



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

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Background

A chronic low-grade inflammatory state has been implicated as a key pathway to numerous diseases including major depression and heart disease, and as the reason for the co-morbidity of these diseases (Capuron et al., 2008; Vaccarino et al., 2007; Vaccarino et al., 2008). It is characterized by elevations in the levels of the pro-inflammatory cytokines TNF- α and IL-6, and the acute phase proteins CRP and fibrinogen. In spite of the obvious importance of these peptides and proteins in depression and cardiac disease, which are both in the top 5 of burden of disease prediction for 2020 (Murray et al., 1996), very little is known about the etiology of the individual differences in TNF- α , IL-6, CRP and fibrinogen levels.

Here 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.

Methodes

Subjects

The data are obtained from the NTR Biobank study that was conducted between January 2004 and July 2008 among twins and their family members registered in the Netherlands Twin registry (Willemsen et al., 2010). In total, 9,530 participants were visited between 7 a.m. and 10 a.m. for collection of fasting blood and urine samples. CRP was determined in heparin plasma using the Immulite 1000 CRP assay. TNF- α and IL6 were measured in EDTA plasma, using R&D systems. Fibrinogen levels were measured in CTAD plasma using a STA Compact Analyzer.

Statistical analyses

Genetic analyses were performed using structural equation modeling in the software package Mx (Neale et al., 2006). 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

Sample descriptives can be found in table 1.

Family analyses

Family correlations are summarized in table 2. Age regression on the mean needed to be included in the model for all parameters. Sex differences needed to be taken into account for CRP and TNF- α , but not for fibrinogen and CRP. A moderate but consistent degree of heritability was found for all immune parameters, ranging from 27 to 41%. E was implicated in all parameters. For fibrinogen and CRP, a small part of the variation was due to C as well (see table 3).

Family correlations	CRP	Fibrinogen	TNF- α	IL-6
MZ twins				
MZ male	0.39	0.48	0.40	0.22
MZ female	0.48	0.42	0.39	0.30
Male siblings				
DZ male	0.25	0.32	0.02	0.14
Brother-male twin/Brother-brother	0.23	0.33	0.13	-0.02
Female siblings				
DZ female	0.36	0.33	0.17	0.20
sister-female twin/Sister-sister	0.22	0.23	0.19	0.16
Opposite sex siblings				
DZ opposite sex	0.25	0.21	0.09	0.12
Brother-female twin/sister-male twin/sister-brother	0.19	0.26	0.14	0.08
Parent-offspring				
mother-daughter	0.15	0.22	0.14	0.15
mother-son	0.18	0.16	0.13	0.19
Father-son	0.22	0.19	0.09	0.18
father-daughter	0.20	0.14	0.11	0.14
Parents				
Mother-Father	0.12	0.20	0.16	0.14

Table 2. Family correlations from the saturated (full) model

Sample	CRP (mg/L)	Fibrinogen (g/L)	TNF- α (pg/ml)	IL-6 (pg/ml)
N Total	8001	7707	7871	7850
Mean age (range)	43.92 (12-90)	45.3 (18-90)	45.22 (18-90)	45.20 (18-90)
% female	62.4	63.1	63.3	63.3
Mean (sd) females	2.73 (2.96)	2.81 (0.66)	1.10 (1.12)	1.59 (1.42)
Mean (sd) males	2.11 (2.47)	2.68 (0.64)	1.08 (0.96)	1.71 (1.65)

Table 1. The resulting sample per parameter

Best fitting model	CRP		Fibrinogen	TNF- α		IL-6
	males	females	both sexes	males	females	both sexes
a2	0.38	0.28	0.31	0.11	0.27	0.27
d2	0.00	0.13		0.27	0.12	
Broad heritability	0.38	0.41	0.31	0.38	0.39	0.27
c2	0.03	0.10	0.11			
e2	0.59	0.52	0.59	0.62	0.61	0.74

Table 3. Estimates on the contribution of genes and environment to the factors comprising the pro-inflammatory state

Conclusions

- Genetic factors play a significant role in explaining individual variation in the pro-inflammatory state.
- A joint genetic basis in chronic inflammation can explain part of the co-morbidity between major depression and heart disease.