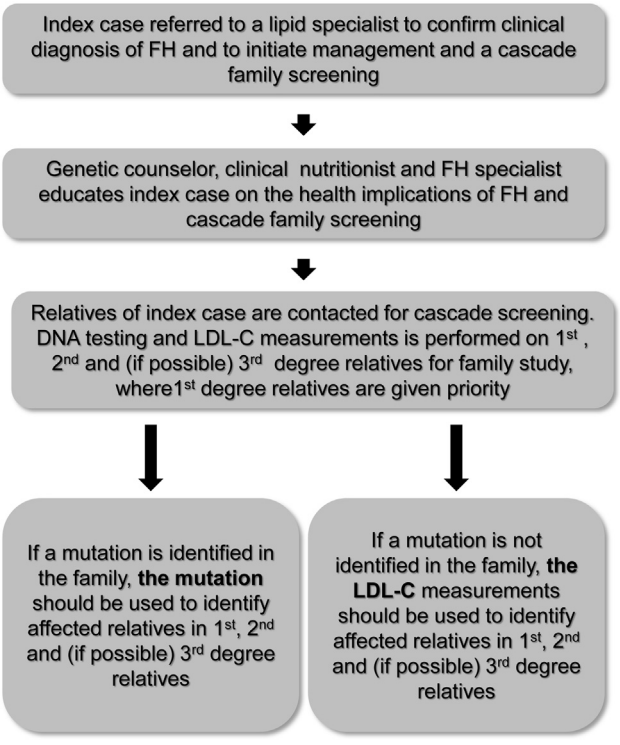

Figure 3 Flow diagram adopted from the United Kingdom–based NICE guideline for cascade screening in prospective MENA FH Registries. FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MENA, Middle Eastern and North African; NICE, National Institute for Health and Care Excellence.

familial-hypercholesterolaemia/diagnosing-familial-hypercholesterolaemia.xml&content=view-node%3Anodes-cascade-testing-of-family-members) and is a flow chart of cascade screening that can be used for the prospective MENA FH registry. Figure 3 is also congruent with Watts et al. Cascade screening was first established in the Netherlands in 1994; cascade screening is a cost-effective and accurate way of identifying FH individuals in a population.[53,56,61] In cascade screening, first-, second-, and third-degree relatives are screened as they have 50%, 25%, and 12.5% likelihood of inheriting the FH-causing mutations, respectively[62]; however, first-degree relatives (ie, parent, sibling, child) are priority for screening.[55] Because FH can be misdiagnosed if based only on early LDL-C measurements,[53] genetic testing is critical in the building of an FH registry. Figures 2 and 3 are made simple to increase the sensitivity of FH screening; confirmation of FH is made after referral to lipid specialists.

Hammond et al[46] underscored including FH-causing mutations in the proposed Australian–New Zealand FH registry. Al-Sarraf et al[52] also emphasized the inclusion of genetic information in his proposed FH registry model in Canada and the United States. Likewise, genetic screening would be performed for known FH-causing genes such as *LDLR*, *APOB*, autosomal recessive hypercholesterolemia (*ARH*), and *PCSK9* (ie, candidate gene approach). Copy number variants search and whole-exome sequencing[63] would be the next line of action if the candidate gene approach fails to identify mutations in the candidate genes. Next-generation resequencing panels for genetic dyslipidemias such as LipidSeq, which was produced by Johansen et al,[64] can also be implemented. Genetic testing must be performed in fully accredited laboratories with standardized procedures across MENA.[55] Thus, partnering with high throughput genetic screening programs would be essential.

Family history would be the best guide for initiation of FH treatment.[52] Networking within the health care infrastructure such as within research centers, clinical services, and university hospitals would help drive awareness.[46]

FH registry: An informational resource

Supplementary Table 4 is an oversimplified model of the database of the prospective MENA FH registry, which would help with potential epidemiologic studies, health policies, and international collaborative studies pertaining to FH. Thus, partnership with a good information technology provider, to develop and maintain a user friendly interface, is essential for the accessibility of the MENA FH registry by health care professionals across MENA. Supplementary Table 5 outlines some "action points" that would be undertaken in setting up the MENA FH registry. Data elements in Supplementary Table 4 are an agreeable minimum and achievable data set across MENA facilities. The final data elements will be confirmed with many stakeholders, including ethic committees, medical staff, and bioinformaticians, before the launch of the MENA FH registry.

Challenges, rights, and responsibilities regarding the MENA FH registry

Establishing FH registries successfully is predicated on population awareness of FH from families, physicians, and government officials; awareness of CVD risks associated with FH would also drive cascade testing. Awareness can be brought about by strong preregistry campaign (through media and walkathons) that could also resolve any cultural barriers in establishing the MENA FH registry. Registries also need to grow within the framework of the regional and local model of care for FH to be successful. Half of the Omani population believes premarital genetic tests should be mandatory.[65,66] In Saudi Arabia, premarital genetic screening is mandatory,[67] and 94.3% of Saudi nationals are very accepting of it.[68] Premarital genetic screening is also mandatory in Bahrain,[69] Iran,[70,71] and Lebanon.[72] These screening tests are usually for hemoglobinopathies that are common in the region; education of health risks was positively correlated with taking such tests.[66–68] So by and large, MENA nations surpass cultural challenges toward genetic screening, which would make acceptability to FH screening a matter of time.

Another challenge would be establishing patient support groups of FH families as FH patients are evidently the real stakeholders in FH screening.[73] Establishing a lipid clinic network throughout MENA would also be a milestone in the success of MENA FH registry[73] as there currently are few lipid specialists in the MENA region.

DNA testing can be funded fully or partially by patients or through partnership among academic centers, charities, and industry (including pharmaceutical). The registry charter, governing board, research, and ethics will be dictated by existing local medical societies working together with lipid specialists in academic centers. Additional funding may also come from charities and industry; many cancer and renal failure registries were supported by nongovernment funding.

Established centers for FH molecular diagnosis in some of the MENA countries can be certified and considered for focal centers for FH molecular diagnosis to support the MENA FH registry. These focal centers can be supported collectively by different grants and fund raising through different governmental and industrial support.

Collaborations of MENA lipid societies such as Oman Society of Lipid and Atherosclerosis and Saudi Heart Association with international lipid societies such as the National Lipid Association, International Atherosclerosis Society, and European Atherosclerosis Society for training and certification would make the task of establishing MENA FH registry more achievable and feasible.

Newson et al[74] showed that direct contact of relatives of index case is the most ethically justifiable method of contact,[57] and Watts et al[55] mandates principles of privacy, respect, justice, and autonomy in cascade screening. Committees will decide and justify authorization of information

access by employers, insurance companies, and family members.[53] Social and/or psychological aspects of FH would also underscore the advantage of employing psychological services in the establishment of the MENA FH registry.[45]

Conclusions

Because of the consanguineous culture of MENA communities, setting an FH registry is a golden opportunity to further unravel genetic etiology of FH. This is because MENA communities are the only communities in the world that have individuals with their gene pools preserved on a large scale, unlike other non-MENA communities that have individuals with their gene pools preserved on a much smaller scale such as the Amish populations. So, the wise saying that "every disappointment is a blessing in disguise" is applicable to the consanguineous culture of the MENA communities. This is because this cultural practice caused MENA communities to be criticized by the medical community. However, on the positive side, this homogenous genetic pool will not only make MENA communities ideal for genetic studies and complex diseases but will also make the MENA FH registry unique compared with all other existing registries.

Acknowledgments

Z.A. was supported by grant # MBK/03/434 from Seraj Kaki Chair for the study of genetic polymorphisms in cardiovascular disease and diabetes, King Abdulaziz University, Jeddah, Saudi Arabia. N.G.S. was supported by a CIHR grant # 102741 and a Canada Chair # 216684. M.A. was supported by Saint Joseph University grant # FPH36, Beirut, Lebanon, and the Lebanese National Council for Scientific Research grant # 04-09-13. We would like to acknowledge the medical bioinformatic assistance provided by Amr Awan.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jacl.2014.11.008.

References

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics–2013 update: a report from the American Heart Association. *Circulation*. 2013;127:e6–e245.
2. Alamoudi OS, Attar SM, Ghabrah TM, Al-Qassimi MA. Pattern of common diseases in hospitalized patients at an University Hospital in Saudi Arabia; a study of 5594 patients. *JKAU Med Sci*. 2009;16:3–12.
3. Ramahi TM. Cardiovascular disease in the Asia Middle East region: global trends and local implications. *Asia Pac J Public Health*. 2010;22:83S–89S.
4. Al-Kaabba AF, Al-Hamdan NA, El Tahir A, Abdalla AM, Saeed AA, Hamza MA. Prevalence and correlates of dyslipidemia among adults in Saudi Arabia: results from a national survey. *Open J Endocr Metab Dis*. 2012;2:89.
5. Al-Nozha MM, Arafah MR, Al-Maatouq MA, et al. Hyperlipidemia in Saudi Arabia. *Saudi Med J*. 2008;29:282–287.
6. Organization WH. World Health Statistics 2008. World Health Organization; 2008.
7. Gollogly L. World Health Statistics 2009. World Health Organization; 2009.
8. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation*. 1998;97:596–601.
9. Gersh BJ, Sliwa K, Mayosi BM, Yusuf S. Novel therapeutic concepts: the epidemic of cardiovascular disease in the developing world: global implications. *Eur Heart J*. 2010;31:642–648.
10. Thornhill NW. The Natural History of Inbreeding and Outbreeding: Theoretical and Empirical Perspectives. University of Chicago Press; 1993.
11. Bener A, Hussain R, Teebi AS. Consanguineous marriages and their effects on common adult diseases: studies from an endogamous population. *Med Princ Pract*. 2007;16:262–267.
12. El Mouzan MI, Salloum A, Herbish A, Qurachi MM, Omar A. Consanguinity and major genetic disorders in Saudi children: a community-based cross-sectional study. *Ann Saudi Med*. 2008;28:169.
13. Goldstein JL, Brown MS. The LDL receptor. *Arterioscler Thromb Vasc Biol*. 2009;29:431–438.
14. Khachadurian AK. The inheritance of essential familial hypercholesterolemia. *Am J Med*. 1964;37:402–407.
15. Brown MS, Goldstein JL. Expression of the familial hypercholesterolemia gene in heterozygotes: mechanism for a dominant disorder in man. *Science*. 1974;185:61–63.
16. Innerarity TL, Weisgraber KH, Arnold KS, et al. Familial defective apolipoprotein B-100: low density lipoproteins with abnormal receptor binding. *Proc Natl Acad Sci U S A*. 1987;84:6919–6923.
17. Abifadel M, Varret M, Rabes JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet*. 2003;34:154–156.
18. Garcia CK, Wilund K, Arca M, et al. Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. *Science*. 2001;292:1394–1398.
19. De Castro-Oros I, Pocovi M, Civeira F. The genetic basis of familial hypercholesterolemia: inheritance, linkage, and mutations. *Appl Clin Genet*. 2010;3:53–64.
20. Alghamdi M, Aljohani E. Clinical outcome of familial hypercholesterolemia (FH) at King Abdulaziz Medical City, Riyadh-A 20 year experience. *J Saudi Heart Assoc*. 2013;25:149.
21. Al-Waili K, Al-Zidi WA, Al-Abri AR, et al. Mutation in the PCSK9 gene in Omani Arab subjects with autosomal dominant hypercholesterolemia and its effect on PCSK9 protein structure. *Oman Med J*. 2013;28:48–52.
22. Muiya P, Wakil S, Al-Najai M, et al. Identification of loci conferring risk for premature CAD and heterozygous familial hyperlipidemia in the LDLR, APOB and PCSK9 genes. *Int J Diabetes Mellit*. 2009;1:16–21.
23. Shawar SM, Al-Drees MA, Ramadan AR, Ali NH, Alfadhli SM. The Arabic allele: a single base pair substitution activates a 10-base downstream cryptic splice acceptor site in exon 12 of LDLR and severely decreases LDLR expression in two unrelated Arab families with familial hypercholesterolemia. *Atherosclerosis*. 2012;220:429–436.
24. Lind S, Eriksson M, Rystedt E, Wiklund O, Angelin B, Eggertsen G. Low frequency of the common Norwegian and Finnish LDL-receptor mutations in Swedish patients with familial hypercholesterolaemia. *J Intern Med*. 1998;244:19–25.
25. Loux N, Benlian P, Pastier D, et al. Recurrent mutation at aa 792 in the LDL receptor gene in a French patient. *Hum Genet*. 1991;87:373–375.
26. Jelassi A, Slimani A, Jguirim I, et al. Effect of a splice site mutation in LDLR gene and two variations in PCSK9 gene in Tunisian families

with familial hypercholesterolaemia. *Ann Clin Biochem*. 2011;48:83–86.
27. Slimani A, Jelassi A, Jguirim I, et al. Effect of mutations in LDLR and PCSK9 genes on phenotypic variability in Tunisian familial hypercholesterolemia patients. *Atherosclerosis*. 2012;222:158–166.
28. Abifadel M, Rabes JP, Jambart S, et al. The molecular basis of familial hypercholesterolemia in Lebanon: spectrum of LDLR mutations and role of PCSK9 as a modifier gene. *Hum Mutat*. 2009;30:E682–E691.
29. Al-Kateb H, Bahring S, Hoffmann K, et al. Mutation in the ARH gene and a chromosome 13q locus influence cholesterol levels in a new form of digenic-recessive familial hypercholesterolemia. *Circ Res*. 2002;90:951–958.
30. Lind S, Olsson AG, Eriksson M, Rudling M, Eggertsen G, Angelin B. Autosomal recessive hypercholesterolaemia: normalization of plasma LDL cholesterol by ezetimibe in combination with statin treatment. *J Intern Med*. 2004;256:406–412.
31. Rodenburg J, Wiegman A, Vissers MN, Kastelein JJ, Stalenhoef AF. A boy with autosomal recessive hypercholesterolaemia. *Neth J Med*. 2004;62:89–93.
32. Al-Hinai AT, Al-Abri A, Al-Dhuhli H, et al. First case report of familial hypercholesterolemia in an Omani family due to novel mutation in the low-density lipoprotein receptor gene. *Angiology*. 2013;64:287–292.
33. El Messal M, Ait Chihab K, Chater R, et al. Familial hypercholesterolemia in Morocco: first report of mutations in the LDL receptor gene. *J Hum Genet*. 2003;48:199–203.
34. Ait Chihab K, Chater R, Cenarro A, et al. Familial hypercholesterolemia associated with severe hypoalphalipoproteinemia in a Moroccan family. *J Genet*. 2007;86:159–163.
35. Slimane MN, Lestavel S, Sun X, et al. Fh-Souassi: a founder frameshift mutation in exon 10 of the LDL-receptor gene, associated with a mild phenotype in Tunisian families. *Atherosclerosis*. 2001;154:557–565.
36. Jelassi A, Slimani A, Rabes JP, et al. Genomic characterization of two deletions in the LDLR gene in Tunisian patients with familial hypercholesterolemia. *Clin Chim Acta*. 2012;414:146–151.
37. Jensen HK, Jensen LG, Hansen PS, Faergeman O, Gregersen N. An Iranian-Armenian LDLR frameshift mutation causing familial hypercholesterolemia. *Clin Genet*. 1996;49:88–90.
38. Lehrman MA, Schneider WJ, Brown MS, et al. The Lebanese allele at the low density lipoprotein receptor locus. Nonsense mutation produces truncated receptor that is retained in endoplasmic reticulum. *J Biol Chem*. 1987;262:401–410.
39. Jelassi A, Jguirim I, Najah M, et al. Limited mutational heterogeneity in the LDLR gene in familial hypercholesterolemia in Tunisia. *Atherosclerosis*. 2009;203:449–453.
40. Pahan K. Lipid-lowering drugs. *Cell Mol Life Sci*. 2006;63:1165–1178.
41. Couture P, Lamarche B. Ezetimibe and bile acid sequestrants: impact on lipoprotein metabolism and beyond. *Curr Opin Lipidol*. 2013;24:227–232.
42. Page MM, Ekinci EI, Jones RM, Angus PW, Gow PJ, O'Brien RC. Liver transplantation for the treatment of homozygous familial hypercholesterolaemia in an era of emerging lipid-lowering therapies. *Intern Med J*. 2014;44:601–604.
43. Khalifeh M, Faraj W, Heaton N, Rela M, Sharara AI. Successful living-related liver transplantation for familial hypercholesterolemia in the Middle East. *Transpl Int*. 2005;17:735–739.
44. Jalel Z, Sobhi M, Skander BO, Adel K. Redux valvular surgery with coronary artery bypass graft in familial hypercholesterolemia. *Ann Pediatr Cardiol*. 2014;7:61–63.
45. Alkhateeb AA, Kassem HH, Wahba WA, Algowhary MI. Delayed diagnosis of familial hypercholesterolemia: a case report of two patients from Egypt. *J Clin Lipidol*. 2013;7:683–688.
46. Hammond E, Watts GF, Rubinstein Y, et al. Role of international registries in enhancing the care of familial hypercholesterolaemia. *Int J Evid Based Healthc*. 2013;11:134–139.
47. Youngblom E, Knowles JW. Familial hypercholesterolemia. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews(R). Seattle (WA): University of Washington, 1993.
48. Leal J, Luengo-Fernandez R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. *Eur Heart J*. 2006;27:1610–1619.
49. Hegele RA. Plasma lipoproteins: genetic influences and clinical implications. *Nat Rev Genet*. 2009;10:109–121.
50. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J*. 2013;34:3478–3490a.
51. Neil HA, Hammond T, Huxley R, Matthews DR, Humphries SE. Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: prospective registry study. *BMJ*. 2000;321:148.
52. Al-Sarraf A, Allard M, Martinka M, Frohlich J. Regional and national familial hypercholesterolemia registries: present international application, importance, and needs for Canada. *Can J Cardiol*. 2013;29:6–9.
53. Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, Scheerder RL, Kastelein JJ. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. *Lancet*. 2001;357:165–168.
54. Franke JG, Lansberg PJ. Dutch national screening and disease management program for Familial Hypercholesterolemia (FH)—a model for Saudi Arabia? *J Saudi Heart Assoc*. 2009;21:259–260.
55. Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. *Int J Cardiol*. 2014;171:309–325.
56. Datta BN, McDowell IF, Rees A. Integrating provision of specialist lipid services with cascade testing for familial hypercholesterolaemia. *Curr Opin Lipidol*. 2010;21:366–371.
57. Ned RM, Sijbrands EJ. Cascade screening for familial hypercholesterolemia (FH). *PLoS Curr*. 2011;3:RRN1238.
58. O'Brien EC, Roe MT, Fraulo ES, et al. Rationale and design of the familial hypercholesterolemia foundation CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia registry. *Am Heart J*. 2014;167:342–349.e317.
59. Identification and Management of Familial Hypercholesterolaemia (FH). London: National Collaborating Centre for Primary Care and Royal College of General Practitioners; 2008.
60. National Collaborating Centre for Primary C. National Institute for Health and Clinical Excellence: Guidance. Identification and Management of Familial Hypercholesterolaemia (FH). London: Royal College of General Practitioners (UK)Royal College of General Practitioners.; 2008.
61. Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HA. Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2000;4:1–123.
62. Wong S, Taraboanta C, Francis GA, Ignaszewski A, Frohlich J. The British Columbia Familial Hypercholesterolemia Registry. *BCMJ*. 2013;55:326–330.
63. Farhan SM, Hegele RA. Exome sequencing: new insights into lipoprotein disorders. *Curr Cardiol Rep*. 2014;16:507.
64. Johansen CT, Dube JB, Loyzer MN, et al. LipidSeq: a next-generation clinical resequencing panel for monogenic dyslipidemias. *J Lipid Res*. 2014;55:765–772.
65. Al Kindi R, Al Rujaibi S, Al Kendi M. Knowledge and attitude of university students towards premarital screening program. *Oman Med J*. 2012;27:291–296.
66. Al-Farsi OA, Al-Farsi YM, Gupta I, Ouhtit A, Al-Farsi KS, Al-Adawi S. A study on knowledge, attitude, and practice towards premarital carrier screening among adults attending primary healthcare centers in a region in Oman. *BMC Public Health*. 2014;14:380.
67. Alswaidi FM, Memish ZA, O'Brien SJ, et al. At-risk marriages after compulsory premarital testing and counseling for beta-thalassemia and sickle cell disease in Saudi Arabia, 2005-2006. *J Genet Couns*. 2012;21:243–255.

68. El-Hazmi MA. Pre-marital examination as a method of prevention from blood genetic disorders. Community views. *Saudi Med J*. 2006;27:1291–1295.
69. Al Arrayed SS, Al H. Premarital genetic counseling: a new law in the Kingdom of Bahrain. *Journal of Health, Social and Environmental Issues, Middle Sex University*. 2005;6:31–34.
70. Samavat A, Modell B. Iranian national thalassaemia screening programme. *BMJ*. 2004;329:1134–1137.
71. Zeinalian M, Nobari RF, Moafi A, Salehi M, Hashemzadeh-Chaleshtori M. Two decades of pre-marital screening for beta-thalassemia in central Iran. *J Community Genet*. 2013;4:517–522.
72. Abi Saad M, Haddad AG, Alam ES, et al. Preventing thalassemia in Lebanon: successes and challenges in a developing country. *Hemoglobin*. 2014;38:308–311.
73. Defesche JC. Defining the challenges of FH screening for familial hypercholesterolemia. *J Clin Lipidol*. 2010;4:338–341.
74. Newson AJ, Humphries SE. Cascade testing in familial hypercholesterolaemia: how should family members be contacted? *Eur J Hum Genet*. 2005;13:401–408.