Genetic architecture of the pro-inflammatory state in an extended twin-family design

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Introduction: The pro-inflammatory cytokines TNFα and IL-6, and the acute phase proteins CRP and fibrinogen are characteristic of the pro-inflammatory state that serves as a risk factor for many diseases including major depression and heart disease. In addition, it is suggested to be the reason for the co-morbidity between the two. We extended the classical twin design with non-twin siblings and parents in the largest set of twins with data on TNF-α, IL-6, CRP and fibrinogen to date. The large sample size and the extended twin-family design allows us to estimate the extent of additive (A) and dominant (D) genetic effects, as well as shared (C) and unique (E) environmental factors with high precision.
Methods: Between January 2004 and July 2008, 9.530 participants registered in the Netherlands Twin Registry were visited at home for collection of blood and urine samples. CRP, fibrinogen, TNF-α, and IL-6 values were determined in fasting blood samples.
Genetic analyses were performed using structural equation modeling in the software package Mx. First, a non-restrictive, fully parametrized model was fitted to the data to freely estimate the sample descriptives and covariance structures among relatives. Next increasingly restricting models were fitted to the data in order to arrive at the most parsimonious model that explained the data best.
Results: A moderate but consistent degree of heritability was found for all immune parameters, ranging from 27 to 41 %. For TNF-α and for CRP in females, dominance was implicated. E was implicated in all parameters. A small part of the variation in fibrinogen and CRP was due to C as well.
Conclusions: Genetic factors play a significant role in explaining individual variation in the pro-inflammatory state. These heritability estimates provide a clear numerical target for ongoing genome-wide screens attempting to find the actual genetic variants underlying the pro-inflammatory risk profile.

Exome sequencing of an isolated Chilean population affected by Specific Language Impairment (SLI)

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Speech and language impairments that are a primary deficit and have no obvious cause (e.g. a comorbid neurological disorder like autism) are diagnosed as Specific Language Impairment (SLI). SLI affects 5–8 % of preschool children and represents a lifelong disability associated with an increased risk of behavioural disorders, social problems and literacy deficits. SLI is highly heritable and twin studies indicate a strong genetic basis. Nonetheless, the underlying genetic mechanisms are expected to be multifactorial and, to date, only three risk variants have been identified. One way to increase the power to detect contributory genetic factors is to study isolated populations derived from relatively recent shared ancestors (founder populations). In 2008, Villanueva described a founder population with a particularly high incidence of SLI (10 times that expected). They inhabit the Robinson Crusoe Island, which lies 677 km to the west of Chile and was colonised in the late 19th century by 8 European and Amerindian families. 77 % of the current island population have a colonising surname and 14 % of marriages involve consanguineous unions. More than 80 % of language impaired individuals can be traced to a pair of founder brothers. This population thus has a short (5-generations) and well-documented history and represents a unique resource which could make valuable contributions to the elucidation of genetic mechanisms underpinning SLI.

We applied exome sequencing technologies to five language-impaired individuals from this population and identified nine non-synonymous coding changes or splice site mutations that were present in at least three of the five affected individuals sequenced. Sequencing of the entire cohort identified a single non-synonymous coding change that was significantly more frequent in cases than controls (genotype frequencies of 46 and 11 % respectively, $p = 4.48 \times 10^{-5}$). We suggest that this rare coding variant may contribute to the elevated frequency of SLI in this population.

Genetic and environmental influences on gender specific income differences

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Previous research has demonstrated that the additive genetic components of a wide range of phenotypes vary across the lifespan (Eaves et al. 2008; Hatemi et al. 2009). Interestingly, for several social traits shared environmental factors dominate the pattern of transmission during childhood and early adolescence, and then markedly drop after the child leaves the family home when additive genetic factors take on greater importance (Hatemi et al. 2009). This study focuses on income differences between opposite sex dizygotic twin pairs (DZO) in order to explore sex specific effects on the means that are masked when focusing on variance decomposition methods. Using cross sectional data from adult twins aged 17–93 (Virginia 30,000), we find male DZO twins ($M = 4.85$, $SD = 2.01$) have significantly higher incomes than females ($M = 3.03$, $SD = 1.83$) ($t(2,373) = 22.84$, $p = 0.0000$). Importantly, there are no significant differences between levels of education for DZO twin pairs, suggesting sex differences in income are not based on previous sex differences in education. Centrally, preliminary analyses suggest that the average inter-pair differences in level of income among DZO twins increase with age. While there is close to no difference in level of income among brother and sister in the late teenage years ($M = 1.62$, $SD = 0.88$) ($M = 1.57$, $SD = 1.04$) ($t(117) = 0.3056$, $p = 0.3802$) the sex specific differences in level of income is found to be significant in all other age cohorts from 23 years of age and up. Most evident is the mean differences in level of income between brother and sister in the age cohorts 41–46 ($M = 5.66$, $SD = 1.71$) ($M = 3.26$, $SD = 1.89$) ($t(213) = 9.77$, $p = 0.0000$) and 53–58 ($M = 6.08$, $SD = 1.56$) ($M = 3.44$, $SD = 2.07$) ($t(225) = 10.91$, $p = 0.0000$). Implications for gender inequalities in income and education are discussed.