Whole Exome Sequencing in Monogenic Dyslipidemias

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Editorial

Advances in Whole Exome Sequencing in Monogenic Dyslipidemias

Whole exome sequencing (WES) has emerged as a promising tool for gene discovery in families with suspected monogenic disorders, including dyslipidemias, with a success rate exceeding 20%\(^1\). The discovery of the genetic basis underlying monogenic forms of dyslipidemia has revealed insights into human lipid metabolism and has accelerated the development of novel therapeutics\(^2\). In this issue of the journal, Chiou et al. tried to extend this approach to a rare condition of familial hypertriglyceridemia (a large family with 22 members). After applying typical variant filtering (functional annotations, allele frequency, and segregation pattern), true causal variants could be determined in these subjects not from target resequencing but from an exome-wide approach\(^3\). Although such comprehensive approach usually ends up to find rare causative variant(s) in an already known gene as shown in this case, it is quite useful to exclude the possibility of other unknown causative genes. In general, hundreds or thousands of variants are found in an individual through WES approach\(^4\). Then, typically, the variants predicted as benign, common, and unmatched assuming co-segregation are to be excluded (Fig. 1). In this process, great advances have been made in the fields of \textit{in silico} variant annotation prediction as well as in the information of allele frequency of a certain variant based on huge efforts of collaborations in exome-sequenced data set publicly available\(^5\). However, the most important part of this process, namely “phenotypical assessments including a segregation pattern” should be recognized. To define a segregation pattern, a lot of phenotypical information from the relatives of the proband needs to be collected\(^6\). Sometimes, it is quite difficult to follow and investigate their relatives because of the physical (and social) distance from the proband. Even the most sophisticated variant annotation prediction with the perfect allele frequency information produces nothing, if detailed phenotypical assessments of the proband (and the relatives) are not available. In this regard, the present study has an advantage of presenting a large family with a clear phenotype in their serum triglyceride (TG) levels to pursue this approach. Moreover, at least one of the following is needed to claim (a) certain variant(s) as causative; 1) functional analysis using genetic modification(s); 2) finding other families with the same variant(s) exhibiting the same phenotype; and 3) follow-up study using controls. The current study successfully demonstrated that the TT genotype of rs2075291 in \textit{APOA5} was significantly associated with very high levels of TG using 65 unrelated cases and 122 controls.

\textit{APOA5}, Triglyceride, and Myocardial Infarction

\textit{APOA5}, which increases lipoprotein lipase (LPL)-mediated TG hydrolysis, has been shown to be associated with plasma TG levels both in common variant association study and in rare Mendelian manner\(^7, 8\). Recently, Kathiresan and coworkers have shown that rare variants in \textit{APOA5}, including Gly185Cys, were significantly associated with elevated risk of early onset myocardial infarction, accounting for approximately 1% of such cases through a case--control study design with WES approach (Fig. 2)\(^9\). This is a quite impressive study, characterized by an unbiased manner with...
a large sample size, revealing that at least 1% of hypertriglyceridemic cases could be hereditable not due to LPL but due to APOA5 mutations. In addition, serum TG level itself has been demonstrated as a causative factor, rather than a mere marker, through recent Mendelian randomization approach. These investigations could lead us to speculate that (severe) hypertriglyceridemia associated with early onset of coronary artery disease caused by APOA5 mutation(s) are rather common and that manipulation of this molecule could be potential therapeutic target to reduce the “residual risk” with statins.

Targeting or Whole Exome?

In this next generation sequencing (NGS) era, the molecular diagnosis for monogenic (or polygenic) dyslipidemia could be in either two ways: custom dyslipidemia-specific NGS panel or bioinformatic analysis of genome-wide data, including WES. The advantages of the former approach are lower cost and limited ability to detect incidental pathogenic variants unrelated to dyslipidemia. However, the latter approach is more flexible and potentially useful in terms of the possibility of discovery of novel genes contributing to the phenotype because the variant filtering can be altered as an advantage of the knowledge about lipid metabolism.

Conclusion

WES has now been clinically feasible based on the development of the novel genotyping and sequencing technology as well as extensive catalogs of human genetic variation together with novel analytical methods. Rigorous efforts are currently underway, and it is indisputable that these efforts could reveal the contribution of rare variants to the overall genetic architecture of lipids and dyslipidemias in the next few years.

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Conflict of interest

None.
Fig. 2. APOA5 mutations discovered after sequencing of 13,432 individuals.
Individual mutations (non-synonymous, indel frameshift, and splice-site variants with minor allele frequency less than 1%) are depicted according to the genomic position along the length of APOA5 starting at the 59th end (top). The number of circles on the left and right represents the number of times that mutation is observed in cases or controls, respectively. Dashed lines across the gene connect the same mutation seen in both cases and controls. Mutations are shaded in red (observed in cases only), blue (observed in controls only), or yellow (observed in both cases and controls). This figure is kindly provided by the author of the reference 9 (Hong-Hee Won).
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References


5) Exome Aggregation Consortium (ExAC), Cambridge, MA (URL: http://exac.broadinstitute.org)


