Genetic influences on carotid velocities using an international twin sample

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Purpose

Atherosclerosis is an inflammatory process and a multifactorial metabolic disorder in which the artery wall thickens as a result of plaque deposition. Atherosclerosis underlies various clinical cardiovascular diseases which are known to aggregate within families, such as coronary heart disease, myocardial infarction and stroke [1-5]. Although there is a consensus that genetic factors play a role in atherogenesis [6], the precise magnitude of the genetic influence is poorly described.

Carotid intima-media thickness (IMT) means that the first two layers (intima and media) of the carotid artery thickens as the consequence of atherosclerosis. Recent studies have shown that carotid IMT is mostly determined by genetic factors [7, 8, 9]. In case of a large carotid plaque it might develop a severe stenosis which causes increased velocity.

The Society of Radiologists in Ultrasound determined that internal carotid artery (ICA) peak systolic velocity (PSV) and presence of plaque on gray-scale and/or color Doppler images are primarily used in diagnosis and grading of ICA stenosis. ICA should be diagnosed as follows [10]:

- normal (ICA PSV<125 cm/sec, no plaque or intimal thickening is visible)
- <50% stenosis (ICA PSV<125 cm/sec, plaque or intimal thickening is visible)
- 50%-69% stenosis (ICA PSV>125-230 cm/sec, plaque is visible)
- ≥70% stenosis to near occlusion (ICA PSV>230 cm/sec, visible plaque and lumen narrowing)
- near occlusion (markedly narrowed lumen at color Doppler US)
- total occlusion (no detectable patent lumen at gray-scale US and no flow at spectral, power, and color Doppler US)

The precise extent to which genetic predisposition explains the variance of carotid velocities is unclear. The goal of this investigation, was to assess the heritability of carotid flow velocities and estimate the genetic influence and the shared and unshared environmental components on the onset of atherosclerosis using a twin sample.
Methods and Materials

136 monozygotic (MZ) and 69 dizygotic (DZ) twin pairs (mean age 53±14 years) underwent carotid ultrasound (Peak Systolic /PSV/ and End Diastolic Velocities /EDV/ in proximal common carotid artery /CCA/ and internal carotid artery /ICA/ on both sides). Twin pairs above the age of 18 were recruited in this classical twin study as part of the International Twin Study 2009 project in Hungary, Italy and USA. Italian twins were enrolled in Rome, Padua and Perugia by the Italian Twin Registry [11].

Lacking genotyping of the sample we used a multiple self-reported question approach to assess zygosity. The most likely zygosity was assigned based on the seven self-reported responses [12].

All participants underwent a carotid ultrasound using Doppler mode (in Rome: Esaote Technos MPX, in Padua: Philips iU22, in Perugia: Technos MP, Esaote, Genoa, Italy, in Hungary: Toshiba Power Vision and Esaote Mylab40, in the USA: Sonosite Titan). Linear array transducers were used (5-10 MHz in Italy, 5-10 MHz in Hungary, L38 linear array transducer 4-7 MHz in the USA).

Carotid flow velocities of proximal and distal (1 cm proximally to the bifurcation) common carotid artery (CCA), and proximal internal carotid artery (ICA) (1 cm distal to the bifurcation) was measured bilaterally using a standard technique. In case of a carotid plaque we measured the velocities above the plaque. Carotid ultrasound tests were conducted by the local physicians.

A descriptive estimate of the genetic influence on carotid flow velocities were calculated using the intraclass correlation in MZ (\(r_{MZ}\)) and DZ (\(r_{DZ}\)) pairs. The corresponding 95% confidence intervals for \(r_{MZ}\) and \(r_{DZ}\) were calculated [13]. If the within pair similarity for a phenotype is greater in MZ than DZ pairs this provides evidence for genetic influence.

Structural equation modelling was used to estimate heritability (Figure 1). Univariate quantitative genetic model was performed to decompose phenotypic variance of the considered parameters into genetic (A), common environmental (C) and unique environmental (E) effects. The common environmental component estimates the contribution of the shared family environment by both twins, whereas the unique environmental component estimates the effects that apply only to each individual twin, and includes measurement error. Model fitting was done with the statistical software MX (Michael C. Neale, Richmond VA) [14] and all the analyses were adjusted by age.
Figure 1. Univariate ACE model

A: additive genetic effects, C: common (shared) environmental effects, E: unique (unshared) environmental effects

Fig. 0: Figure 1. Univariate ACE model

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Results

Intraclass correlations were higher in MZ than in DZ pairs for right proximal CCA EDV (MZ=0.60, DZ=0.32; heritability: 0.60, 95% CI: 0.49-0.69), right proximal ICA PSV (MZ=0.46, DZ=0.17; heritability: 0.46, 95% CI: 0.32-0.57) and EDV (MZ=0.26, DZ=-0.50; heritability: 0.25, 95% CI: 0.11-0.38), left proximal ICA PSV (MZ=0.61, DZ=0.48; heritability: 0.25, 95% CI: 0.00-0.67) and EDV (MZ=0.47, DZ=0.40; heritability: 0.15, 95% CI: 0.00-0.57), left proximal CCA EDV (MZ=0.48, DZ=0.41; heritability: 0.14, 95% CI: 0.00-0.58), suggesting a moderate genetic effect on these measures. A large proportion of variance was attributable to unshared environmental factors. No genetic effects were detected between right and left proximal CCA PSV; total variance was due to shared (57% and 52%, respectively) and unshared (43% and 48%) environmental influences.
Conclusion

In summary, the results of our study indicate that most of the investigated velocity parameters appeared to be moderately influenced by genetic factors. Environmental factors of relevance for these measures appeared to be related to individual experience (e.g., smoking habits, diet, physical activity). These findings may highlight the genetic and environmental etiology of atherosclerosis and the importance of early atherosclerosis screening, detection, follow-up and prevention in high-risk patients.

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References


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