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Maintenance of genetic variation in human personality: Testing evolutionary models by estimating heritability due to common causal variants and investigating the effect of distant inbreeding

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Abstract

Personality traits are basic dimensions of behavioural variation, and twin, family, and adoption studies show that around 30% of the between-individual variation is due to genetic variation. There is rapidly-growing interest in understanding the evolutionary basis of this genetic variation. Several evolutionary mechanisms could explain how genetic variation is maintained in traits, and each of these makes predictions in terms of the relative contribution of rare and common genetic variants to personality variation, the magnitude of nonadditive genetic influences, and whether personality is affected by inbreeding. Using genome-wide SNP data from >8,000 individuals, we estimated that little variation in the Cloninger personality dimensions (7.2% on average) is due to the combined effect of common, additive genetic variants across the genome, suggesting that most heritable variation in personality is due to rare variant effects and/or a combination of dominance and epistasis. Furthermore, higher levels of inbreeding were associated with less socially-desirable personality trait levels in three of the four personality dimensions. These findings are consistent with genetic variation in personality traits having been maintained by mutation-selection balance.

Introduction

Personality traits are basic dimensions of behavioural variation, comprising various more specific characteristics that tend to correlate together. In humans, much of the behavioural variation between individuals is thought to be accounted for by between three and seven roughly independent personality dimensions (Eysenck and Eysenck 1976; Cloninger 1987; Digman 1990; Almagor et al. 1995), and more than 50 years of twin, family, and adoption studies indicate that around 30% or more of the personality variation between individuals can be accounted for by genetic variation (see Johnson et al. 2008 for a recent review). In other animals, personality traits (or 'behavioural syndromes') have been the subject of fewer genetic studies, but there is ample evidence in several species that inter-individual variation in behavioural tendencies is also due substantially to genetic variation (Bakker 1986; Drent et al. 2003; Sinn et al. 2006). The proportion of total trait variation that is accounted for by genetic variation is called broad-sense heritability. This consists of the additive component of heritability (due to the accumulation of the average allelic effects) and may also include nonadditive genetic variation (due to interaction of alleles within (dominance) or between (epistasis) loci). Although it is statistically difficult to distinguish nonadditive from additive genetic variation, there is evidence in humans suggesting that both contribute to personality variation (Eaves et al. 1998; Lake et al. 2000; Keller et al. 2005).

Recently, there has been a rapidly growing interest in understanding the evolutionary basis of heritable personality variation, both in humans (Bouchard and Loehlin 2001; Nettle 2005, 2006; Penke et al. 2007; Alvergne et al. 2010; Gangestad 2010; Nettle and Penke 2010; Verweij et al. 2010; Buss and Hawley 2011; Lukaszewski and Roney 2011; Del Giudice 2012) and in other animals (Dingemanse et al. 2004; Cote et al. 2008; Bergmuller and Taborsky 2010; Dingemanse and Wolf 2010; Dochtermann and Roff 2010; van Oers and Mueller 2010; Wolf and Weissing 2010). Indeed, the broader line of inquiry is one of the major outstanding questions in evolutionary biology (Mitchell-Olds et al. 2007): how is genetic variation maintained in traits where there is selection for only the most advantageous genotypic trait values?

Broadly, there are three main possibilities for explaining the maintenance of genetic variation in personality. The first, *selective neutrality*, is that genetic variants underlying personality traits do not affect individuals' fitness and so are free to randomly drift in frequency without being affected by selection. Under selective neutrality, individual genetic variants will be lost due to drift, but in the meantime new mutations will also arise and maintain genetic variation in the population (i.e. a mutation-drift balance). An argument against selective neutrality in humans is that personality traits are associated with traits that are presumably related to fitness such as mental and physical health (Lahey 2009; Kotov et al. 2010), mortality (Shipley et al. 2007; Mosing et al. 2012), attractiveness (Lukaszewski and Roney 2011), mating behaviour (Zietsch et al. 2010), and number of offspring (Eaves et al. 1990; Jokela et al. 2009; Alvergne et al. 2010; Jokela et al. 2010). However, positive correlations with one fitness component can be counterbalanced by negative correlations with other fitness components (e.g. Nettle 2005; Alvergne et al. 2010), which could potentially result in a zero net effect on fitness (Roff and Fairbairn 2007). In this vein, MacDonald (1995) proposed that human personality dimensions each represent a continuum of alternative strategies for maximising fitness, so that average fitness would be approximately uniform (selectively neutral) across the normal personality range. Expanding on this view, Nettle (2006) proposed concrete cost-benefit trade-offs associated with five of the major dimensions of personality variation in humans. For example, he proposed that high extraversion conferred the benefits of greater mating and social success, which were balanced by increased risk of accident and injury due to greater novelty seeking behaviour. In line with this type of view, recent theoretical work has emphasised that genetic variants affecting multiple traits can be invisible to selection when multivariate genetic constraints result in little or no variation in fitness effects; this can occur even when the individual traits correlate with fitness and have substantial genetic variation (Walsh and Blows 2009).

A second possibility for explaining the maintenance of genetic variation in personality traits is *mutation-selection balance* (Lande 1975; Zhang and Hill 2005; Keller and Miller 2006). In this view, deviations from an optimal personality trait level (averaged across environments) are selected against, eliminating alleles that do not predispose to this optimum, and thus reducing genetic variation. In the meantime though, new mutations affecting the trait arise in the population. The vast

majority of mutations that affect fitness are deleterious (Eyre-Walker and Keightley 2007), since they randomly disrupt finely-tuned systems. Mutations with strong and dominant effects are purged quickly by selection; mutations with recessive and/or weak effects, which are less visible to selection, may persist for many generations before being eliminated, but are unlikely to become common in the population because of the selection against them (Eyre-Walker 2010). As a result of this and the constant influx of new mutations, individuals each carry an accumulated 'mutation load' consisting of alleles that tend to be rare, (partially) recessive, and mildly deleterious. Individuals' mutation loads can vary in many ways, such as their numerousness, recessiveness, and which trait(s) they affect. Traits that are affected by a large number of loci and that therefore have a large "mutational target size" will tend to be disrupted to a larger extent by mutations (Houle 1998). Given that over half the genome is expressed in the brain (Sandberg et al. 2000), it is possible that personality traits have a large mutational target size and that much of their genetic variation is mutational.

The third possibility for explaining the maintenance of genetic variation in personality traits is *balancing selection*. Under balancing selection, genetic variation is maintained rather than depleted by selection; for example by selection pressures that fluctuate over time and space (environmental heterogeneity), that differ between the sexes (sex-dependent selection), or that favour rarer trait values (negative frequency-dependent selection) or heterozygotes (overdominance). Investigating the relationship of exploratory personality with survival and reproduction rates in Great Tits, Dingemanse et al. (2004) found that selection pressures were opposite in males and females and fluctuated from year to year depending on food and space availability. They argued that this variation in selection was likely to maintain the substantial heritable component of exploratory behaviour in these birds. Similarly, Penke et al (2007) noted the varied and changing physical and social environments that humans have experienced and created for themselves in their evolutionary history, and argued that genetic variation in personality traits is most likely to be actively maintained by balancing selection by environmental heterogeneity, often mediated by negative frequency-dependent selection on life-history strategies. Another perspective (Tooby and Cosmides 1990) is that genetic variation in personality is a side effect of pathogen-driven balancing selection, whereby rare alleles are of higher fitness because pathogens are usually poorly adapted to attacking the rarest host genotypes (Garrigan

and Hedrick 2003) – this would be an example of 'pleiotropic balancing selection' (Turelli and Barton 2004).

Evaluating these possibilities has proved difficult. In humans, quantifying total fitness and relating it to personality traits is challenging even in contemporary societies, and it is harder still to infer relationships between total fitness and personality traits in the varied environments of our evolutionary history. However, using recently-developed methodologies in statistical genetics, it is possible to test competing predictions from the three evolutionary models. In the present investigation, we attempt to gain insight into several properties of alleles underlying human personality—their number, their effect sizes, their commonness in the population (i.e. minor allele frequency; MAF), and their degree and direction of recessiveness –to gain traction on the mechanisms most likely influencing their genetic variation (Keller et al. 2011a).

Predictions from different mechanisms of maintaining genetic variation

Selective neutrality predicts that the distribution of the additive genetic variance explained as a function of MAF is uniform (Eyre-Walker 2010; Visscher et al. 2011). For example, loci with MAF between 0 and 0.01 should account for 2% of the additive genetic variation, and loci with MAF between 0.01 and 0.50 should account for the other 98%. Furthermore, the proportion of genetic variation that is non-additive should be lower in neutral traits than in traits under directional or stabilising selection because these forms of selection erode additive genetic variation (Fisher 1930; Merila and Sheldon 1999; Stirling et al. 2002; Penke et al. 2007). There should also be no systematic tendency for recessive alleles to influence a personality trait in any particular direction if it is selectively neutral (Lynch and Walsh 1998; DeRose and Roff 1999). Inbreeding depression, which only occurs in the presence of directional recessiveness (Lynch and Walsh 1998), is therefore not expected to affect personality traits if they have been selectively neutral.

Predictions regarding the genetic architecture of traits under mutation-selection balance differ from those of selective neutrality above. If personality traits have been under mutation-selection balance, alleles underlying personality traits should be rarer than expected under selective neutrality (Eyre-Walker 2010). Second, the depletion of additive alleles should result in a substantial

nonadditive component to the genetic variation underlying personality (Crnokrak and Roff 1995; Merila and Sheldon 1999; Stirling et al. 2002). Third, inbreeding should affect personality trait levels by pushing them in the opposite direction to that in which selection is acting; the exception is if the population mean is already at the optimum (i.e. stabilising selection), in which case inbreeding depression would not be expected because recessive allele effects pushing the trait away from its mean in each direction would cancel each other out on average.

Evolutionary genetic modelling on all forms of balancing selection reveals that it only maintains polymorphisms at high frequencies (i.e. both alleles are common), because at low allele frequencies the balancing mechanisms become unstable and the rare allele is lost (Mani et al. 1990; Curtsinger et al. 1994; Turelli and Barton 2004; Kopp and Hermisson 2006; Penke et al. 2007). Thus, alleles responsible for personality trait variation should be at a higher frequency than expected under neutrality if they have been maintained by balancing selection (Johnson and Barton 2005). Most models in which balancing selection acts directly on a trait (e.g. negative frequency-dependent selection, sex-dependent selection, overdominance resulting from antagonistic pleiotropy) make the additional prediction that variation can only be maintained at a small number of genetic loci per trait (Curtsinger et al. 1994; Burger 2000; Barton and Keightley 2002; Turelli and Barton 2004; Kopp and Hermisson 2006). However, despite statistical power to detect SNPs of even very small effect size (~0.5% of trait variance), large genome-wide association studies on personality have failed to find strong evidence of association with any SNPs (de Moor et al. 2010; Verweij et al. 2010), suggesting a highly polygenic basis to personality. Nevertheless, modelling suggests that some forms of balancing selection - namely, spatial and temporal environmental heterogeneity, and pleiotropic selection as a side effect of balancing selection on another trait - can maintain variation at a large number of genetic loci, although the requisite conditions are quite restrictive (Burger and Gimelfarb 2002; Turelli and Barton 2004). As such, it remains possible that either of these balancing selection mechanisms could have maintained polymorphisms at many genetic loci underlying personality variation; this would lead to the prediction that the genetic architecture of personality traits consists largely of genetic variants of high frequency. Nonadditive genetic variation in the trait of interest (as opposed to fitness itself) is not a requirement of these latter forms of balancing selection (Turelli and Barton 2004), and

since additive genetic variation is maintained (rather than depleted) by balancing selection, a high proportion of nonadditive variation is not expected. Furthermore, there would be no reason to expect inbreeding to affect the trait since that requires directional dominance with respect to the trait (Charlesworth and Charlesworth 1987; Roff 2005).

While they make different sets of predictions, these three main mechanisms for maintaining genetic variation are not mutually exclusive possibilities. For example, if genetic variation in personality traits is under very weak selection (e.g. because trade-offs reduce its fitness consequences), many mutations with small effects will be governed largely by drift and the overall genetic architecture will look like that of selective neutrality with only a slight bias in the frequency distribution of alleles (Eyre-Walker 2010). It is also important to note that current genetic architecture reveals past evolutionary processes, so implications regarding selective pressures on personality traits may not be reflected in today's environment. With these issues in mind, predictions from the different evolutionary mechanisms are summarised in Table 1. (Hill et al. 2008),

-- Table 1 --

In this study we test the strongest competing predictions of selective neutrality, mutation-selection balance, and balancing selection: (a) the extent to which all common genetic variants contribute to variation in personality; and (b) whether or not inbreeding affects personality traits. To do this, we use genotypic and phenotypic data from four community-based samples from Australia and Finland (total N>8,000) who were assessed on Cloninger's Harm Avoidance, Novelty Seeking, Reward Dependence, and Persistence dimensions. To test (a) above, we use recently-developed methodology (Visscher et al. 2010; Yang et al. 2010; Yang et al. 2011b) to estimate the proportion of variation in these personality traits that can be accounted for by ~270,000 SNPs taken together. This method captures the vast majority of the combined effect of common variants, but much less of the combined effect of rare (MAF<0.01) variants (Yang et al. 2010), since the rarer a variant is the less it can possibly be correlated with a common SNP in a sample of unrelated people (Wray 2005; Wray et

al. 2011)[1]. To test (b), we examine the association between personality traits and the level of inbreeding in the ancestry of each individual as indexed by the extent to which their genome is in 'runs of homozygosity' (i.e. homozygous stretches of DNA that can be observed in the offspring of even distant relatives (Keller et al. 2011b)).

Methods

Participants

This study incorporates data from one Australian and three Finnish subsamples. Table 2 provides an overview of available individuals with both phenotype and genotype data.

-- Table 2 --

The Young Finns Study (YFS) subsample derives from longitudinal data collection from five Finnish university cities and surrounding areas (Akerblom et al. 1991; Raitakari et al. 2008). The Helsinki Birth Cohort Study (HBCS) is a birth cohort sample of individuals born at Helsinki University Central Hospital between 1934 and 1944 (Barker et al. 2005; Eriksson et al. 2006; Raikkonen et al. 2008). The Northern Finland 1966 Birth Cohort (NFBC) is a population based birth cohort comprising 12,058 individuals born in 1966 in the northernmost provinces (Rantakallio 1969).The Queensland Institute of Medical Research (QIMR) subsample includes two population based cohorts of Australian twins and their families. The first cohort was assessed in 1988 and the second in 1990. The total QIMR subsample is 5530 individuals from 2791 independent families. More details about the phenotypic and genotypic data collection at QIMR can be found elsewhere

[1] Common genotyped SNPs that trace distant relatedness will to some extent reflect the relatedness at distant causal mutations that have been co-inherited with the SNPs, so some of the combined effect of distant rare variants may be captured, but not the effect of relatively recent mutations.

(Keller et al. 2005; Verweij et al. 2010). Note that the core analyses required unrelated individuals; discarding related individuals (using different levels of relatedness as cut-offs for different analyses) reduced the subsamples.

Ethical constraints preclude us from making the phenotypic and genotypic data publically available because participants, who took part in the studies on the condition that their data would remain confidential, could potentially be identified from their DNA.

Personality measures

The different subsamples used different versions of Cloninger's personality scales (see Table 2 - Tridimensional Personality Questionnaire (TPQ short version, see Cloninger et al. 1991; Heath et al. 1994) and Temperament and Character Inventory (TCI, Cloninger et al. 1993). To get homogenous phenotypes, in this study we only included the 54 items of the revised short version of the TPQ (as used in the QIMR sample); all these items were also incorporated in the other questionnaires. This yielded 18 Harm Avoidance, 19 Novelty Seeking, 12 Reward Dependence, and 5 Persistence items. Internal consistency of the scales of this short version of the TPQ were acceptable and comparable with those reported for the full TPQ scales and the short-term test-retest reliability of the scales was good (see Table 1 in Keller et al. 2005 for these statistics on the QIMR subsample). These items and scales are the same as used in Keller et al (2005) to estimate genetic and environmental variance components from twin-family data, except that they analysed one item as contributing to the Reward Dependence scale while we assigned it to the Novelty Seeking scale in accordance with the scales' revision (Cloninger 1994).

The following data cleaning procedure was performed separately for each subsample. The personality scale scores were calculated by summing the relevant item scores, reverse scoring where necessary. (Note that, for consistency, the rating scale used in the YFS study was converted to a 0-1 measure by converting the item scores as follows: 1=0, 2=0.25, 3=0.5, 4=0.75, and 5=1.0.) Missing items were imputed with the sample mean score on the item. Personality scale scores for individuals with more than 25% missing values on that scale were assigned as missing. To minimize departures from normality the scale scores were then angular transformed (Freeman and Tukey 1950; Eaves et al.

1989), as was also done in Keller et al (2005). Last, scale scores were corrected (by regression) for sex, age, age^2, sex*age, and sex*age^2 effects and each scale was standardised separately per sex. Note that because all individuals in the NFBC sample were 31 years old we only corrected for sex effects in that cohort.

Genotyping and quality control

The genotype data from each subsample first underwent separate standard quality control (QC) procedures (not reported here), before undergoing two additional, more stringent rounds of QC for this project (see Supplementary Table 1). In each subsample, we removed SNPs with a MAF <0.01, with a Hardy-Weinberg equilibrium (HWE) test p-value<.001, and a call rate <95% (i.e. missing genotype calls > 5%). We further removed individuals with an overall call rate <95%. Note that the QIMR subsample consisted of data from three genotype platforms - SNP and individual call rates were checked separately for data from each platform prior to this study. After combining the data from all subsamples we performed another round of QC on the total sample, again checking for Hardy-Weinberg equilibrium and SNP call rate. Our final sample included 12,859 individuals and 269,616 SNPs that were genotyped in at least 95% of individuals in the sample.

Estimating the proportion of personality trait variation accounted for by all autosomal SNPs

The method used here does not estimate the effect of each individual SNP as is the case in (genome-wide) association studies (Manolio 2010) and genetic prediction studies (Wray et al. 2007) – in those methodologies, summing the estimates of SNP effects also sums the error component of those estimates and thus does not yield an unbiased estimate of the variance explained by the aggregate of all SNP effects. Instead, we computed one unbiased estimate of the aggregate effect of all SNPs. Conceptually, this is achieved by determining to what extent genetic similarity (at the SNPs) between all individuals corresponds to their phenotypic similarity. Technically, the SNP effects are treated as random effects in a mixed linear model and the total trait variance explained by all the SNPs is estimated by restricted maximum likelihood (REML) analysis, as implemented in the freely available Genome-wide Complex Trait Analysis (GCTA) program (Yang et al. 2011b; see

http://gump.qimr.edu.au/gcta/). Technical details of the method are described in Yang et al (2010) and Yang et al (2011b), and a plainer language explanation of the method and common misunderstandings is provided by Visscher et al (2010).

We estimated the genetic similarity matrix between all individuals using the 269,616 autosomal SNPs that passed quality control and were common to at least 95% of individuals in the combined sample. We excluded one of each pair of individuals with an estimated genetic similarity of >0.05 (approximately closer than second cousins), in order to reduce the possibility that the phenotypic resemblance between close relatives could be caused by shared environmental effects and/or causal variants not correlated with SNPs but captured by pedigree (Visscher et al. 2010; Yang et al. 2010). This led to an exclusion of 4,197 individuals, resulting in a retained dataset of 8,662 individuals. To check if shared environmental effects and/or causal variants captured by pedigree were still biasing our estimate, we also tested a more stringent cut-off by excluding one of each pair of individuals with an estimated genetic relationship of >0.025 (~ closer than third or fourth cousins). This led to an exclusion of 7,957 individuals, resulting in a retained dataset of 4,902 individuals. Population structure (i.e. differences in allele frequencies between subpopulations which might also differ in personality) can inflate the genetic variance estimates, so to control for this we included the first 20 principal components (eigenvectors of the genetic relatedness matrix) and cohort status (i.e. which subsample they belong to) as covariates in the analysis. We checked to what extent population structure would have affected the results by comparing results from analyses with and without the 20 principal components as covariates.

While we have dense SNP coverage across the genome, the SNPs may not be in complete linkage disequilibrium (LD) (i.e. perfectly correlated) with all common causal variants. We therefore adjusted the variance estimates explained by our SNPs for incomplete LD with causal variants, under the assumption that the causal variants have the same allelic spectrum as the genotyped SNPs. This adjustment procedure is based on a formula empirically established by Yang et al. (2010) and is described in detail in their paper. The adjustment is implemented in the GCTA program. In this way we tested to what extent the variance explained by the SNPs captured the variance explained by all common variants (including common structural variants e.g. copy number variants). Additionally, we

tested whether including more SNPs in our analyses (all SNPs that were genotyped for at least a third of our sample, N=532,030 SNPs) would affect the variance accounted for.

Because there is some evidence that partly different genetic factors influence males and females for Harm Avoidance and Reward Dependence (Keller et al. 2005), for these scales we performed separate analyses by sex in addition to the main analyses with the sexes pooled.

Testing the effect of inbreeding on personality traits

To test whether inbreeding influenced the personality traits we obtained an index of the level of inbreeding in each individual's ancestry based on their SNP data, and then tested if this coefficient was correlated with the personality scale scores.

Using PLINK software (Purcell et al. 2007), we quantified individuals' level of inbreeding by estimating the proportion of their genome that is in runs of homozygosity (ROH), by summing the total length of all their autosomal ROHs divided by the total SNP-mappable autosomal genome length ($2.77*10^9$). ROHs are homozygous stretches of DNA that can be observed in the offspring of even distant relatives (Howrigan et al. 2011; Keller et al. 2011b)). The *Runs of Homozygosity* program (PLINK; Purcell et al. 2007) slides a moving window of a specified number of SNPs across the genome in order to detect long runs of homozygous genotypes. Runs are flexibly definable in terms of the required number of homozygous SNPs spanning a certain distance.

We define ROHs following recommendations in Howrigan et al. (2011), in which simulations were used to determine the ROH definitions that yield the most power to detect distant inbreeding (i.e. within the last 50 generations). Accordingly, we define ROHs as stretches of at least 65 continuously homozygous SNPs, using lightly pruned SNP data (i.e. removing SNPs with a MAF<.05 and with a variance inflation factor [VIF] > 10 using PLINK (Purcell et al. 2007) (see Supplementary Table 2)). To minimise underestimation of the number of runs, three (~5%) missing genotypes within an otherwise unbroken homozygous segment were allowed in a run. Further details of the parameters used - based on recommendations from Howrigan et al. (2011) - can be found in Supplementary Information Table 3.

Additionally, we examined the relative importance of close versus distant inbreeding by comparing the effect on personality traits of short (<5Mb) versus long (>5Mb) ROHs. ROHs with a length of 5Mb or less should originate from a common ancestor ten or more generations ago, whereas longer ROHs should originate from a common ancestor less than ten generations ago.

To test the robustness of our results to different types of inbreeding measures, we also calculated a different type of inbreeding coefficient based on the correlation between uniting gametes, as implemented in GCTA (i.e. $\hat{F}_{III}$ (Yang et al. 2011b); termed F_{alt} in Keller et al 2011b); no pruning was used). We chose this coefficient over the other two inbreeding coefficients implemented in GCTA because it is independent of the MAF and therefore less biased and is predicted to have lower error (Yang et al. 2011b).

For these analyses there was no need for a stringent genetic relatedness cut-off as in the heritability estimation described earlier, but we did exclude one of each pair of individuals with a genetic relatedness larger than 0.3 so that twin and sibling pairs did not bias the p-values. This resulted in a sample of 10,247 individuals. Population structure (first 20 principle components) was corrected for before analysis.

Results

Descriptive statistics of the four personality scales in the four subsamples are in Supplementary Table 4, and correlations between the personality scales are in Supplementary Table 5.

Variance explained by all autosomal SNPs

Common SNPs explained between 4.2% and 9.9% of the total variation in the four personality traits, at an average of 7.2% (Table 3). Due to the large sample size, the standard errors of these estimates were small (~3.7%), and estimates for Harm Avoidance, Novelty Seeking and Persistence were significantly different from zero (p<.05). Correcting for incomplete LD between the

SNPs and causal variants, or almost doubling the number of SNPs used, had a negligible effect on the estimates (see Supplementary Table 6), indicating that our estimates captured the vast majority of all common additive genetic variant effects. Re-running the tests without the 20 principal components as covariates increased the estimates only a little (see Supplementary Table 6), and re-running analyses with a more stringent cut-off for relatedness (0.025) somewhat lowered the estimates for Harm Avoidance, Novelty Seeking and Persistence (see Supplementary Table 6), suggesting that our main estimates (Table 3) could be slightly inflated due to causal variants not correlated with SNPs but captured by pedigree. As such, the estimates in Table 3 are best considered upper limits, reinforcing that common additive genetic variant effects play only a minor role in personality variation.

Based on previous findings suggestive of sex-limitation, we also re-ran the analyses separately for males and females for Harm Avoidance and Reward Dependence. These estimates (see Supplementary Table 6) did not differ substantially from those in Table 3. We also tested for heterogeneity of the estimates from the different subsamples - the estimates from individual subsamples were very imprecise and varied widely, but a formal test revealed no significant heterogeneity ($p>0.1$ for all scales).

Total heritability estimates for the different scales range from 0.28 to 0.36, as obtained from an additive genetic + residual (AE) model based on a large twin-sibling study (N~13,000; Keller et al. 2005). These are essentially estimates of broad-sense heritability and include any nonadditive genetic variance (separate unbiased estimates of additive and nonadditive genetic influences are not available), whereas the GCTA heritability estimates from the SNPs (h^2_{SNPs}) do not include nonadditive genetic variance – this is considered further in the Discussion section.

-- Table 3 –

Overall, these results suggest that common additive genetic variants account for a small percentage (~20%) of the total genetic variation in all four personality traits, consistent with mutation-selection balance but not consistent with selective neutrality or balancing selection models for highly

polygenic traits. The rest of the genetic variation is likely to comprise of rare variant effects and/or some combination of dominance and epistasis.

The effect of inbreeding on personality traits

We tested for a correlation between personality traits and an index of inbreeding in individuals' ancestry – i.e. the proportion of the genome in runs of homozygosity (Table 4). Descriptives of the number of runs and the total proportion of the genome in homozygous runs for the overall sample and each subsample are shown in Supplementary Table 7. As shown in Table 4, proportion of genome in runs of homozygosity correlated significantly and positively with Harm Avoidance, and significantly and negatively with Novelty Seeking and Reward Dependence. The alternative inbreeding coefficient based on uniting gametes ($\hat{F}_{III}$) (Yang et al. 2011b) gave very similar results, the only difference being that Persistence was also significantly correlated with inbreeding (negatively, p=.02, see Supplementary Table 8). Multiple regression (data not shown) indicated the significant effects were at least partly unique to each trait, rather than a result of their intercorrelation. Furthermore, results were almost identical whether or not inbreeding coefficients were winsorised (i.e. extreme values set at 3 standard deviations from the mean; see Supplementary Table 8), suggesting that the results are not driven by outliers resulting from close inbreeding. Finally, significant effects could be observed within separate subsamples (though not consistently, due to reduced power), reinforcing that the effect is not due to population stratification (see Supplementary Table 8).

-- Table 4 --

Table 4 also shows that both short (<5Mb) and long (>5Mb) ROHs affected personality traits highly significantly, and in the same directions to very similar degrees. ROH (short) and ROH (long) did not correlate very highly with each other (r=0.40), and both predicted the traits when entered together in multiple regression (data not shown), implying very similar and somewhat independent effects of distant and close inbreeding, respectively.

Overall, these results provide strong evidence that inbreeding affects some personality traits, consistent with being influenced by a load of mutations that tend to be rare, recessive, and deleterious, as predicted under mutation-selection balance. These inbreeding effects are not consistent with selective neutrality or balancing selection models for highly polygenic traits, as these provide no reason to expect bias in the direction of dominance across many loci.

Discussion

Using ~270,000 SNPs, we created a genetic similarity matrix of over 8,000 unrelated individuals. By determining to what extent individuals' genetic similarity corresponded to their similarity in personality traits, we estimated the proportion of total personality trait variance that could be explained by the additive genetic effects of common causal variants that are associated with these SNPs. The variation explained by SNPs (4.2-9.9%) was statistically significant in three of the four traits, but for all four traits it represented a small proportion (~20%) of the total genetic variation previously estimated by various designs (twin, family, and adoption studies). The heritability estimated using the 270,000 SNPs captured the effects of the vast majority of common (MAF>0.01) causal variants, due to linkage disequilibrium between the SNPs and other common variants, but only a small portion of the genetic variation due to rare causal variants. As such, these results suggest that common additive genetic variants account for little of the variation in Cloninger's personality traits, and therefore rare genetic variants and/or some combination of dominance and epistasis are likely to account for most of the variation. This is consistent with the hypothesis that genetic variation in human personality traits has been maintained by mutation-selection balance, but is less consistent with it being selectively neutral or maintained by pleiotropic balancing selection or balancing selection via environmental heterogeneity. Overdominance might also be consistent with these results because it predicts high levels of dominance variation, but it also predicts that genetic variation is due to common alleles at a relatively small number of loci per trait (Curtsinger et al. 1994; Burger 2000), which is inconsistent with previous research on these and other personality scales (de Moor et al. 2010; Verweij et al. 2010). The contribution of common additive genetic variants to genetic variation

492 in personality traits is less than that of some other traits that have been subject to the same analysis -
493 for example, the proportion of the genetic variation that can be explained by common SNPs is around
494 half for height (Yang et al. 2010) and intelligence (Davies et al. 2011), one-third for risk of
495 schizophrenia (Lee et al. under review), and one-quarter for body mass index (Yang et al. 2011a).
496 We also investigated whether inbreeding affects personality by testing for correlation of
497 personality traits with runs of homozygosity, which are homozygous stretches of DNA that indicate
498 distant as well as close inbreeding. We found that inbreeding correlated significantly and positively
499 with Harm Avoidance, and negatively with both Reward Dependence and Novelty Seeking, but did
500 not correlate significantly with Persistence. The absolute values of the correlations were very small,
501 but this was to be expected given the modest effects of inbreeding depression reported in the literature
502 (Roff 1997; Charlesworth and Willis 2009) and the small variation in inbreeding in outbred
503 populations (Keller et al. 2011b). An effect of inbreeding on personality traits is consistent with
504 mutation-selection balance, but is not expected under selective neutrality, balancing selection via
505 environmental heterogeneity, or pleiotropic balancing selection (Charlesworth and Charlesworth
506 1987; Turelli and Barton 2004; Roff 2005). Consistent with inbreeding pushing traits towards their
507 low fitness ends, high Novelty Seeking, high Reward Dependence, and low Harm Avoidance are all
508 associated with the socially desirable (and supposed high-fitness) end of the so-called 'general factor
509 of personality' (Rushton and Irwing 2008; Rushton et al. 2009). The lack of a significant inbreeding
510 effect on Persistence might suggest that the population mean is close to the optimum (i.e. under
511 stabilising rather than directional selection) or might be due to lack of power to detect a true
512 inbreeding effect. If our inbreeding results reflect the influence of a load of pleiotropic deleterious
513 mutations, the three personality traits should be genetically intercorrelated in line with the direction of
514 the inbreeding effects – i.e. high Harm Avoidance with low Novelty Seeking and low Reward
515 Dependence. This is indeed what has been found in previous research (Gillespie et al. 2003).
516 Our findings have important implications for how personality is positioned in an evolutionary
517 framework. Results consistent with most of the genetic variation being due to rare variants and/or
518 nonadditive genetic effects suggest that personality traits have been under selection, and results
519 consistent with inbreeding depression suggest that three of the personality traits have been under

directional selection. Directional selection does not necessarily mean that extremely high or low values are favoured, just that the mean trait level in the population deviates from the optimum. Several possibilities exist for why the means of personality traits are not at the evolutionarily optimal levels. One is that personality traits are condition-dependent; for example, Lukaszewski and Roney (2011) have argued that high extraversion (closely related to Novelty Seeking) is usually displayed by physically attractive individuals (through facultative calibration) because it is a more beneficial strategy for them than for less extraverted individuals. Under this model, the heritable variation in extraversion is a side effect of the heritable variation in physical attractiveness (which is presumably condition-dependent and under mutation-selection balance). Similarly, low (optimal) levels of Harm Avoidance might only be adaptive in high-fitness individuals that are able to successfully avoid the dangers associated with risk taking behaviours.

There are several limitations to the current research that warrant caution regarding the conclusions we have drawn. First, the Cloninger scales may not represent a comprehensive assessment of personality, and it remains to be seen to what extent the results generalise to other personality traits, such as the Big Five. However, results from an international consortium show that SNP-based heritability estimates for two of the Big Five traits, Extraversion and Neuroticism, very closely accord with our results for the related traits Novelty Seeking and Harm Avoidance, respectively (Vinkhuyzen et al. in press). Second, we had to rely on previous twin-sibling studies for the heritability of Cloninger's scales due to all genetic variants. Twin-sibling studies provide fairly robust estimates of broad-sense heritability (i.e. H^2 in Table 3), but they do not allow separate unbiased estimates of additive and nonadditive genetic variation (Keller and Coventry 2005; Keller et al. 2010). Extended twin-family designs (which can make good estimates of these parameters) are only available for Neuroticism (closely related to Cloninger's Harm Avoidance), for which a very large (N=45,850) study including parents, aunts/uncles, and spouses estimated additive and nonadditive genetic influences in females at 34% and 13% respectively, and in males at 31% and 10%.

While it is unfortunate not to have good estimates of separate additive and nonadditive genetic variance components for Cloninger's scales, it should be remembered that a greater proportion

548 of a trait's genetic variation is expected to be nonadditive if it is maintained by mutation-selection
549 balance than if it is maintained by selective neutrality, pleiotropic balancing selection, or
550 environmental heterogeneity. As such, our conclusion that genetic variation in personality traits is best
551 explained by mutation-selection balance would hold regardless of the extent to which the gap between
552 $h^2_{(SNPs)}$ and H^2 is due to rare variants or genetic nonadditivity.

553 A third limitation is that we may have overestimated the variance accounted for by common
554 genetic variants. One reason is that population stratification can potentially inflate the variance
555 accounted for by SNPs even after controlling for population structure (Browning and Browning
556 2011), though probably very little (Goddard et al. 2011). Another reason is that common genotyped
557 SNPs that trace distant relatedness will to some extent reflect the relatedness at old causal mutations
558 that have been co-inherited with the SNPs, so the effects of these rare variants may be partially
559 captured. As such, our estimates are best considered as an upper limit of the additive variance that can
560 be due to common genetic variants, but this only strengthens our conclusions regarding the small role
561 they play in personality traits and the evolutionary implications of this.

562 A fourth limitation is that we cannot rule out the possibility that certain personality traits
563 cause greater inbreeding, rather than (or as well as) the other way around. For example, those with
564 greater Novelty Seeking may tend to choose a mate further from their birthplace (and, possibly, less
565 related to themselves) - resulting offspring may inherit greater Novelty Seeking and also have a lower
566 inbreeding coefficient.

567 Notwithstanding these limitations, this study provides empirical findings that bolster our
568 understanding of the evolutionary genetics of personality, suggesting that genetic variation is
569 maintained primarily by a balance between an influx of deleterious mutations and selection against
570 them. While this study focuses on human personality, the results may help guide theory and empirical
571 research in other species and other traits; indeed, the methodology used here can in principle be used
572 to investigate maintenance of variation in any trait in any species, providing sufficiently large samples
573 can be obtained. Furthermore, methodological developments in the near future (e.g. low-cost genome
574 sequencing) may allow more direct assessment of the effect of mutation load on personality and other
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Table 1. Predictions from evolutionary models for maintenance of genetic variation in complex traits.

Model	No. of causal variants [a]	% V_A due to common variants (MAF>.01)	V_{NA}/V_G [b]	$h^2_{(SNPs)}/H^2$	Inbreeding affects trait	Useful references
Selective neutrality	No prediction	98%	Low	High	No	(Eyre-Walker 2010)
Mutation-selection balance	Many	<< 98%	Higher	Low	Possibly [c]	(Eyre-Walker 2010)
Balancing selection						
pleiotropic balancing selection	No prediction	> 98%	Low	High	No	(Turelli and Barton 2004)
environmental heterogeneity	No prediction	> 98%	Low	High	No	(Turelli and Barton 2004)
negative frequency-dependent selection	Few	> 98%	Low	High	No	(Mani et al. 1990; Kopp and Hermisson 2006)
sex-dependent selection	Up to two	> 98%	Low	High	No	(Turelli and Barton 2004)
overdominance for fitness, resulting from antagonistic pleiotropy [d]	Few	> 98%	Higher	Low	Possibly [e]	(Curtsinger et al. 1994; Hedrick 1999; Burger 2000)

V_A additive genetic variation; V_{NA}: nonadditive genetic variation; MAF: minor allele frequency

[a] Previous research strongly suggests a highly polygenic basis to personality (Verweij et al. 2010)

[b] V_{NA}/V_G is expected to be fairly low under neutrality (Hill et al. 2008), though no specific level can be predicted; 'higher' predicted levels are in comparison this baseline

[c] Yes under directional selection, no under stabilising selection

[d] These predictions appear to approximately generalise to overdominance in general (Burger 2000)

[e] Inbreeding is expected to decrease fitness, but does not necessarily affect the trait in question

Table 2. Overview of available data.

Sample	Country	N	N males	N females	Age (M±SD)	Year collected	Questionnaire	Genotyping platform
YFS	Finland	1,382	634	748	32.5 (±5.1)	2001	TCI, 240 rating scale items	Illumina 670K Custom BeadChip
HBCS	Finland	1,441	578	863	63.4 (±2.9)	2004	TPQ, 98 dichotomous items	Illumina 610K Quad Chip
NFBC	Finland	4,506	2,013	2,493	31†	1997	TPQ, 107 dichotomous items	Illumina 370duo Chip
QIMR	Australia	5,530	2,006	3,524	36.7 (±12.3)	1988-1990	TPQ, 54 dichotomous items	Illumina 317K Illumina HumanCNV370-Quadv3 Illumina Human610-Quad
Total		**12,859**	**5,231**	**7,628**				

†all participants in the NFBC sample were 31 years old

Table 3. Estimation of variance accounted for in each personality scale from the genetic relationship matrix based on all autosomal SNPs.

Personality Scale	H^2	N	h^2_{SNPs} (SE)	p-value	h^2_{SNPs}/H^2
Harm Avoidance	.36	8613	.066 (.037)	.04	.18
Novelty Seeking	.34	8620	.099 (.036)	.003	.28
Reward Dependence	.30	8606	.042 (.036)	.12	.14
Persistence	.28	8618	.081 (.037)	.01	.29

Includes SNPs genotyped for at least 95% of the sample, excludes one of each pair of individuals with an estimated genetic relatedness > .05.
H^2 = heritability estimate of the trait from AE models of twin-siblings (from Keller et al. (2005)) – p <.001 for each trait.
N refers to the size of sample that h^2_{SNPs} is estimated from
h^2_{SNPs} = proportion of variance accounted for by all autosomal SNPs; SE=standard error of estimate.
p-values denote whether the variance accounted for by SNPs is significantly different from zero.

Table 4. Correlations of close and distant inbreeding (runs of homozygosity >5Mb and <5Mb) with Cloninger's Personality scales, along with corresponding regression betas (personality standardised and inbreeding coefficient as a proportion between 0 and 1).

Personality scale	N	Runs of homozygosity: Proportion of genome in ROH		Close inbreeding: proportion of genome in ROH > 5Mb		Distant inbreeding: proportion of genome in ROH < 5Mb	
		r	Beta (SE)	r	Beta (SE)	r	Beta (SE)
Harm Avoidance	10,197	.058**	7.65 (1.31)	.047**	9.11 (1.91)	.051**	13.12 (2.57)
Novelty Seeking	10,202	-.052**	-6.81 (1.30)	-.042**	-8.08 (1.90)	-.045**	-11.75 (2.56)
Reward Dependence	10,185	-.038**	-4.92 (1.30)	-.030**	-5.83 (1.90)	-.033**	-8.52 (2.55)
Persistence	10,202	-.006	-0.76 (1.30)	-.005	-1.02 (1.90)	-.004	-1.10 (2.56)

** p<.01