Myocardial infarction (MI), a severe manifestation of coronary artery disease (CAD), is a leading cause of death worldwide. Although many environmental, social, and behavioral risk factors contribute to its pathogenesis, genetic factors exert a substantial influence on disease risk, particularly for early onset forms of CAD and MI. To date, genome-wide association studies (GWASs), predominantly using samples of European or South Asian ancestry, have identified >45 independent common CAD loci, as well as 9 early onset MI loci. Although some of the identified gene regions impact lipid or blood pressure regulatory pathways, many more offer new and unexpected pathogenic insights. Despite these large-scale efforts, leveraging large sample sizes in both case–control and longitudinal cohort study designs, a substantial proportion of the heritable risk of CAD and MI remains unexplained. Furthermore, despite the known epidemiological link between type 2 diabetes mellitus and CAD/MI, none of the established common genetic risk variants for these diseases has a known association with type 2 diabetes mellitus.

Although the majority of replicated CAD and MI risk variants have been detected using GWAS methodologies, linkage analysis has also been used to varying degrees of success. Linkage analysis across 3 generations of a family with multiple members with CAD identified a strong linkage signal at 15q26, mapped to a deletion in the gene. Although some of the identified gene regions impact lipid or blood pressure regulatory pathways, many more offer new and unexpected pathogenic insights. Despite these large-scale efforts, leveraging large sample sizes in both case–control and longitudinal cohort study designs, a substantial proportion of the heritable risk of CAD and MI remains unexplained. Furthermore, despite the known epidemiological link between type 2 diabetes mellitus and CAD/MI, none of the established common genetic risk variants for these diseases has a known association with type 2 diabetes mellitus.

Although the majority of replicated CAD and MI risk variants have been detected using GWAS methodologies, linkage analysis has also been used to varying degrees of success. However, linkage analysis across 3 generations of a family with multiple members with CAD identified a strong linkage signal at 15q26, mapped to a deletion in the MEF2A gene. Although this locus was attractive from a mechanistic standpoint attributable to its high levels of expression in embryonic coronary vasculature, replication efforts failed to identify this mutation in sporadic cases, and in further analyses, it seems that the reported low-frequency deletion does not segregate with CAD or MI outside of the discovery family. Another genome-wide linkage analysis in 300 Icelandic families identified a linked haplotype in the ALOX5AP gene, which encodes a protein involved in leukotriene production, in association with both MI and stroke. Although this discovery may offer new insights into the pathogenesis of multiple manifestations of vascular disease, this locus has not yet been replicated in large-scale GWASs, and therefore its significance remains unclear. Linkage analysis works most efficiently when genotypes segregate closely with phenotypes, as in Mendelian disease, and suffers when multiple pleiotropic genetic and environmental factors act in concert to cause disease. Although GWASs are more scalable to address small and less-penetrant effects, it is possible that in certain situations linkage analysis retains superior statistical power. Whether the sometimes divergent results from linkage and GWAS analyses will ultimately resolve with aggregation of even greater study power remains to be seen.

In this issue of Circulation: Cardiovascular Genetics, Ichihara et al use a multimodal approach using both linkage and GWAS analysis techniques in an East Asian population to identify a novel gene, ALMS1, as a putative risk factor for early onset MI. In their discovery phase, the authors performed linkage analysis in 455 individuals from 221 families with CAD, using both single-nucleotide polymorphisms and microsatellites, and identified an MI-linked region on chromosome 2p13. Next, using 112 MI probands from the discovery phase and 495 controls, the authors performed single-nucleotide polymorphism–based association testing on the window from 2p12 to 2p14, revealing MI-associated variants in the AMLS1-C2orf78 gene region. This locus was then examined in 2 rounds of association-based independent replication in sporadic and early onset MI populations of both Japanese and Korean ancestry, confirming the associations from the discovery stage. In further exploration, the authors sequenced the coding region of ALMS1 in 24 MI probands from the discovery phase and identified a glutamate repeat polymorphism in exon 1. This rare polymorphism was then independently replicated in 351 early onset MI cases and 6026 controls of Japanese ancestry, confirming the association. Finally, the authors performed functional work using transformed lymphoblastoid cells, with results suggesting increased ALMS1 expression related to the risk genotype.

Ichihara et al conclude that ALMS1 represents a novel risk locus for early onset MI in the East Asian population and postulate that ethnic population–specific effects combined with methodological differences between linkage analysis and GWAS account for the fact that this locus has not yet been identified in published GWAS efforts of early onset MI. Certainly, ALMS1 is an interesting gene, best known for its association with the autosomal recessive Alström syndrome, which is characterized by obesity, insulin resistance, type 2 diabetes mellitus, cardiomyopathy, and renal and hepatocellular dysfunction. Although ALMS1 is widely expressed in multiple human tissue types, its exact function is unknown.

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Because multiorgan fibrotic changes are prevalent in Alström syndrome, a role in regulation of extracellular matrix has been postulated. Although CAD is not a feature of this syndrome, most affected individuals do not live far into adulthood, which may limit expression of such a phenotype. If these results can be independently validated, the presence of hyperinsulinemia and type 2 diabetes mellitus in Alström syndrome merits further exploration as a potential mechanism of ALMS1 in early onset MI.

The present study by Ichihara et al 15 highlights several issues pertinent to genetic discovery in the modern era. First is the importance of multistage replication and an integrative genomic approach to gene discovery, which is particularly crucial in this study given the checkered history of linkage analysis in complex human cardiovascular disease. Combining linkage and common variant association strategies in independent samples of differing East Asian ethnicities strengthens the case for the ALMS1 locus in that population. Furthermore, by identifying a potentially functional glutamic acid repeat rather than a tagging single-nucleotide polymorphism, the authors provide evidence for a biological correlate to their genetic findings. Not only does this support their hypothesis, but it also provides a clearer path for future efforts to validate and build on their findings. Finally, this study emphasizes the importance of using multiethnic populations in the analysis of complex human traits because this strategy may maximize power for discovery for subpopulations in which pleiotropic genetic or environmental factors act serendipitously to strengthen genotype–phenotype associations.

Whether ALMS1 will become a validated genetic risk factor for early onset MI remains to be seen. Further efforts to explore this locus in existing CAD and MI cohorts of multiple ethnicities should be considered to determine whether trending associations below the genome-wide significance threshold exist in other populations and whether the common variants identified by Ichihara et al 15 exhibit substantial stratification by ethnicity. If the effect of ALMS1 on early onset MI cannot be explained by population specificity, then explanations for why large-scale GWASs have not yet revealed risk associations at ALMS1 must be sought. Certainly, if the differences in loci identified using linkage versus genome-wide association strategies could be explained by variation in study power between the 2 approaches, then the information gleaned from these follow-up investigations could yield new information not only on the pathogenesis of early onset MI but also on techniques to maximize power and reproducibility in future large-scale genetic discovery efforts.

Disclosures

None.

References


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Genome-Wide Linkage Approach Yields Novel Early Onset Myocardial Infarction Locus in East Asians
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