Genetic Susceptibility of Myocardial Infarction

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The aim of this study was to determine the influence of genetic factors on the first episode of acute myocardial infarction. Probandwise concordances, tetrachoric correlations and quantitative genetic analyses of liability were applied to data drawn from the Swedish Twin Registry and the Swedish Acute Myocardial Infarction Register. All same-sexed twin pairs born between 1886 and 1958 who were alive in 1987 were included in the analyses. Our results show that concordance rates for acute myocardial infarction in monozygotic (MZ) twins were similar across sexes (among males .26 and females .27). For dizygotic (DZ) twins the concordances were .20 for males and .16 for females, yielding a greater MZ–DZ concordance differential for females than males. Tetrachoric correlations were greater for MZ than DZ twins for both sexes (.49 for male MZ and .34 for male DZ-twins and .56 and .35 for female MZ and DZ twins respectively). Quantitative genetic analyses of liability resulted in equal variance components for males and females (.36) but significantly different thresholds (prevalences). In conclusion, liability to first occurrence of acute myocardial infarction is moderately influenced by genetic variants in both sexes. The familial influence on phenotypic variance is exclusively explained by additive genetic factors.

Coronary heart disease (CHD) is a complex disease caused by both genetic and environmental factors. Thus far, a number of studies have focused on the impact of genetic and environmental factors, and, where possible, the interaction between these factors on the coronary phenotype in total, rather than sub-phenotypes, due to considerations of statistical power. Genetic studies require large data sets with a substantial number of events. Early studies typically focused on family history, suggesting a correlation between family history of myocardial infarction (MI) and CHD (Friedlander et al., 1985). Others demonstrated familial resemblance in the clinical manifestations of CHD (Rissanen, 1985), an effect of age, and that most of the familiarity of early CHD is mediated through familial hyperlipidemias and hypertension (Rissanen, 1979). In addition, Thelle and Forde (1979) reported that familial occurrence of MI is to be considered as a coronary risk factor. However, a family study focusing on 85 male MI survivors found a relation to premature occurrence of MI, but no relation between family history and severity of coronary artery disease (Hamsten & de Faire, 1987). Evans et al. (2003) elegantly summarized the contribution of twin studies to CHD, concluding that genetic variance is moderate for many cardiovascular phenotypes. A large number of individual genes seem to be associated with the development of atherosclerosis and CHD, but the influence from each gene is only minor. A meta-analysis (Chiodini & Lewis, 2003) summarizing four genome-wide screens concluded that regions 3q26-27 and 2q34-37 probably contain important candidate genes for CHD.

Thus far, CHD has been one of the leading causes of death in the industrialized world. However, during the last three decades CHD death is on the decline. In Sweden, a major decrease in CHD and acute myocardial infarction (AMI) has been observed in the last decades (Linnersjo et al., 2000; Peltonen & Asplund, 1997). The main reasons behind this progress have been improvements in medical interventions and changes in lifestyle habits (Rosen et al., 2000). Genetic susceptibility to various types of exposures may differ between sexes as well as between various CHD phenotypes such as CHD death, angina pectoris and AMI. The aim of this study was, therefore, to determine the relative contribution of genetic factors for the first episode of AMI, by applying a quantitative genetic approach using twin data obtained from the Swedish Twin registry merged with the Swedish Acute Myocardial Infarction register.

Material and Methods

The Swedish Twin Registry

The Swedish Twin Registry was established in the late 1950s, primarily for studying the effect of smoking on health. It includes all twins born in Sweden between 1886 and 1990 and is currently the largest population based twin register in the world. The registry consists mainly of several different cohorts: cohort I (all like-sexed pairs born between 1886 and 1925, who still

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lived within the country as unbroken pairs and responded to a questionnaire in 1961), cohort II (same-sexed twins born between 1926 and 1958), and twins born from 1959 onwards. Detailed information on the registry is presented elsewhere (Lichtenstein et al., 2002; Pedersen et al., 2002).

The Swedish National Acute Myocardial Infarction Register

Record linkage of two registers, the Hospital Discharge Register and the Cause of Death Register, established the Acute Myocardial Infarction Register (AMI register) in 1996. The register includes all persons (with correct Swedish personal identification numbers) who had an AMI, both fatal and nonfatal, reported to the Hospital Discharge Register or to the Cause of Death Register between 1987 and 2000. The Hospital Discharge Register records all patients discharged from public hospitals in the country. The Cause of Death Register includes the deaths of all people registered as Swedish residents, regardless of whether or not death occurred in Sweden. AMI events are identified by the date of admission or death. An event is classified as fatal if the patient dies from AMI outside the hospital, or if the patient dies from AMI (as an underlying or a contributing cause of death) within 28 days from the admission, and nonfatal if the patient survives beyond this time frame. All AMI events that occur 28 days after the date of admission are treated as new events. More detailed information regarding the register is presented elsewhere (Hammar et al., 1991).

For this study, only twin pairs where both twins were alive in 1987 were included in the analyses because the acute myocardial infarction register started in this year. In total 41,492 twins were included in the analyses.

Probandwise Concordances

Concordance rates (McGue, 1992) were calculated separately for MZ and DZ twins, and if higher rates were observed among MZ than DZ twins, the difference was interpreted to be caused by genetic factors. Pairs considered as concordant (C) were those where both twin partners experienced the event under study. Pairs considered as discordant (D) were those where only one twin partner experienced the event under study. The probandwise concordance rates were calculated as two times the concordant pairs divided by the sum of two times the concordant and discordant pairs (2C/[2C+D]).

Table 1

Number of Concordant and Discordant Pairs, Probandwise Concordance Rates and Tetrachoric Correlation for the First Episode of AMI, by Zygosity and Sex

	Males		Females	
AMI	MZ twins	DZ twins	MZ twins	DZ twins
Concordant pairs	63	83	50	50
Discordant pairs	352	682	276	539
Probandwise concordance rate	.26	.20	.27	.16
Tetrachoric correlation	.48	.34	.56	.35

Genetic Analysis of Liability

Liability (susceptibility to an event under study) is considered to be an underlying unknown trait influenced by both genetic and environmental factors (Falconer, 1965). This approach uses threshold models, where the threshold is a point reflecting prevalence on a latent distribution of liability. The prevalence for the present study was calculated from all twins included in the analyses. Individuals above the threshold were assumed to develop the disease and individuals below this point were assumed not to develop the disease. Structural equation modeling approaches implemented through the Mx software (Neale, 1997) were adopted to calculate tetrachoric correlations and to evaluate heritability based on the liability threshold model. Tetrachoric correlations estimate the within-pair correlation in disease liability under the assumption of bivariate normal distribution. Calculation of tetrachoric correlations was performed by use of raw data. Liability was assumed to consist of additive (A) and nonadditive (D) genetic factors as well as shared (C) and nonshared (E) environmental factors. Four models (ACE, ADE, AE, and CE) can be run to obtain estimates of variance components representing these factors. In order to determine which full model was the most suitable, the correlation estimates, based on gender and zygosity, were compared. An ACE model is preferred when the correlation among MZ twins is approximately two times greater than the correlation among DZ twins. If the DZ correlation is less than half the MZ correlation, the ADE model is preferred. If the DZ correlation is greater than half the MZ correlation, shared environmental influences are indicated. The likelihood ratio test was used to compare nested models with the full model. Sex differences were tested through a series of models: (1) Sex-specific variance components and thresholds, (2) thresholds equal in men and women, (3) variance components constrained to be equal in men and women, and (4) reduced models (AE, CE). The software used for this study were SPSS (SPSS, 1989–1997), and Mx (Neale, 1997).

Results

A total of 2341 first episode cases of AMI were observed (1326 among males and 1015 among females); 824 of these first episode cases died within 28 days, of which 786 died from AMI. Females experienced their first episode of AMI at older ages compared to men (74.5 and 68.4 respectively).

Probandwise Concordances and Tetrachoric Correlation

Probandwise concordances were in general larger in MZ than in DZ pairs (presented in table 1). The esti-

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Table 2

Age Adjusted Heritability Estimates for AMI Combined and Separate by Sex

AMI		a^2	c^2	e^2	2 log-likelihood	Degrees of freedom	p value *
Model 1	Males	.30	.03	.67	16862.19	41481	
	Females	.39	.00	.61			
Model 2	Males	.27	.06	.68	16956.28	41482	.00
	Females	.40	.00	.60			
Model 3		.36	.00	.64	16863.13	41484	.82
Model 4		.36		.64	16863.13	41485	.92
Model 5			.25	.75	16881.58	41485	.00

Model 1: Sex-specific variance component estimates and thresholds

Model 2: Thresholds equal in men and women

Model 3: Variance components constrained to be equal in men and women ACE-model, sex-specific thresholds

Model 4: Variance components constrained to be equal in men and women AE-model, sex-specific thresholds

Model 5: Variance components constrained to be equal in men and women CE-model, sex-specific thresholds

Note: *Model comparisons (p value) are based on comparisons with Model 1.

mates for MZ pairs were similar for both sexes (.26 for males and .27 for females). For DZ pairs the estimates were .20 for males and .16 for females. The difference between the zygosity groups by gender indicates a genetic influence for both sexes, although it is somewhat greater in females. The tetrachoric correlations were also larger in MZ than DZ twins (presented in Table 1). Again, the MZ–DZ differential was greater for females. The patterns of correlations indicate both a genetic and shared environmental predisposition for the first occurrence of AMI.

Genetic Analysis of Liability

First a model with sex-specific variance components and thresholds was calculated and second, the thresholds were set to be equal in men and women. The second model resulted in a significant worsening of the fit (difference in 2-logl = 94.09 with 1 degree of freedom), indicating that the thresholds were significantly different in men and women.

Further models had sex-specific thresholds. When variance components were set to be equal in men and women, the model fit did not worsen significantly compared to Model 1. Hence the best model was an AE model in which the heritability was .36 in men and women (see Table 2).

Discussion

To our knowledge this is the first report on heritability of first occurrence of AMI. Our results suggest that the first episode of AMI has a moderate genetic influence among both males and females, witnessed by concordances and tetrachoric correlations as well as quantitative genetic model fitting.

A large body of evidence suggests that CHD is a multifactorial disease caused by a number of genetic and environmental factors. Population-based twin studies have contributed substantially to improvements in understanding environmental and genetic risk factors for CHD death (Evans et al., 2003). Risk of MI increases with a positive family history of CHD (Leander et al., 2001). Furthermore, the risk of CHD increases with a positive family history of MI (Friedlander et al., 1985; Thelle & Forde, 1979). Colditz et al. (1986) have shown that parental history of MI before 60 years of age significantly increased the risk of nonfatal MI in women compared with women without a parental history. They have also shown that a parental history of MI increased the risk of CHD death as well as angina pectoris and concluded that parental history of MI has an independent effect on risk not solely explained by risk factors. Similarly, studies on fatal CHD by Marenberg et al. (1994) showed that the risk of CHD death is partly due to genetic factors and that genetic influences decrease with increasing age. Quantitative genetic studies based on Danish and Swedish twins and focusing on CHD death in total also suggest that CHD death is moderately influenced by genetic factors in both sexes (Wienke et al., 2001; Zdravkovic et al., 2002, 2004). Our findings go one step further, by quantifying the importance of genetic influences for first occurrence of AMI.

The heritability results presented in this study demonstrate a modest genetic predisposition for the first occurrence of AMI for both sexes. Because MI typically occurs in males at a younger age than in females, the estimates in this study may have been attenuated. Due to the relatively short follow-up period it was not possible to study probable age-dependence in heritability that has previously been shown for CHD death in Swedish twins (Marenberg et al., 1994; Zdravkovic et al., 2002).

Women experience AMI at older ages than men do and therefore have a survival advantage until

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they experience a first AMI. However, studies focusing on survival after the occurrence of MI have shown that this survival advantage is diminished after a MI. In younger age groups (under 50 years) this advantage is transformed to a disadvantage and young women face worse survival prognosis than men (Rosengren et al., 2001). Vaccarino et al. (2000) concluded that MI had a greater impact on mortality in women and that it narrowed the survival advantage. Rosengren et al. (2001) concluded in their study on Swedish AMI data that much of the excess mortality in young women seemed to be associated with diabetes. Quantitative genetic studies on Swedish twins (Zdravkovic et al., 2004) suggest that genetic factors for CHD among women are shared with known risk factors to a higher degree than among males.

Improvements in statistical methodology and software during recent years have facilitated studies of molecular genetic data (linkage, association studies) and a large number of genes have been suggested to be associated with cardiovascular diseases (Tang & Tracy, 2001). Meta-analyses summarizing four independent genome-wide scans showed that regions 3q26-27 and 2q34-37 probably contain candidate genes for CHD, in line with the newly suggested link between the metabolic abnormalities and CHD (Chiodini & Lewis, 2003). These may contribute to the genetic variation we see here for AMI.

As always, quantitative genetic analyses rely on several important assumptions, including equal environments and assortative mating. It is not likely that violations of either of these assumptions are important for this late life outcome. Other limitations of the study are worth noting. The short follow-up resulted in a lower number of AMI cases for the younger cohort (cohort II). There may have been some selection for survival due not only to the ascertainment of the twin registry but also due to the AMI Register in 1987. The validity of the AMI Register has been studied and is considered good. Rosen et al. (2000) studied the validity of AMI diagnosis by analyzing medical records in 1987 and 1995, and showed that the proportion of false-positive AMI diagnoses decreased from 5.6% in 1987 to 4.6% in 1995. Similarly, the proportion of false negatives was about 3% in both years (Rosen et al., 2000). Furthermore, Hammar et al. (2001) found a high sensitivity and a high positive predictive value for ICD-9 code 410 (for definite AMI) in hospital discharge data. Finally, we considered a frailty approach for the calculation of heritability, but chose a liability approach in order to keep the model as simple as possible and to avoid technical difficulties inherent in the complex frailty model.

In conclusion, our findings confirm and extend earlier genetic findings on death from CHD. Additive genetic factors moderately influence the occurrence of a first AMI episode in both males and females.

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