Result of Genetic Analysis in FH Case

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Dear Editor,

In the last issue of Bangkok Med J 2018, Vol. 14(1): page 57-62, we reported an aborted sudden coronary death in a very young man, age of 29 years.[1] Although he had no other atherosclerotic risk factors, severe hypercholesterolemia was noted with LDL cholesterol of 186 mg/dl, tendinous xanthoma and family history of dyslipidemia, suggestive of an inherited condition. By clinical criteria, he was diagnosed with familial hypercholesterolemia (FH).[2-4]

FH is an inherited hypercholesterolemia, caused by mutations in any of the three major genes encoding cholesterol trafficking proteins including LDL receptor *(LDLR)*, *APOB* (the ligand for the *LDLR*) and PCSK9 (the regulator of *LDLR*'s turnover), required for hepatic clearance of plasma LDL.[4] Figure 1 below summarizes the effect of mutations resulting in reduced or dysfunctional LDLR, malfunction of APOB, or excessive function of PCSK9. The fourth gene, *LDLRAP1*, controls production of a chaperone protein that carries the LDLR on the sinusoidal side of the hepatocyte.[5] All of these changes have been reported to cause lifelong exposure to hypercholesterolemia, xanthomatosis, premature atherosclerosis, and sporadic sudden coronary death at a young age, as in our reported case.[2-4] Prevalence of heterozygous mutations in LDLR, APOB, and PCSK9 mutations is > 90%, ~5%, and ~1%, respectively among patients with genetically determined FH.[6] Further detail of FH has been summarized in this Journal by Shapiro and Fazio.[4]

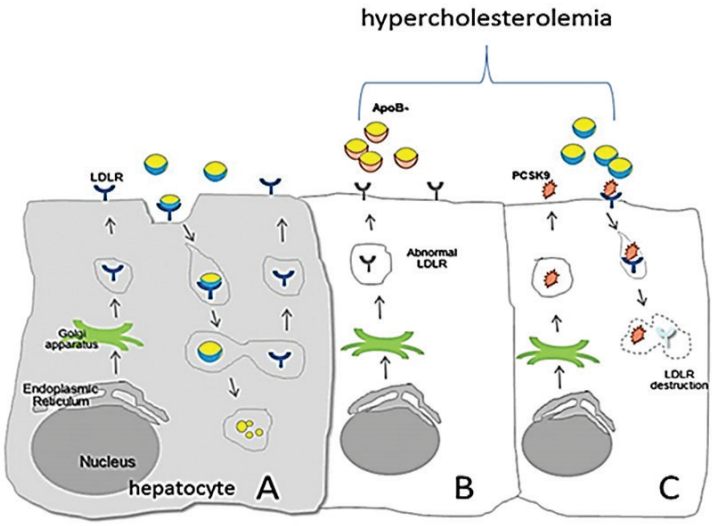

Figure 1: In A, LDL cholesterol (yellow circles) is carrying by normal APOB (blue segment) and is internalized by the hepatocyte via the action of normal LDL receptor (dark blue LDLR in A). Mutations in LDLR (black LDLR in B) or ApoB (orange segment in B), and in PCSK9 (C) impair hepatic LDL transport and result in lifelong hypercholesterolemia.

We now report on the result of genetic analysis performed on blood DNA from our patient. No mutation was found in *APOB*, *LDLRAP1 or PCSK9*. However, a heterozygous mutation was found in the *LDLR*: c1241T>G (p.Leu414Arg). This mutation changes the amino acid at position 414, where the highly co nserved leucine is substituted by arginine. This L414R mutation has been previously reported in several Chinese patients but was designated differently as L393R in some publications.[7-9] It is categorized as likely pathogenic and likely related to hypercholesterolemia in this patient, since it is predicted to be disruptive to the function of LDLR protein by three prediction algorithms (SIFT, PolyPhen-2 and Align-GVGD) and is also found at a very low allele frequency of 0.001% in ExAc database (rs748554592). The functional effect of this mutation is uncertain due to the location of L414R is in the beta strand region but outside of the calcium binding EGF-like domain.[10] It might be hypothesized to interfere with LDLR protein folding and thus LDLR recycling. The patient and family members have been informed and genetic counselling is provided.

This case illustrates the importance of properly diagnosing familial hypercholesterolemia in younger patients to implement aggressive preventive therapy and reduce the risk of cardiac complications including sudden death. In addition, the case supports our contention that a prospectively designed cohort study is necessary to determine the true prevalence of FH and its mutation spectrum in the Thai population.

References

1. Veerakul G, Shapiro M, Fazio S et al. Aborted Sudden Cardiac Death in Young Man with Familial Hypercholesterolemia: A Case Report and Review of The Literature. *BKK Med J* 2018; 14(1):57-62.
2. Scientific Steering Committee on behalf of the Simon Broome Register Group. Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. *Atherosclerosis* 1999;142:105-12.
3. Civeira F. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis* 2004;173: 55-68.
4. Shapiro M, Fazio S. Familial Hypercholesterolemia: Use of Registries, Biobanks, and Cohort Studies To Improve its Diagnosis and Management in Non-Western Populations. *Bangkok Med J* 2018; 14(1):63-8.
5. Garcia CK, Wilund K, Arca M et al. Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. *Science* 2001;292(5520):1394-8.
6. Austin MA, Hutter CM, Zimmern RL, et al. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *Am J Epidemiol* 2004;160:407-20.
7. Mak YT, Pang CP, Tomlinson B et al. Mutations in the Low-Density Lipoprotein Receptor Gene in Chinese Familial Hypercholesterolemia Patients. *Arterioscler Thromb Vasc Biol* 1998;18: 1600-5.
8. Livy A, Lye SH. Familial hypercholesterolemia in Asia: A Review. *OMIC Res* 2011;1:22-31.
9. Jeenduang N, Ruangpracha A, Promptmas C, et al. Two novel D151Y and M391T LDLR mutations causing LDLR transport defects in Thai patients with familial hypercholes- terolemia. *Clin Chim Acta* 2010;411:1656-61.
10. The UniProt Consortium. UniProt: the universal protein knowledge base. *Nucleic Acids Res*. 2017;45:D158-D169.

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