Genetics and early-onset myocardial infarction

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Background

Coronary heart disease (CHD) is the leading cause of death in the Western world. For effective treatment and prevention, the complex molecular processes underlying CHD, as well as factors predisposing to atherosclerosis, should be identified. Clinical and epidemiological studies have documented that several types of risk factors – such as age, male sex, family history of myocardial infarction (MI), increased serum total and low-density lipoprotein cholesterol, decreased serum high-density lipoprotein cholesterol, smoking history, and presence of diabetes mellitus – predict the risk for atherogenesis[1-5]. Furthermore, both inflammation linked with disadvantageous plasma lipoprotein profile and chronic infections have also been proposed as risk factors for CHD[6,7]. Clearly, CHD is a multifactorial disease in which risk factors tend to cluster and interact in individuals and families to determine the level of risk. In addition, risk evaluation is further complicated by the unknown relationship between the underlying genetic and environmental risk factors.

The genetic background in common diseases merges from combinations of risk alleles that, together with environmental risk factors, lead to the development of the disease phenotype[8]. Numerous studies have been carried out to identify the genes that have alleles that can predispose to CHD. Considerable evidence now indicates that variation in genes encoding the apolipoprotein E, apolipoprotein(a), methyltetrahydrofolate reductase, and angiotensin-converting enzyme play a role in the development of CHD[9-12]. However, the size and nature of the effects of these and other genes influencing the risk of CHD are still largely unknown. Evidence for genetic involvement in the development of CHD has been obtained from studies showing that family history of CHD increases the risk for CHD[13-15] and also from family studies estimating heritability of CHD to be 56-63%[16]. To increase the impact of genetic involvement and the possibility of identifying contributing predisposing genes, a careful selection of the study sample is advised[17-19]. Families with multiple affected individuals, extreme phenotypes, young subjects with early-onset disease, and individuals originating from populations with restricted genetic variation may increase the possibility of indentifying genetic risk factors by decreasing etiological heterogeneity. Genomewide linkage studies have been utilized to identify loci for complex disorders and to search for evidence of major gene effects. To date, however, no genome scans have been reported for premature CHD but the scan described by Pajukanta et al.[20] who conducted a genome-wide search for CHD loci in well-documented families affected by premature CHD that originate from the genetically isolated population of Finland. By using a two-stage strategy, in which the first stage of the scan, with an average marker interval of 10 cM, was followed by fine mapping of interesting regions, they were able to identify two chromosomal regions that may harbor loci with alleles that predispose to premature CHD: one on chromosome 2q21.1-22 and another on chromosome Xq23-26.

Early-onset coronary heart disease

The idea that the dissection of genetic factors predisposing to (or protecting

from) CHD is easier in affected individuals without apparent risk factors (or alternatively in non-affected individuals with risk factors) has been implemented in a collaborative effort by some Cardiology Units operating in the region of Piedmont (Italy) and the Department of Genetics, Biology and Biochemistry of the University of Turin (Italy). Our sampling design was to consider age as a primary risk factor and to select cases without this risk factor (young individuals) with early-onset acute MI as a preferential target to identify possible genetic components. The preliminary results reported by Brscic et al.[21] were based on a sample of 106 patients aged < 45 years with a diagnosis of acute MI. The following genetic polymorphisms: angiotensin I-converting enzyme, angiotensin II type 1 receptor, apolipoprotein E, endothelial constitutive nitric oxide synthase and platelet glycoprotein IIIa, were tested and compared with a control group without acute MI matched for age and sex. The conclusion was that the only clear-cut genetic independent predictor of an early-onset MI is the presence of the allele ε4 of the apolipoprotein E polymorphism, confirming the remarkable influence of this genetic marker in anticipating CHD onset.

In a more recent and updated study[22] a total of 174 young subjects with acute MI (including the previous ones) and 174 healthy controls matched for age and sex have been tested for other two genetic polymorphisms, the transforming growth factor (TGF)-β_1 and the aldosterone synthase (CYP11B2). The prevalence of the CC genotype of CYP11B2 gene was 28.7% in the cases vs 17.2% in controls (p = 0.040, odds ratio-OR 1.56, 95% confidence interval-CI in the range 1.10-2.20); the prevalence of the GG genotype of TGF-β_1 gene was 28.1% in the cases vs 12.8% in controls (p = 0.002, OR 1.94, 95% CI 1.33-2.81). At follow-up of the group of the cases which lasted more than 4 years, a statistically significant increase in the frequency of the apolipoprotein E ε4 allele has been found among the cases who experienced a second MI event (ε4 vs non-ε4 carriers p = 0.020, OR 3.59, 95% CI 1.40-9.19). A significant increase in the frequency of the C allele of angiotensin II type 1 receptor gene has also been observed in the same group (AC + CC vs AA p = 0.017, OR 2.75, 95% CI 1.36-5.56).

In conclusion our preliminary findings seem to show that:

• the proteins coded by the genes TGF-β_1 and CYP11B2, which play a pivotal role in many regulatory processes, may be also involved in vascular remodeling[23] and pathogenesis of atherosclerosis[24];

• the GG genotype of TGF-β_1 gene and the CC genotype of CYP11B2 gene should be considered as risk factors for the occurrence of acute MI at young age, while the presence of the apolipoprotein E ε4 allele or angiotensin II type 1 receptor C allele may be associated with a worse prognosis after acute MI has occurred.

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