Mini Review

Interventional Cardiology

Familial Hyperlipidemia Caused by Apolipoprotein B Mutation in the Pediatric Amish Population: A Mini Review

Corey Snyder[1], Amber L. Beitelshees[2], Devyani Chowdhury[1*]

[1]Cardiology Care for Children, Lancaster, PA, USA

[2]Department of Medicine and Program for Personalized and Genetic Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

*Author for correspondence:
Devyani Chowdhury, Cardiology Care for Children, Lancaster, PA, USA, E-mail: dchowdhury@cardiologylancaster.com

Received date: 02-Jun-2023, Manuscript No. FMIC-23-101131;
Editor assigned: 05-Jun-2023, PreQC No. FMIC-23-101131 (PQ);
Reviewed date: 19-Jun-2023, QC No. FMIC-23-101131;
Revised date: 26-Jun-2023, Manuscript No. FMIC-23-101131 (R);
Published date: 04-Jul-2023, DOI: 10.37532/1755-5310.2023.15(S17).433

Abstract

Familial Hypercholesterolemia (FH) is an autosomal dominant genetic disorder that causes increased low density lipoprotein cholesterol (LDL-C) levels and a higher risk of premature atherosclerosis and cardiovascular disease (CVD). Common causes of FH include inherited genetic mutations in the *LDLR*, *APOB*, and *PCSK9* genes. *LDLR, APOB,* and *PCSK9* mutations account for 79%, 5%, and <1% of cases of FH respectively. Apolipoprotein B (ApoB) is the necessary atherogenic lipoprotein which can serve as a determinant of cardiovascular disease including hypercholesterolemia. A founder variant in Apolipoprotein B (*APOB p.R3527Q*) causes FH and is found in 12% of the Pennsylvania Amish population. This article provides an overview of ApoB metabolism and clinical manifestations associated with *APOB* mutations. An understanding of the clinical manifestations caused by *APOB p.R3527Q* can be beneficial for the clinical diagnosis and treatment of FH in the Amish. Based on previous studies, changes in LDL cholesterol (LDL-C), LDL particles (LDL-P), small dense LDL particles, and ApoB levels can be seen among these patients putting them at an increased risk for atherosclerotic issues, vascular hardening, and changes in endothelial function, particularly among homozygous individuals.

Keywords: Familial hyperlipidemia • Amish • Apolipoprotein-B

Abbreviations: FH: Familial Hypercholesteromia; LDL-(P): Low Density Lipoprotein (Particles); LDL-C: Low Density Lipoprotein-Cholesterol; CVD: Cardiovascular Disease; ApoB: Apolipoprotein B; ApoA-1: Apolipoprotein A-1; HDL-(P): High Density Lipoprotein (Particles); sdLDL-(C): Small dense Lipoprotein (Cholesterol); Lp(a): Lipoprotein(a); CIMT: Carotid Intima-Media Thickness; PWV: Pulse Wave Velocity; NLA: National Lipid Association

Introduction

Familial hypercholesterolemia

FH is an autosomal dominant genetic disorder which typically causes increased LDL-C levels starting from a very young age and a higher risk of premature atherosclerosis and CVD [1,2]. Symptoms of CVD typically emerge in adulthood, but atherosclerosis begins during childhood [3-5]. Diagnosis for FH can be made through family history, genetic testing, and LDL levels. FH is caused by pathogenic genetic variants in *LDLR, APOB,* or *PCSK9*. This review will focus on *APOB* associated FH.

Amish population and founder effect

The Amish community is an isolated population that has a high prevalence of FH. A founder variant in Apolipoprotein B-100 (rs5742904, NC_000002.12; NM_000384.3; *APOB* c.10580G>A; p.Arg3527Gln; previously described as p.Arg3500Gln; referenced here as *APOB p.R3527Q*) has a 12% carrier frequency among the Amish of

Lancaster County, Pennsylvania [6]. A founder effect occurs when a small number of "founders" migrate out of a larger population to establish a new smaller population in which outside members cannot marry in, reducing the genetic variation in the new smaller group. The frequency of some genetic variants can become greatly enriched due to founder effects when one of the original founders carries a genetic variant that may be rare in other populations [7]. Such is the case with the *APOB p.R3527Q* variant which has a minor allele frequency of 6.7% in the Amish and only 0.08% in European populations [8,9].

This founder variant in *APOB* is a major determinant of LDL-C levels and coronary artery calcification in the Amish [6]. In previous studies, adults who were heterozygous for *APOB p.R3527Q* had 58-70 mg/dL higher LDL-C than non-carriers and were about 4.5 times more likely to have detectable coronary artery calcification [6,10]. Other lipid components, such as ApoB, Apolipoprotein A-1 (ApoA-1), LDL and HDL particles (LDL-P and HDL-P), small dense LDL Cholesterol (sdLDL-C), and Lipoprotein(a) may also be elevated and associated with atherosclerosis. Thus, to prevent or delay atherosclerotic complications caused by the *APOB p.R3527Q* variant in the Amish community, it is necessary to decrease LDL-C levels [11,12].

Lipid physiology

Apolipoprotein B can be found in two forms ApoB-48 and ApoB-100. ApoB-48 functions as part of a chylomicron which is used to transport fats through blood vessels. ApoB-100 protein's main function is to transport cholesterol through the arterial wall to be broken down in the liver. ApoB-100 is a necessary protein which helps LDLs to attach with their specific cell-surface receptors. A description of the function of Apolipoprotein B. ApoB is a crucial health determinant as high levels of ApoB may indicate a higher risk of cardiac disease due to elevated LDL levels leading to atherosclerotic changes [13]. Normal ApoB levels in adults are considered to be <100 mg/dL. It is widely accepted that an ApoB level of >110 mg/dL is considered high risk for cardiovascular disease.

In addition to LDL-C, other serum lipids are associated with atherosclerosis risk in adults, but their predictive utility in pediatrics is largely unknown. All pro-atherogenic lipoproteins, including LDL-C, contain one ApoB surface protein, so serum measurements of ApoB or the ratio of ApoB to ApoA-1 (the primary lipoprotein on HDL, a protective lipoprotein) may more accurately reflect the number of atherogenic particles and better predict CVD risk. Some studies support this hypothesis [2,14-19], while others have found ApoB and ApoB:ApoA-1 to be equivalent to LDL-C in predicting CVD risk [2,20-23]. Consistent with this observation, it was found that *APOB p.R3527Q* heterozygotes had elevations of ApoB and ApoB: ApoA-1 that were strongly correlated with LDL-C, suggesting that in patients with FH, these biomarkers might be interchangeable with predicted CVD risk [2].

Cholesterol content in LDL varies because some particles are large and have an abundance of cholesterol, whereas others are smaller in size and lack cholesterol. LDL-P has been shown to be a stronger predictor of CVD risk compared to LDL-C [24-26]. Others have shown its predictive value to be comparable to LDL-C [27]. *APOB p.R3527Q* heterozygotes had significantly increased LDL-P and LDL-C and LDL-P correlated strongly with LDL-C [2].

Lp(a) consists of a single ApoB with a plasminogen-like protein apolipoprotein(a). Lp(a) levels vary greatly among individuals and do not correlate with LDL-C, non-HDL-C, ApoB, or LDL particle number [28]. Lp(a) has been shown to be predictive of CVD risk in adults, independent of LDL-C, especially in those with elevated LDL-C and FH [11,29-32]. Lp(a) is higher in individuals with FH and it is theorized that severe increases of Lp(a) have an FH-like clinical phenotype [33-35].

Discussion

Other tests to assess atherosclerosis and vascular stiffness in children

Previous studies in children with FH, have shown higher carotid intima-media thickness (CIMT) among the affected children as compared to unaffected siblings beginning at 8 to 12 years of age [36]. It is unclear whether children with the *APOB p.R3527Q* variant have the same increases in CIMT [2]. In a study of 16 Amish young people ages 3-28 years with *APOB p.R3527Q* variant (13 heterozygotes, 3 homozygotes) and their unaffected age matched siblings, the study did not find a significant increase in CIMT [2]. The interaction of LDL-C and age was significant in the overall cohort, suggesting a cumulative effect of age and LDL-C on CIMT. Pulse wave velocity (PWV) is a method used to measure vascular stiffness and while it varies greatly in healthy pediatric subjects [37], it increases with age [38]. PWV has been found to be increased in children with FH [39]. However, in this study of *APOB p.R3527Q*, PWV did not differ significantly from controls and we found no correlations between PWV and either age or LDL-C [2]. Abnormal flow-mediated dilation is found in children with a family history of cardiovascular events, FH, and familial combined hyperlipidemia in other studies [40]. It is important to note that this study cohort of *APOB p.R3527Q* had lower LDL-C values than seen in many other forms of FH, which may explain the lack of differences in CIMT and PWV [2]. Taken together, these data suggest that *APOB p.R3527Q* may be less severe than other forms of FH. Additional studies of larger cohorts will help confirm whether these findings hold true.

Cascade screening

Genetic testing of at-risk family members of individuals with the *APOB p.R3527Q* variant (also known as cascade screening), can effectively identify individuals with FH so that early screening and treatment of high cholesterol can be undertaken. Even with similar LDL levels, people with FH have a higher risk of CVD than people without FH [41]. Homozygotes have a poor prognosis with mortality usually before the thirty years of age from a cardiovascular event [41]. Thus, wide spread and early screening to identify and treat FH can have significant improvements in disease management [42]. According to the National Heart, Lung, and Blood Institute, it is recommended that universal cholesterol screening occurs for all patients ages 9-11 and 17-21 because of hormonal changes through puberty [43]. Among individuals with a family history of high LDL (or FH), screening should begin at age 2 [43].

Pediatric cholesterol levels

Without genetic testing, heterozygous FH is typically suspected in children with LDL-C above 160 mg/dL and a positive family history or LDL-C above 190 mg/dL [44]. Cholesterol levels normally peak around age 9-11 years, decrease during adolescence, and steadily increase after age 17 years [45-48]. Studies have found that children and adolescents with *APOB p.R3527Q* have elevated levels of LDL-C compared to age-matched controls, similar to what is observed in adults with the same gene variant [2]. However, some individuals with *APOB p.R3527Q* may have normal or only slightly elevated LDL-C and may be overlooked using current cholesterol screening guidelines [49]. Other factors that may lead to the variability in LDL-C elevations among *APOB p.R3527Q* heterozygotes may include lifestyle or other environmental factors. At-risk family members of these individuals with normal or slightly elevated LDL-C could easily be missed, underscoring the necessity of cascade genotyping.

Treatment with statins is recommended for heterozygous FH starting at age 8-10 years after ruling out secondary causes and may occur simultaneously with lifestyle changes [50]. For homozygotes, statin therapy should be started at the time of diagnosis often occuring in infancy [50]. Given the increased cardiovascular risk in homozygotes, immediate therapeutics is recommended to improve atherosclerotic changes that may follow into adulthood [50-51].

Pregnancy and FH challenges

Pregnancy outcomes tend to be favorable in women with FH, however there are some special challenges that need to be considered [52]. This issue is of particular importance in the Amish given their large family sizes. During pregnancy, LDL-C serum levels typically increase for normal fetal growth. Increasing estrogen levels during pregnancy are thought to enhance synthesis of total cholesterol and LDL-C by about 30%–50% [52,53]. According to National Lipid Association (NLA) recommendations, women diagnosed with FH are advised to cease cholesterol reducing medications such as statins during pregnancy. While considered low risk, the use of cholesterol-lowering medications in pregnant women has shown fetal complications [54]. Lipoprotein apheresis is the treatment of choice for high-risk FH patients. Women with homozygous FH or with an established atherosclerotic vessel or aortic disease should be offered therapy with statins during pregnancy if lipoprotein apheresis is not readily available. Given the recommendations for stopping statin therapy during pregnancy, it is advantageous for women to be diagnosed as early as possible to manage their lipids properly before ending statin therapy while pregnant [55].

Conclusion

This review provides an overview of FH caused by *APOB p.R3527Q* in the Amish community with an emphasis on the pediatric population. Cascade genetic screening can provide early diagnosis of family members that have the variant. This early diagnosis is important given that, while fasting LDL-C is higher on average in children with *APOB p.R3527Q*, some heterozygous individuals have levels normal or below the threshold for suspecting FH, thus highlighting the value of genetic screening over LDL alone. Data remain conflicting, likely due to small sample sizes, on the extent to which elevations in LDL-C due to *APOB p.R3527Q* lead to premature cardiovascular disease. While our study in children and young adults with *APOB p.R3527Q* did not identify significantly increased CIMT or endothelial dysfunction, a study in middle-age adults did find increased coronary artery calcification among those with the variant. Nonetheless, it is prudent to screen for *APOB p.R3527Q* among Amish individuals, provide careful monitoring and offer treatment for elevated LDL.

Funding

This work was supported by the National Institute of Health (Grant number-NIH R01HL163514).

Conflicts of Interest

None.

Data Statement

None.

References

1. Wiegman A, Gidding SS, Watts GF, et al. Familial hyper cholesterolaemia in children and adolescents: Gaining decades of life by optimizing detection and treatment. Eur Heart J. 36(36):2425-2437 (2015).

2. Williams KB, Horst M, Young M, et al. Clinical characterization of familial hypercholesterolemia due to an amish founder mutation in apolipoprotein B. BMC Cardiovasc Disord.22(1):1-0 (2022).

3. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple

cardiovascular risk factors and atherosclerosis in children and young adults. N Engl J Med. 338(23):1650-1656 (1998).

4. Freedman DS, Wattigney WA, Srinivasan S, et al. The relation of atherosclerotic lesions to antemortem and postmortem lipid levels: The bogalusa heart study. Atherosclerosis. 104(1-2):37-46 (1993).
5. Homma S, Troxclair DA, Zieske AW, et al. Histological changes and risk factor associations in type 2 atherosclerotic lesions (fatty streaks) in young adults. Atherosclerosis. 219(1):184-190 (2011).
6. Shen H, Damcott CM, Rampersaud E, et al. Familial defective apolipoprotein B-100 and increased low-density lipoprotein cholesterol and coronary artery calcification in the old order amish. Arch Intern Med. 170(20):1850-1855 (2010).
7. Payne M, Rupar CA, Siu GM, et al. Amish, mennonite, and hutterite genetic disorder database. Paediatrics & child health. 16(3):e23 (2011).
8. GnomAD. SNV: 2-21229160-C-T(GRCh37). (2023).
9. rs5742904. Reference SNP (rs) Report. (2022).
10. Gary F, Lotas M. A population health approach to health disparities for nurses. Care Vuln Pop. (2022).
11. Willeit P, Ridker PM, Nestel PJ, et al. Baseline and on-statin treatment lipoprotein (a) levels for prediction of cardiovascular events: Individual patient-data meta-analysis of statin outcome trials. Lancet. 392(10155):1311-1320 (2018).
12. Luirink IK, Wiegman A, Kusters DM, et al. 20-year follow-up of statins in children with familial hypercholesterolemia. N Engl J Med. 381(16):1547-1556 (2019).
13. Behbodikhah J, Ahmed S, Elyasi A, et al. Apolipoprotein B and cardiovascular disease: Biomarker and potential therapeutic target. Metabolites. 11(10):690 (2021).
14. Benn M, Nordestgaard BG, Jensen GB, et al. Improving prediction of ischemic cardiovascular disease in the general population using apolipoprotein B: The copenhagen city heart study. Arterioscler Thromb Vasc Biol. 27(3):661-70 (2007).
15. Chien KL, Hsu HC, Su TC, et al. Apolipoprotein B and non-high density lipoprotein cholesterol and the risk of coronary heart disease in Chinese. J Lipid Res. 48(11):2499-505 (2007).
16. Holme I, Aastveit AH, Jungner I, et al. Relationships between lipoprotein components and risk of myocardial infarction: Age, gender and short versus longer follow- up periods in the Apolipoprotein Mortality Risk Study (AMORIS). J Intern Med. 264(1):30-38 (2008).
17. McQueen MJ, Hawken S, Wang X, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the Inter heart study): A case-control study. Lancet. 372(9634):224-233 (2008).
18. Parish S, Peto R, Palmer A, et al. The joint effects of apolipoprotein B, apolipoprotein A1, LDL cholesterol, and HDL cholesterol on risk: 3510 cases of acute myocardial infarction and 9805 controls. Eur Heart J. 30(17):2137-2146 (2009).
19. Pischon T, Girman CJ, Sacks FM, et al. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation. 112(22):3375-3383 (2005).
20. Ingelsson E, Schaefer EJ, Contois JH, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. JAMA. 298(7):776-785 (2007).
21. Mora S, Otvos JD, Rifai N, et al. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. Circulation. 119(7):931-939 (2009).
22. Ridker PM, Rifai N, Cook NR, et al. Non-HDL cholesterol, apolipoproteins AI and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA. 294(3):326-333 (2005).
23. Shai I, Rimm EB, Hankinson SE, et al. Multivariate assessment of lipid parameters as predictors of coronary heart disease among postmenopausal women: Potential implications for clinical guidelines. Circulation. 110(18):2824-2830 (2004).
24. Cromwell WC, Otvos JD, Keyes MJ, et al. LDL particle number and risk of future cardiovascular disease in the framingham offspring study-implications for LDL management. J Clin Lipidol. 1(6):583-592 (2007).
25. Mora S, Buring JE, Ridker PM, et al. Discordance of Low-Density Lipoprotein (LDL) cholesterol with alternative LDL-related measures and future coronary events. Circulation. 129(5):553-561 (2014).
26. Otvos JD, Mora S, Shalaurova I, et al. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. J Clin Lipidol. 5(2):105-113 (2011).
27. Blake GJ, Otvos JD, Rifai N, et al. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. Circulation. 106(15):1930-1937 (2002).
28. Feingold KR. Introduction to lipids and lipoproteins. (2021).
29. Alonso R, Andres E, Mata N, et al. Lipoprotein (a) levels in familial hypercholesterolemia: An important predictor of cardiovascular disease independent of the type of LDL receptor mutation. J Am Coll Cardiol. 63(19):1982-1989 (2014).
30. Bennet A, Di Angelantonio E, Erqou S, et al. Lipoprotein (a) levels and risk of future coronary heart disease: Large-scale prospective data. Arch Intern Med. 168(6):598-608 (2008).
31. Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, et al. Lipoprotein (a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 302(4):412 (2009).
32. O'Donoghue ML, Morrow DA, Tsimikas S, et al. Lipoprotein (a) for risk assessment in patients with established coronary artery disease. J Am Coll Cardiol. 63(6):520-527 (2014).
33. Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: Insights from epidemiology, genetics, and biology. J Lipid Res. 57(11):1953-1975 (2016).
34. Orsó E, Ahrens N, Schmitz G. Familial hypercholesterolemia and lipoprotein (a) hyperlipidemia as independent and combined cardiovascular risk factors. Atherosclerosis Supplements. 10(5):74-78 (2009).
35. Schmitz G, Orsó E. Lipoprotein (a) hyperlipidemia as cardiovascular risk factor: Pathophysiological aspects. Clin Res Cardiol Suppl. 10:21-25 (2015).
36. Braamskamp MJ, Hutten BA, Wiegman A, et al. Early initiation of statin treatment in children with familial hyper cholesterolaemia. Curr Opin Lipidol. 26(3):236-239 (2015).
37. Urbina EM, Williams RV, Alpert BS, et al. Noninvasive assessment of subclinical atherosclerosis in children and adolescents: Recommendations for standard assessment for clinical research: A scientific statement from the American heart association. Hypertension. 54(5):919-950 (2009).
38. Avolio AP, Deng FQ, Li WQ, et al. Effects of aging on arterial distensibility

in populations with high and low prevalence of hypertension: Comparison between urban and rural communities in China. Circulation. 71(2):202-210 (1985).

39. Riggio S, Mandraffino G, Sardo MA, et al. Pulse wave velocity and augmentation index, but not intima-media thickness, are early indicators of vascular damage in hyper cholesterolemic children. Eur J Clin Invest. 40(3):250-257 (2010).

40. Mietus-Snyder M, Malloy MJ. Endothelial dysfunction occurs in children with two genetic hyperlipidemias: Improvement with antioxidant vitamin therapy. J Pediatr. 133(1):35-40 (1998).

41. Nanchen D, Gencer B, Muller O, et al. Prognosis of patients with familial hypercholesterolemia after acute coronary syndromes. Circulation. 134(10):698-709 (2016).

42. Ned RM, Sijbrands EJ. Cascade screening for Familial Hypercholesterolemia (FH). PLoS currents. 3 (2011).

43. de Jesus JM. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Pediatrics. 128(S5):S213-S256 (2011).

44. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients: Clinical guidance from the national lipid association expert panel on familial hypercholesterolemia. J Clin Lipidol. 5(3):133-140 (2011).

45. Dai S, Fulton JE, Harrist RB, et al. Blood lipids in children: Age-related patterns and association with body-fat indices: Project heart beat! Am J Prev Med. 37(1):S56-S64 (2009).

46. Gooding HC, Rodday AM, Wong JB, et al. Application of pediatric and adult guidelines for treatment of lipid levels among USA adolescents transitioning to young adulthood. JAMA pediatrics. 169(6):569-574 (2015).

47. Hickman TB, Briefel RR, Carroll MD, et al. Distributions and trends of serum lipid levels among United States children and adolescents ages 4-19 years: Data from the third national health and nutrition examination survey. Prev Med. 27(6):879-890 (1998).

48. Kwiterovich Jr PO, Barton BA, McMahon RP, et al. Effects of diet and sexual maturation on low-density lipoprotein cholesterol during puberty: The Dietary Intervention Study in Children (DISC). Circulation. 96(8):2526-2533 (1997).

49. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics. 128:S213-S256 (2011).

50. Fiorentino R, Chiarelli F. Statins in children, an update. Int J Mol Sci. 24(2):1366 (2023).

51. Khoury M, McCrindle BW. The rationale, indications, safety, and use of statins in the pediatric population. Can J Cardiol. 36(9): 1372-1383 (2020).

52. Graham DF, Raal FJ. Management of familial hypercholesterolemia in pregnancy. Curr Opin Lipidol. 32(6):370-377 (2021).

53. Piechota W, Staszewski A. Reference ranges of lipids and apolipoproteins in pregnancy. Eur J Obstet Gynecol Reprod Biol. 45(1):27-35 (1992).

54. Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolemia from the international FH foundation. J Clin Lipidol. 8(2):148-172 (2014).

55. Lundberg GP, Mehta LS. Familial hypercholesterolemia and pregnancy. Am Coll Cardiol. 2018.