A positive family history is frequently reported by patients with coronary artery disease (CAD) or myocardial infarction. For risk stratification, it is crucial to distinguish between accidental reoccurrence of sporadic cases and cases with a true heritable component of the conditions. A familial predisposition is assumed when a myocardial infarction is diagnosed by a male first degree relative before the 55th year of life or a female first degree relative before the 65th year of life. The current manuscript reviews major studies from which a familial risk of CAD or myocardial infarction can be inferred. Moreover, a brief overview summarizes the current results of molecular genetic research on chromosomal loci and genes relevant for CAD and myocardial infarction.

Epidemiology of CAD and myocardial infarction

Within Europe, the incidence of myocardial infarction shows a prominent north-south gradient. Whereas 500 cases per year out of 100,000 inhabitants are observed in Finland, only 125/100,000 cases are recorded in South Eastern Europe [1]. Differences in lifestyle, e.g., dietary and smoking habits as well as climate are thought to be responsible for this regional distribution [1]. In addition, the prevalence of lipid metabolism disorders is increased in Scandinavian countries [2]. The INTERHEART Study concluded that vascular risk factors explain just under 90% of the risk of myocardial infarction. This may imply that significance of the hereditary risk is low [3]. However, this apparently high figure neglects to consider that risk factors such as hypertension, hypercholesterolemia, diabetes mellitus and even addictive behavior (smoking) are crucially affected by genetic factors [4–6]. Moreover, multiethnic comparisons may largely underestimate factors that are of relevance for the variability within an ethnic group.

Thus, the variability in the manifestation of MI and CAD cannot be explained exclusively in terms of the variations in the frequency of vascular risk factors [7–14], indicating the high clinical importance of ethnic or genetic differences in the pathogenesis of the conditions [1].

The familial risk of CAD and myocardial infarction

In the setting of a large epidemiological survey 35% of all patients with CAD fulfilled the criteria for a positive family history of the disease. This high prevalence underscores the quantitative significance of this risk factor [15].
The Framingham Heart Study demonstrated that a positive family history of a parent or a sibling is a risk factor for CAD [16, 17]. The excessive risk related to a positive family history was independent of all other risk factors tested. Moreover, the familial risk was found to be greater the lower the age at first manifestation of disease was in the affected family members [18]. The analysis of a genealogical data bank from Utah (USA), in which data from more than 2.2 million persons were collected over the past 100 years, revealed a significantly raised risk of myocardial infarction even when second degree relatives were affected before the 65th year of life [19]. The associated relative increase in risk of myocardial infarction is lower for first degree relatives, but again not explained by traditional risk factors [19].

In families with a repeated occurrence of CAD, vascular risk factors are also found with increased frequency [20]. Furthermore, lifestyle habits associated with a raised incidence of CAD (e.g., smoking) are more frequently encountered in the families [7]. The 2nd Northwick Park Heart Study (NPHS-II) documented that a positive family history of CAD entails an increase in risk by the factor 1.65 even after adjustment for multiple risk factors [15, 18]. Likewise, the Reykjavik Cohort Study on 10062 women and 9328 men showed that the increase in risk in terms of the positive family history remains high with a factor of 1.5 to 1.8 even after adjustment of multiple risk factors [21].

The Swedish Twin Study broadens our knowledge concerning the heritability of myocardial infarction by comparing the 10-year risk between monozygotic and dizygotic twins [22]. The relative increase in risk for an apparently healthy twin to die from myocardial infarction was 2.6 in dizygotic twins who can be regarded genetically as siblings. The risk increased by the factor 8.1 if a monozygotic, i.e., genetically identical, twin was affected (Fig. 1).

**Heritability of left main disease**

We recently demonstrated that the heritability estimates of CAD depend, in part, on the pattern of coronary morphology. Particularly, left main disease and proximal coronary stenoses were observed to carry a high risk for reoccurrence in affected sibling pairs (Fig. 2) [23]. A highly significant heritability was found for ostial and proximal coronary stenoses, respectively ($h^2 = 0.32; p = 0.008$ and $h^2 = 0.30; p = 0.01$),

![Fig. 1](image1.png) The relative increase in risk of myocardial infarction/CAD is shown in relation to different familial susceptibilities. The risk for identical and nonidentical twins is based on the hypothesis that the partner twin had died of myocardial infarction at an age of 55 years

![Fig. 2](image2.png) Heritability of coronary morphology in myocardial infarction of sibling pairs in different cardiac vessel regions – regions with significant heritability are marked
whereas a distal involvement did not show any heritability.

In addition, significant heritability of extraluminal calcification and the ectatic form of coronary sclerosis was demonstrated in the sibling pairs with CAD [23]. Further investigations of our group replicated these results in a second sample [24] and substantiate familial risk prediction on the basis of the coronary morphology findings.

Molecular genetics of CAD and myocardial infarction

Genes associated with complex human diseases such as CAD or myocardial infarction may be grouped into two major categories: susceptibility genes and disease-causing genes. Susceptibility genes are genes that increase or decrease the risk of disease manifestation. These genes may or may not contribute to the variability of the disease in the context of other genetic and environmental factors. Genetic variants of these genes are present, albeit with different frequency, in both, apparently healthy and affected individuals within a population. Disease-causing genes are the genes that are, if mutated, directly responsible for the pathogenesis of disease. In this case, mutations can be clearly defined as the primary cause of the disease. An unequivocal diagnosis can be made for such mutations on the basis of a molecular analysis (as a rule, identification of the nucleotide sequence of the gene). However, the search and subsequent detailed sequence analysis of a disease causing gene is more difficult than screening for frequent variants in susceptibility genes. Moreover, on the population level disease causing genes for myocardial infarction may be extremely rare, whereas susceptibility genes may be highly prevalent. Certain genetic variants of these genes entail a higher risk of disease, but do not automatically induce disease, since further genetic and non-genetic factors also modulate the risk of disease. The investigation of only one susceptibility gene is hence not sufficient in order to fully appraise the risk of disease.

In the case of myocardial infarction, it must be assumed that several predisposing susceptibility factors located in one or several genes interact. Such interactions may or may not result in the manifestation of disease in conjunction with corresponding environmental factors in an insidious process. Myocardial infarction can thus be considered as a multifactorial polygenic disease (Fig. 3). The effect of a single variant may be small. This gives rise to major difficulties in the identification and clinical weighting of possibly contributing gene defects or genetic variants. On the one hand, respective molecular-genetic analyses must be carried out in enormously large populations to identify functional variants which may affect the risk of myocardial infarction or CAD. On the other hand, the cardiovascular risk profile certainly varies from subject to subject further complicating the analysis. Likewise, genetic risk alleles for hypercholesterolemia, hypertension, and diabetes mellitus may interact in a complex fashion further complicating the scenario [25–27].

Analyses of candidate genes in myocardial infarction and CAD

Candidate genes are usually chosen on the basis of pathophysiological considerations. For example, the link between a polymorphism in the gene of the angiotensin-converting enzyme and myocardial infarction initiated this field in the year 1992 [28]. Since then, multiple investigators have tested the functional relevance of this variant [29, 30]. The conclusion of these studies is that an ACE I/D polymorphism may result in a small risk increase for myocardial infarction and left ventricular hypertrophy [31, 32].

Up to now, nearly 5000 studies have analyzed candidate genes in relation to myocardial infarction and CAD (pubmed search by myocardial infarction and association study, myocardial infarction and polymorphism, and coronary artery disease and polymorphism in December 2005). According to this search a total of 329 variants from 152 candidate genes have been analyzed. Positive and reproducible findings were shown for 192 polymorphisms from 102 genes in at least two independent populations.
These genes represent different signal transduction cascades. Most studies have investigated the renin-angiotensin system [28], lipid metabolism [33], inflammation [34–37] and the clotting cascade [38]. However, both positive and negative associations were found for nearly all variants. Some of the discrepant results can be explained by relatively small study populations with the possibility of false positive association. Moreover, ethnic variation must be taken into consideration in the appraisal of divergent results. Finally, the functional relevance of most polymorphisms still needs demonstration since, alternatively, these variants may only display association with disease because of their close neighborhood or linkage disequilibrium, with responsible mutations. According to present-day knowledge, none of these candidate gene variants allows genetic risk prediction with sufficient reproducibility for myocardial infarction or CAD in the clinical setting.

The approach in genome-wide analysis is free of any hypothesis as to whether any given gene may predispose to the phenotype. By analyzing genetic markers located at short intervals throughout the entire human genome, regions can be identified in which a gene causing disease is localized with a high probability. In a study conducted by our group a locus on human chromosome 14 was identified [8]. Figure 5 shows a schematic overview of the entire human genome. Regions displaying linkage for CAD or myocardial infarction and the genes so far identified with this methodological approach are marked [39]. These chromosomal loci require further studies in order to identify the disease causing genes.
Autosomal dominant inheritance of myocardial infarction

Wang and co-workers recently succeeded in identifying a mutation in the gene of the transcription factor MEF2A in a family with an autosomal-dominant form of myocardial infarction. For the first time, a familial genetic defect was shown to give rise to myocardial infarction in humans [40]. A 21-bp deletion in the gene appeared to result in alterations of the coronary walls, thus favoring plaque deposition, which ultimately may lead to myocardial infarction. Interestingly, the same pathway is crucial in preventing apoptosis in endothelial cells and death due to vascular obstruction in mice [41]. However, at the present time the significance of this gene with respect to the heritability in humans is still unclear given the multifactorial background of the disease [42–44].

In everyday clinical routine, extremely raised incidences of myocardial infarction are often recorded in the history of multiple families. With the exception of the family studied by Wang et al. [28], many of such families could not be systematically analyzed genetically due to the high lethality of the disease. In the German myocardial infarction family study, we specifically looked for myocardial infarction in large families with at least four surviving affected individuals. We succeeded in systematically interviewing members of 19 such families and investigating them in detail [45]. On the basis of family pedigree analysis and statistical simulations, the presence of an autosomal dominant inheritance pattern was probable in all cases. The family pedigrees will hopefully extend the knowledge of genes involved in myocardial infarction (Fig. 6).

Outlook

Myocardial infarction and CAD are diseases which occur with increased frequency in certain families. About one – third of all patients with myocardial infarction or CAD fulfill the criteria of a positive family history of the disease. In clinical practice this important information needs to be included for risk stratification particularly in unaffected individuals, as suggested by the PROCAM score [46]. Moreover, the information on coronary morphology might become an important additional characteristic for disease prediction in families with CAD or premature myocardial infarction.

It is obvious that multiple genetic factors make a crucial contribution to the pathogenesis of the conditions. However, current scientific knowledge is not sufficient to recommend routine use of genetic test procedures for prediction of risk. Nevertheless, the technical possibilities for genetic testing are increasing with enormous speed. In fact, it is now feasible to analyze 500,000 gene variants on a single DNA chip within minutes. As soon as the functional relevance of some of these polymorphisms can be estimated, the prediction of CAD or myocardial infarction may improve considerably. Such test procedures which were regarded as visionary years ago now appear conceivable for the near future provided that molecular genetics continues its rapid technological development. The European commission and the NIH currently stimulating the field by enormous funding (http://fp6.cordis.lu/).

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References


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