Hostility is a multidimensional personality trait with changing expression over the life course. We performed a genome-wide association study (GWAS) of the components of hostility in a population-based sample of Finnish men and women for whom a total of 2.5 million single-nucleotide polymorphisms (SNPs) were available through direct or in silico genotyping. Hostility dimensions (anger, cynicism and paranoia) were assessed at four time points over a 15-year interval (age range 15–30 years at phase 1 and 30–45 years at phase 4) in 982–1780 participants depending on the hostility measure. Few promising areas from chromosome 14 at 99 cM (top SNPs rs3783337, rs7158574, rs3783332, rs2181102, rs7159195, rs11160570, rs941898, \( P \) values <3.9 \( \times \) 10\(^{-8} \) with nearest gene Enah/Vasp-like (EVL)) were found suggestively to be related to paranoia and from chromosome 7 at 86 cM (top SNPs rs802047, rs802028, rs802030, rs802026, rs802036, rs802025, rs802024, rs802024, rs802049, rs802051, \( P \) values <6.9 \( \times \) 10\(^{-7} \) with nearest gene CROT (carnitine O-octanoyltransferase)) to cynicism, respectively. Some shared suggestive genetic influence for both paranoia and cynicism was also found from chromosome 17 at 2.8 cM (SNPs rs12936442, rs944664, rs6502671, rs7216028) and chromosome 22 at 43 cM (SNPs rs7510759, rs7510924, rs7290560), with nearest genes RAP1 GTPase activating protein 2 (RAP1GAP2) and KIAA1644, respectively. These suggestive associations did not replicate across all measurement times, which warrants further study on these SNPs in other populations.

**Introduction**

Hostility is a personality trait characterizing how trustworthy individuals perceive other people and how they handle these feelings toward others. The cognitive component of hostility characterizes cynical and distrustful attitudes, which is the primary reference of the term hostility, whereas the affective component reflects feelings of irritability and anger. The behavioral component covers expression of these attitudes and feelings as either expressing them out, that is, aggression, or as suppressing or repressing them. Hostility traits have been found to be related to various social and health problems, such as criminality and violence, isolation and relationship aggression, depression, cardiovascular diseases and all-cause mortality risk, although the findings are not entirely consistent. Identifying the origins of hostility may help to understand the developmental paths related to hostility and to develop effective preventions to reduce problems related to hostile behaviors.

Both genetic and environmental factors are involved in the development of hostility, with heritability estimated to be 30–50%. However, the molecular nature of the genetic background and the specific regions of the genome that underlie hostility remain mainly unknown. To our knowledge, only one genome scan study of hostility has been published to date. That study covered 387 autosomal short-tandem-repeat polymorphisms and did not find significant linkage with hostility. In the present study, we report a large-scale genome-wide association study (GWAS) of hostility where over 2.5 million single-nucleotide polymorphisms (SNPs) were analyzed, thereby mapping the most potentially significant areas of the genome regarding hostility for further inspection and providing preliminary evidence of the genetic basis of hostility.

As cognitive, affective and behavioral components of hostility may vary in their etiology and have different genetic backgrounds, we used three different scales of hostility, each of which was measured four times over a 15-year time span extending from adolescence and young adulthood (age 15–30 years) into adulthood (age 30–45 years) in a Caucasian Finnish population. It has been argued that personality is still transient and amenable to environmental effects in young adulthood, but between 30 and 50 years of age, it begins to stabilize and genetic effects become more prominent. Thus,
an additional aim of the present study was to test whether
genetic effects underlying hostility are stable across different
ages or whether they gain importance with advanced age
in adulthood.

Materials and methods

Population and study design. Participants were from the
population-based prospective Young Finns (YF) cohort
study, which started in 1980 with 3596 boys and girls from
different geographical areas of Finland. The genome of the
participants was genotyped in 2009 and personality tests
assessing hostility were administered in four follow-up
phases in 1992, 1997, 2001 and 2007. At the baseline of
the present study (1992), participants were 15, 18, 21, 24, 27
and 30 years old, and they were followed up for 15 years until
they were 30, 33, 36, 39, 42 and 45 years, respectively. The
final study sample with complete measurements consisted of
982–1781 men and women depending on the measure
of hostility (n for anger between the four measurement
phases ranges between 1619 and 1776, n for cynicism
between 1622 and 1781 and n for paranoia between 1622
and 1780).

Measures of hostility components. We assessed three
aspects of hostility, that is, cynicism and paranoia, which
both reflect the cognitive component, and anger, which
represents the affective component. Cynicism was measured
with a seven-item self-completion cynicism scale derived
from the Minnesota Multiphasic Personality Inventory (for
example, ‘It is safer to trust nobody’).16 Paranoia was
assessed with the six-item self-completion paranoid ideation
subscale of the Symptom Checklist-90R (for example,
‘Others do not give me proper credit for my achieve-
ments’).16 Anger was assessed with a seven-item Irritability
Scale of the Buss-Durkee Hostility Inventory (for example,
‘I lose my temper easily but get over it quickly’).19 Detailed
description of the scales has been published in previous
papers.9 The response format for all scales was on a five-point
scale, ranging from totally disagree (1) to totally agree (5),
and the mean of each scale was calculated for only those
who had responded to at least 50% of the items on the scale.
In addition, for each scale we calculated the mean score over
the four measurements in 1992, 1997, 2001 and 2007 to
capture a more stable trait of hostility. Reliability for the
four measurements within each hostility scale the sample sizes are increased to
~1780 subjects. These analyses were powered to detect
the effects of common variants down to 2.1% of explained
variability.

Genotyping and quality control of YF study. The
genome-wide SNP genotyping of YF study was done by a
custom Illumina BeadChip (San Diego, CA, USA) containing
670 000 SNPs and copy-number variant probes from 2442
YF participants (1123 males and 1319 females). The custom
670K chip shares 562 643 SNPs in common with the Illumina
Human610 BeadChip. Genotypes were called using
Illumina’s clustering algorithm (Illuminus). Genotypes
were excluded based on Hardy–Weinberg equilibrium test
(P<1×10^-6). We assessed three
components. We assessed three

Statistics of GWAS. Quasi-continuous mean variables of
hostility subscales were Box–Cox transformed. Residuals
were obtained using linear regression model in which hostility
variables were adjusted for sex and age in order to control
the most obvious environmental factors related to hostility.
Residuals were standardized (mean 0, s.d. 1) and their
distributions were confirmed to be very close to normal by
visual Q–Q plot analysis. We also verified that the estimates for the β-coefficients from the GWAS are not driven by few
outliers by plotting leverage vs standardized residuals plots
for the residuals.

We have an 80% power of identifying SNPs that explain at
least 4% of the variability with sample size of 985 (mean of
four measurement). For the four measurements within
each hostility scale the sample sizes are increased to
~1780 subjects. These analyses were powered to detect
the effects of common variants down to 2.1% of explained
variability.

Tests for additive genetic effects were carried out on a linear
scale using linear regression. Genotypes were coded as 0, 1
or 2 when the SNP was genotyped and by dosage (scale 0–2)
when imputed. These tests were performed to assess
association of SNPs with the standardized residuals using
PLINK22 for the genotyped data. ProbABEL24 was used to fit
the model, taking account of the genotype uncertainty at
imputed SNPs. The P-values were combined from the
analysis by favoring genotyped tests over imputed ones.
The Q–Q and Manhattan plots were drawn for the analysis of the
results. The P-value for genome-wide significance was set at
P<9×10^-8, corresponding to a target α of 0.05 with a
Bonferroni correction for 550 000 million independent tests
with direct genotyping. Cynicism was normally distributed,
whereas the distributions of paranoia and anger were slightly
positively skewed. Thus Box–Cox transformations were used
for all the outcomes.
Results

As shown in Table 1, the average age of the genotyped sample is 37.56 (s.d. = 5.03). The bivariate correlations between hostility measures are shown in Table 2. The stability of the measures (r’s range 0.45–0.69) as well as their bivariate correlations (r’s range 0.38–0.77) are moderate (all Ps < 0.001). Cynicism and paranoia correlate higher with each other than with anger. Younger participants scored higher on the three hostility measures (r = -0.12, P < 0.001, r = -0.08, P = 0.01, and r = -0.05, P = 0.123 for mean cynicism, paranoia and anger, respectively). Females scored higher on anger (r = -0.20, P < 0.001) and males on cynicism (r = 0.18, P < 0.001) and paranoia (r = 0.09, P < 0.01). All the subsequent models were therefore adjusted for sex and age.

Table 1: Characteristics of the study group

| Variable | n  | %    | Mean (s.d.) | Range |
|----------|----|------|-------------|-------|
| Sex      |    |      |             |       |
| Male     | 1135 | 46.0 |             |       |
| Female   | 1320 | 54.0 |             |       |
| Age in 2007 | 2443 | 37.56 (5.03) | 30–45 | |

| Hostility | Mean of 1992, 1997, 2001 and 2007 | | |
|-----------|-----------------------------------|----------||
| Anger     |                                    |          | 1.00–4.25 |
| Cynicism  |                                    |          | 1.11–4.54 |
| Paranoia  |                                    |          | 1.00–4.62 |
| 1992      |                                    |          | 1.00–5.00 |
| Anger     |                                    |          |          |
| Cynicism  |                                    |          |          |
| Paranoia  |                                    |          |          |
| 1997      |                                    |          | 1.00–4.67 |
| Anger     |                                    |          |          |
| Cynicism  |                                    |          |          |
| Paranoia  |                                    |          |          |
| 2001      |                                    |          | 1.00–4.50 |
| Anger     |                                    |          |          |
| Cynicism  |                                    |          |          |
| Paranoia  |                                    |          |          |
| 2007      |                                    |          | 1.00–4.83 |

We tested 2,577,640 SNPs for association with the three hostility scales measured in four different time points. The top SNPs derived from SNPs with P-values < 1 × 10^{-5} are presented in the Tables 3 and 4. Table 3 shows the top SNPs when hostility is measured as a mean score of four measurement phases (phase 1 + phase 2 + phase 3 + phase 4). Chromosome 14 at 99 cM (SNPs rs3783337, rs7158754, rs3783332, rs2181102, rs7159195, rs11160570, rs941898) predicted suggestively the mean paranoia during the 15 years at the genome-wide statistical significance (P < 9 × 10^{-8}, Table 2). However, this suggestive association did not replicate at each single measurement point over time (Table 4). Table 4 shows the top SNPs when the most significant associations are selected, irrespective of measurement phase (selected from phase 1, phase 2, phase 3 or phase 4). The most significant SNP suggestively associated with anger was found on chromosome 17 at 11 cM SNP rs11656526 (P-value < 9 × 10^{-8}, Table 4) for anger measured in 1992. Also, loci on chromosome 6 at 6.7 cM seemed promising when predicting anger in 2007, which shows the most reliable results for anger according to Q-Q plot analyses. However, these suggestive associations did not replicate in other measurement years, and hence the stability of these associations was weak.

Table 2: Correlations between hostility measures (n ranges between 983 and 2443 from mean cynicism–mean paranoia correlation with age–sex correlation)

| 1   | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| 1.00|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| -0.00|   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 0.67|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 0.82|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 0.86|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 0.90|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 0.91|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 0.92|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 0.93|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 0.93|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 0.94|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 0.94|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 0.95|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 0.96|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 0.97|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

*P < 0.05; **P < 0.01; ***P < 0.001.
Sex: 1 = male, 0 = female.
Table 3 Genetic markers showing top 10 SNPs within mean of four measurement years in each hostility scale

| CHR | SNP       | Base pair | Minor allele | MAF | n  | β     | s.e.  | P-value | ρ2  | Closest gene |
|-----|-----------|-----------|--------------|-----|----|-------|-------|---------|-----|--------------|
|     |           |           |              |     |    |       |       |         |     |              |
| 1   | rs2882650 | 6 517 472 | C            | 0.34| 986| -0.22| 0.05 | 4.3 × 10^{-6} | 0.02 |               |
| 2   | rs10929436| 6 518 881 | T            | 0.34| 986| -0.22| 0.05 | 4.3 × 10^{-6} | 0.02 |               |
| 2   | rs4668497  | 6 517 422 | T            | 0.34| 986| -0.22| 0.05 | 4.4 × 10^{-6} | 0.02 |               |
| 2   | rs7593230  | 6 519 359 | T            | 0.34| 986| -0.22| 0.05 | 4.4 × 10^{-6} | 0.02 |               |
| 4   | rs4859315  | 32 867 764| C            | 0.06| 986| 0.83 | 0.18 | 4.6 × 10^{-6} | 0.02 |               |
| 8   | rs17648656| 30 973 921| T            | 0.47| 986| 0.21 | 0.05 | 4.6 × 10^{-6} | 0.02 | PURG         |
| 8   | rs11776713| 30 981 149| T            | 0.47| 986| 0.21 | 0.05 | 4.6 × 10^{-6} | 0.02 | PURG         |
| 8   | rs11779521| 30 983 843| T            | 0.47| 986| 0.21 | 0.05 | 4.7 × 10^{-6} | 0.02 | PURG         |
| 8   | rs11775287| 30 983 881| C            | 0.47| 986| 0.21 | 0.05 | 4.7 × 10^{-6} | 0.02 | PURG         |
| 8   | rs10929438| 6 522 878 | A            | 0.34| 986| -0.21| 0.05 | 4.7 × 10^{-6} | 0.02 |               |
| 14  | rs12936442| 100 cM    | A            | 0.14| 985| 0.63 | 0.20 | 2.9 × 10^{-7} | 0.03 |               |
| 14  | rs3783332 | 99 655 010| T            | 0.17| 984| -0.34| 0.06 | 3.5 × 10^{-8} | 0.03 | EVL          |
| 14  | rs7159759 | 99 653 102| A            | 0.17| 984| -0.34| 0.06 | 3.5 × 10^{-8} | 0.03 | EVL          |
| 14  | rs3783332 | 99 655 010| A            | 0.17| 984| -0.34| 0.06 | 3.5 × 10^{-8} | 0.03 | EVL          |
| 14  | rs1160570 | 99 651 389| T            | 0.17| 984| -0.34| 0.06 | 3.5 × 10^{-8} | 0.03 | EVL          |
| 14  | rs941898  | 99 669 190| G            | 0.17| 984| -0.34| 0.06 | 3.8 × 10^{-8} | 0.03 | EVL          |
| 14  | rs941900  | 99 673 152| C            | 0.19| 984| -0.28| 0.06 | 1.3 × 10^{-6} | 0.02 | CROT         |
| 22  | rs7101759 | 43 083 359| A            | 0.16| 984| 0.50 | 0.1  | 1.6 × 10^{-6} | 0.02 | KIAA1644     |
| 22  | rs7510924 | 43 039 988| T            | 0.16| 984| 0.50 | 0.1  | 1.6 × 10^{-6} | 0.02 | KIAA1644     |

Abbreviations: CHR, chromosome; MAF, minor allele frequency; SNP, single-nucleotide polymorphism.
Bold values = P < 9 × 10^{-10}.

(rs12936442, rs894664, rs6502671, rs7216028) and from chromosome 22 at 43 cM (rs7510759, rs7510924, rs7290560) and at 36 cM (rs8136107) were suggestively associated with both cynicism and paranoia. Replications of the genetic linkage between different measurement of hostility and different measurement years are presented in Table 5.

Discussion

Our study reports results of a large-scale GWA analysis of hostility, with hostility measured in four follow-ups across 15 years of time span with three different scales. Although only few associations achieved genome-wide significance, many associations approached significance. We attempted to capture more reliable findings of the genotype over time by using the mean of hostility levels in the four time points as the outcome. Most of the suggestive associations did not replicate across measurement times, which undermines the robustness of the single significant associations. These suggestive associations should therefore be interpreted with appropriate caution. The inconsistent findings resemble those from many previous GWA studies of personality, most of which have not yet found robust evidence for specific candidate genes.13,25–27

The strongest associations were found for mean score of paranoia with a number of closely linked SNPs in chromosome 14 at 99 cM, although this suggestive association had limited replicability over time. Chromosome 14 at ~ 100 cM has been previously linked to neuroticism and anxiety27,28 and at 103 cM to bipolar disorder.29 The present study thus adds evidence that this region may include genetic markers or determinants for general anxiety and distrust (that is, paranoia) as well as for susceptibility to psychiatric diagnoses involving distrust against others. The finding that the mean paranoia for four different time points had significant genetic linkage, but single measurements of paranoia did not, may imply that paranoia as a stable trait has wider genetic basis, but high distrust in one point in time may depend more on transient environmental factors and be more prone to fluctuate. The closest gene for the found paranoia linked SNPs is EVL gene in chromosome 14, which is proposed as a possible candidate gene for colorectal cancer.30

Another significant genomic region found in the current study is in chromosome 17 at 2.8 cM, which was suggestively linked with both paranoia and cynicism in the most recent measurement when the participants were at age 30–45 years. The closest gene for this region is RAP1GAP2, which affects GTPase-activating protein, has a role in regulating the platelet aggregation, and is expressed especially in heart, testis and blood leukocytes, and also in stomach, pancreas and intestines, and slightly in brain.31 Thus, this might
also be a possible link between hostility and health problems. Both cynicism and paranoia mean scores were also associated with a region in chromosome 22 at 36 cM and at 43 cM for which the closest gene is \textit{KIAA1644}. Neither \textit{RAP1GAP2} nor \textit{KIAA1644} have previously been linked to personality traits, although chromosome 22 at 36 cM has been linked to bipolar disorder and schizophrenia.\cite{32}

Although the results for cynicism did not reach the Bonferroni corrected statistical significance level, there were
many marginally significant associations. Especially, areas on chromosome 7 at 86 cM were related to cynicism in 1992, 1997 and mean of cynicism measurements. The nearest gene for this region is CROT (carnitine O-octanoyl transferase) that affects fatty acid functioning in a cell level and is expressed at least in mice almost everywhere in the body, especially in liver and intestines, and also slightly in heart and brain.  

The observed suggestive associations may have some theoretical implications. Theoretically, cynicism is assumed to develop more in response to environmental experiences, which may explain the less significant relation to genetic background. However, it may be that there are multiple overlapping genetic effects and gene \times gene and gene \times environment interactions that prevent SNPs to reach the Bonferroni corrected significance level. Same locations in chromosome 17 at 2.8 cM and chromosome 22 at 36 and 43 cM were associated with both cynicism and paranoia, which may imply shared genetic background with these hostility dimensions. Such hostile attitudes might be seen as core of the hostility construct.  

Anger, on the other hand, is theoretically a separate construct having its developmental roots in temperament-like characteristics.  

Our finding that anger did not share similar genetic background with cynicism or paranoia implies that the consideration of anger as a separate construct seems justified also from the genetic perspective. The phenotypic and genotypic differences behind hostility measures may thus in part explain the mixed findings between hostility and cardiovascular health.  

Measuring complex personality traits, like hostility, involves challenges of accurate measurement of the phenotype. Measurement error due to imperfect assessment of the phenotype reduces the ability to capture stable phenotype over time (test–retest correlations) and introduces time-specific variance in the measures. The lack of adjustment for relevant environmental factors influencing personality development may partly explain why the GWAS findings of personality traits rarely replicate in different time points or in different samples. This is not a unique problem to our study, as previous studies with well-established personality scales, for example, Temperament and Character Inventory (TCI) and ‘Big Five’ have rarely found consistent associations with GWAS.  

In summary, this GWAS showed preliminary evidence for specific regions possibly related to hostility. The suggestive associations were small in magnitude and did not replicate across all measurement times, and thus they warrant further study in other populations. Single SNPs are likely to have small and thereby variable effects on personality traits, and many real effects may be lost in plenty of associations because of insufficient statistical power and measurement imprecision related to the identification of the phenotype. Accumulating evidence from several cohorts should provide more accurate and reliable data on the genetic background of hostility and other personality traits.

**Conflict of interest**
The authors declare no conflict of interest.
23. Li Y, Abecasis GR. Mach 1.0: rapid haplotype reconstruction and missing genotype inference. Am J Hum Genet 2006; 79: 2290.

24. Aulchenko YS, Ripke S, Isaacs A, van Duijn CM. GenABEL: an R library for genome-wide association analysis. Bioinformatics 2007; 23: 1294–1296.

25. Verweij KJH, Zietsch BP, Medland SE, Gordon SD, Benyamin B, Nyholt DR et al. A genome-wide association study of Cloninger’s temperament scales: implications for the evolutionary genetics of personality. Biol Psychol 2010; 85: 306–317.

26. Terracciano A, Sanna S, Uda M, Deiana B, Usala G, Busonero F et al. Genome-wide association scan for five major dimensions of personality. Mol Psychiatry 2010; 15: 647–656.

27. Wray NR, Middeldorp CM, Birley AJ, Gordon SD, Sullivan PF, Vischer PM et al. Genome-wide linkage analysis of multiple measures of neuroticism of 2 large cohorts from Australia and the Netherlands. Arch Gen Psychiatry 2008; 65: 649–658.

28. Middeldorp CM, Hottenga JJ, Slagboom PE, Sullivan PF, de Geus EJ, Posthuma D et al. Linkage on chromosome 14 in a genome-wide linkage study of a broad anxiety phenotype. Mol Psychiatry 2008; 13: 84–89.

29. Burton PR, Clayton DG, Cardon LR, Craddock N, Deloukas P, Duncanson A et al. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007; 447: 661–678.

30. Sjöström T, Jones S, Wood LD, Parsons DW, Lin J, Barber TD et al. The consensus coding sequences of human breast and colorectal cancers. Science 2006; 314: 268–274.

31. Schultess J, Danielewski G, Smoleniski AP. Rap1GAP2 is a new GTPase-activating protein of Rap1 expressed in human platelets. Blood 2005; 105: 3185–3192.

32. Badner JA, Gershon ES. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. Mol Psychiatry 2002; 7: 405–411.

33. Westin MA, Hunt MC, Alexson SE. Short- and medium-chain carnitine acyltransferases and acyl-CoA thioesterases in mouse provide complementary systems for transport of beta-oxidation products out of peroxisomes. Cell Mol Life Sci 2008; 65: 982–990.

34. Nigg JT. Temperament and developmental psychopathology. J Child Psychol Psychiatry 2006; 47: 395–422.

35. Cloninger CR, Van Eendewegh P, Goate A, Edenberg HJ, Blangero J, Hesselbrook V et al. Anxiety proneness linked to epistatic loci in genome scan of human personality traits. Am J Med Genet 1998; 81: 313–317.

36. Terracciano A, Tanaka T, Sutin AR, Sanna S, Deiana B, Lai S et al. Genotype-wave association scan of trait depression. Biol Psychiatry 2010; 68: 811–817.

37. de Moor MHM, Costa PT, Terracciano A, Krueger RF, de Geus EJC, Toshiko T et al. Meta-analysis of genome-wide association studies for personality. Mol Psychiatry; e-pub ahead of print 21 December 2010; doi:10.1038/mp.2010.128 (in press).