Genetic Differences between Five European Populations

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Genetic Differences between Five European Populations

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Key Words
Population • Gene • Stratification • Pigmentation • Immunity

Abstract
Aims: We sought to examine the magnitude of the differences in SNP allele frequencies between five European populations (Scotland, Ireland, Sweden, Bulgaria and Portugal) and to identify the loci with the greatest differences.

Methods: We performed a population-based genome-wide association analysis with Affymetrix 6.0 and 5.0 arrays. We used a 4 degrees of freedom χ² test to determine the magnitude of stratification for each SNP. We then examined the genes within the most stratified regions, using a highly conservative cutoff of p < 10⁻⁴⁵.

Results: We found 40,593 SNPs which are genome-wide significantly (p ≤ 10⁻⁸) stratified between these populations. The largest differences clustered in gene ontology categories for immunity and pigmentation. Some of the top loci span genes that have already been reported as highly stratified: genes for hair color and pigmentation (HERC2, EXOC2, IRF4), the LCT gene, genes involved in NAD metabolism, and in immunity (HLA and the Toll-like receptor genes TLR10, TLR1, TLR6). However, several genes have not previously been reported as stratified within European populations, indicating that they might also have provided selective advantages: several zinc finger genes, two genes involved in glutathione synthesis or function, and most intriguingly, FOXP2, implicated in speech development.

Conclusion: Our analysis demonstrates that many SNPs show genome-wide significant differences within European popu-
ulations and the magnitude of the differences correlate with the geographical distance. At least some of these differences are due to the selective advantage of polymorphisms within these loci.

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Introduction

Traditionally, genetic differences between populations have been identified with genetic markers on the Y-chromosome, mitochondrial DNA, alleles that have reached fixation in certain populations, and classical genetic markers such as blood groups. Recent studies have provided genome-wide information on differences between populations and have shown that despite close genetic similarities among white Europeans, some subtle but informative differences exist. When using genome-wide arrays, the cumulative effects of these differences in allele frequencies allow the place of birth of individual subjects to be predicted quite well [1–4], to the point that 90% of individuals can be placed to within 700 km of their reported origin by using SNP genotypes [4, 5], or within single countries, e.g. Finland [3], Iceland [4] and the UK [6]. Therefore, the use of these arrays has opened up possibilities to explore the population history of very closely related ethnic groups. The loci showing the highest stratification contain some very likely candidate genes that can account for these differences via effects on selection [6]. The Wellcome Trust Case Control Consortium (WTCCC) was the first study to report a set of highly differentiated SNPs clustered in several genomic regions, which had different allele frequencies even within the boundaries of a single European country, the UK. The strongest signals came from loci harboring genes involved in immunity, lactose metabolism, and the gene encoding for NAD synthetase 1, which might have a role in involvement in immunity, lactose metabolism, and the gene encoding for NAD synthetase 1, which might have a role in...
arrays. We also excluded individuals that were shown to be related, and those who were population outliers (more information on the filtering criteria are presented in [8, 9]). The exclusion of population outliers effectively excluded subjects that might have been migrants to that country, or offspring of parents from different countries.

Statistical Analysis

We compared each population against each other pair-wise, using the Armitage trend test with 1 degree of freedom (d.f.). The different sample sizes result in more significant p values between the larger samples, even when the distribution of genotypes is the same. In order to account for this, we scaled down the genotype counts, making each population the same size, so that all differences were directly comparable. In order to achieve this, we multiplied the observed genotype counts by the ratio between the smallest sample size and the current sample size $n_k = N_s/N_s$, where $k$ indicates 11, 12 or 22 genotypes, $n_k$ and $n_s$ are the observed and adjusted counts of genotype $k$; $N_s$ is the current sample size and $N_s = 563$ is the sample size of the smallest population (Portugal). This scaling-down produces more conservative estimates of the differences.

In order to find the SNPs that are most highly differentiated between all five populations, we applied a 4 d.f. $\chi^2$ test for a 5 × 2 contingency table (5 – number of populations, 2 – number of alleles). The populations were not scaled by size for this analysis.

Another way to examine the patterns of genetic variation between populations is through the Wright’s fixation index $F_{ST}$ [11]. $F_{ST}$ was estimated according to Wright’s approximate formula $F_{ST} = (H_T - H_S)/H_T$, where $H_T$ represents expected heterozygosity per locus of the total population and $H_S$ is calculated as weighted average over populations of expected heterozygosity of each subpopulation (weighted by sample size). In the current study, they ranged from 0 to 0.061. However, $F_{ST}$ values correlated almost perfectly ($r = 0.999$) with the negative log$_{10}$ of the p values from the above $\chi^2$ test, indicating that the two tests provide the same measures for the genetic variation. This effect has been observed before [12]. For the rest of the paper we use the p value results, as these are more intuitive for readers who are not population geneticists. They are also easier to use in comparisons of the different analyses that we performed and give a more familiar measure for population stratification magnitude in GWA studies ($F_{ST}$ results for the best SNP within every gene are given in online suppl. table 1).

Having processed the data and identified the SNPs that displayed the largest differences between populations, we determined the genes to which these SNPs mapped. As these genes were found to cluster in discrete loci, we selected only the most significant loci in the genome in order to limit our discussion to the top hits, and used an arbitrary cutoff of $p < 10^{-45}$ for a SNP association with ethnic origin derived with the $\chi^2$ test. We defined the region involved, again arbitrarily, as flanked by SNPs that were stratified at $p < 10^{-30}$, with a gap of >500 kb distance that contains no such SNPs, as defining the end of the region on either side.

We also assessed population structure within the data using principal components analysis as implemented in EIGENSTRAT [13]. Eigenvectors were calculated based on a linkage disequilibrium (LD)-pruned subset of 101,532 SNPs with $r^2 \leq 0.5$. LD pruning was performed using PLINK version 1.06 [14]. We show the plot of the first two principal components extracted from EIGENSTRAT.

Gene Ontology Analysis

Standard methods for testing of enrichment of gene ontology (GO) categories on a gene list could not be used, since these rely on there being a single measurement per gene, whereas GWA study data consists of different numbers of SNPs per gene, each with a measure of significance of differentiation. These are not independent, due to LD. We therefore used the ALIGATOR program [15] to test enrichment of GO categories on lists of significantly-differentiated SNPs. SNPs were assigned to genes if their physical position (NCBI SNP build 129) lay between the start and end points of the gene (as defined by NCBI sequence build 36.3). A list of significant genes was defined as those genes that contain a SNP that is stratified at a conservative $p < 10^{-30}$, in order to minimize the noise. Each gene was counted only once, regardless of the number of significant SNPs it contained, thereby correcting for bias caused by multiple significant SNPs in a gene arising from LD. As described by Holmans et al. [15], 50,000 random gene lists of the same length were simulated, and the number of genes in each category present on each simulated gene list compared to that observed on the actual list of significant genes. Thus, an empirical p value for enrichment was obtained for each category. The gene lists were simulated by sampling SNPs at random, thus correcting for variable numbers of SNPs per gene. An empirical distribution for the number of significantly enriched categories was also obtained, enabling a test for an excess of such categories in the real data to be performed. All GO categories containing 3 or more genes were tested, but a minimum of 2 significant genes was required for a category to count as over-represented (to prevent small categories being over-represented on the basis of one chance hit).

Results

There are ten pair-wise comparisons of the five populations. Given the stratification between populations, not unexpectedly, there was a substantial excess of SNPs at a 5% significance level for the number of SNPs tested and the 10 comparisons performed (table 1). We opted to use a conservative Bonferroni correction (although many of the tests are not independent) and multiplied each of the p values by 363,411 · 10 (number of SNPs by number of comparisons). Despite this, there were still large numbers of genome-wide significant results in all comparisons. We present both the original results, to demonstrate the true number of significant results in the study, and the rescaled results (to the sample size of the smallest population, see Material and Methods), in order to provide a measure for the relative differences between the populations. The rescaled results are of course more conservative.

As expected, the number of significant differences correlated with the distance between the countries, but...
even the neighboring Scottish and Irish samples had 14 SNPs with alleles that differed in frequency at a genome-wide significant level after Bonferroni correction.

Figure 1 shows the negative log10 of the p values produced by the χ² test for the five populations (y-axis) according to their genomic positions (x-axis). Chromosomes are indicated in shades of grey. The black horizontal line indicates the genome-wide significance level (p = 10⁻⁸). The corresponding figures for each pair-wise comparison between all populations are presented in online Table 1.

### Table 1. Pair-wise comparisons between five European populations

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Original results</th>
<th>Bonferroni corrected</th>
<th>Rescaled results</th>
<th>Bonferroni corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SNP with p ≤ 0.05, n</td>
<td>min. p value</td>
<td>SNP with p ≤ 0.05, n</td>
<td>min. p value</td>
</tr>
<tr>
<td>Bulgaria–Ireland</td>
<td>184,367</td>
<td>3.3 × 10⁻⁶⁵</td>
<td>21,603</td>
<td>1.2 × 10⁻⁵⁸</td>
</tr>
<tr>
<td>Bulgaria–Sweden</td>
<td>165,431</td>
<td>3.1 × 10⁻⁴⁰</td>
<td>11,091</td>
<td>1.1 × 10⁻³³</td>
</tr>
<tr>
<td>Bulgaria–Scotland</td>
<td>149,935</td>
<td>1.2 × 10⁻⁵⁰</td>
<td>7,114</td>
<td>4.4 × 10⁻⁴⁴</td>
</tr>
<tr>
<td>Scotland–Ireland</td>
<td>37,024</td>
<td>3.0 × 10⁻¹³</td>
<td>14</td>
<td>1.1 × 10⁻⁶</td>
</tr>
<tr>
<td>Scotland–Sweden</td>
<td>89,071</td>
<td>7.9 × 10⁻²²</td>
<td>306</td>
<td>2.9 × 10⁻¹⁵</td>
</tr>
<tr>
<td>Ireland–Sweden</td>
<td>125,217</td>
<td>5.2 × 10⁻¹⁴</td>
<td>2,309</td>
<td>1.9 × 10⁻²⁷</td>
</tr>
<tr>
<td>Bulgaria–Portugal</td>
<td>126,493</td>
<td>2.1 × 10⁻²⁸</td>
<td>2,796</td>
<td>7.5 × 10⁻²²</td>
</tr>
<tr>
<td>Scotland–Portugal</td>
<td>128,232</td>
<td>3.2 × 10⁻³³</td>
<td>2,637</td>
<td>1.2 × 10⁻²⁶</td>
</tr>
<tr>
<td>Ireland–Portugal</td>
<td>154,435</td>
<td>5.7 × 10⁻⁵⁰</td>
<td>8,446</td>
<td>2.1 × 10⁻⁴³</td>
</tr>
<tr>
<td>Sweden–Portugal</td>
<td>159,353</td>
<td>9.9 × 10⁻³³</td>
<td>8,188</td>
<td>3.6 × 10⁻²⁶</td>
</tr>
</tbody>
</table>
supplementary figure 1. They give a direct comparison of the population differences, which are greater between more distant populations. This conclusion is confirmed by the Principal Component analysis (online suppl. fig. 2a) which placed the two-dimensional positions of the five populations quite accurately over the map of Europe (online suppl. fig. 2b).

We then identified the list of genome-wide significant SNPs between all five populations using the 4 d.f. \( H^2 \) test, i.e. we tested for differences in the allele counts between all five populations. There were 40,593 SNPs that were genome-wide significant with \( p \) values \( \leq 10^{-8} \).

GO analysis on the top-ranked SNPs (with \( p \) values \( < 10^{-30} \), which lay in a total of 100 genes) using ALIGATOR revealed a number of significantly over-represented categories; 43 categories were over-represented at \( p < 0.01 \) (not shown), and 18 at \( p < 0.001 \) (online suppl. table 2). Both numbers are significantly greater than the number of categories expected (13.23 and 1.98 at \( p < 0.01 \) and \( p < 0.001 \), respectively) generated from random sets of SNPs.

<table>
<thead>
<tr>
<th>Region flanked by SNPs with ( p &lt; 10^{-30} )</th>
<th>Relevant gene function</th>
<th>Genes within the regions</th>
<th>Corresponding region in studies [3] or [6]</th>
<th>Region size kb</th>
<th>SNPs with ( p &lt; 10^{-30} )</th>
<th>Most significant SNP and allele frequencies (Bg/Ir/Sc/Sw/Port)</th>
<th>Significance –( \log_{10}(p) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chr1: 8.27–8.66</td>
<td>Arginine-glutamic acid dipeptide repeats</td>
<td>RERE</td>
<td></td>
<td>390</td>
<td>8</td>
<td>rs12136676 0.499/0.321/0.316/0.297/0.485</td>
<td>56.31</td>
</tr>
<tr>
<td>Chr2: 134.63–137.34</td>
<td>Immunity (CXCR4), NAD (ACMSD), lactase (LCT)</td>
<td>MGAT5, TMTM163, ACMSD, CCNT2, YSK4, RAB3GAP, UBXN4, LCT, McM6, DARS, CXCR4</td>
<td>134.75–137.46</td>
<td>2,710</td>
<td>109</td>
<td>rs7582192 0.082/0.286/0.268/0.252/0.141</td>
<td>76.79</td>
</tr>
<tr>
<td>Chr4: 38.38–38.58</td>
<td>Immunity</td>
<td>TLR10, TLR 1, TLR 6 (Toll-like receptors)</td>
<td>38.53–38.74*</td>
<td>200</td>
<td>20</td>
<td>rs6835514 0.420/0.164/0.134/0.286/0.363</td>
<td>85.14</td>
</tr>
<tr>
<td>Chr6: 0.33–0.49</td>
<td>Skin, hair, eye color</td>
<td>IRF4, EXOC2</td>
<td>0.33–0.49</td>
<td>160</td>
<td>9</td>
<td>rs920655 0.404/0.207/0.318/0.403/0.398</td>
<td>55.43</td>
</tr>
<tr>
<td>Chr6: 28.5–28.64</td>
<td>Zink fingers; glutathione peroxidase family</td>
<td>ZSCAN3, ZSCAN12, ZSCAN23, GPX5, GPX6</td>
<td>210</td>
<td>3</td>
<td></td>
<td>rs13215804 0.179/0.401/0.392/0.251/0.316</td>
<td>64.30</td>
</tr>
<tr>
<td>Chr6: 29.41–35.28</td>
<td>Immunity</td>
<td>HLA region</td>
<td>31.1–31.6*</td>
<td>5,870</td>
<td>114</td>
<td>rs486416 0.169/0.450/0.392/0.367/0.181</td>
<td>86.61</td>
</tr>
<tr>
<td>Chr6: 37.86–38.24</td>
<td>Zink finger, protein-protein interactions</td>
<td>ZFAND3, BTBD9</td>
<td>380</td>
<td>10</td>
<td></td>
<td>rs2281266 0.255/0.433/0.438/0.433/0.289</td>
<td>51.40</td>
</tr>
<tr>
<td>Chr7: 113.70–114.14</td>
<td>Speech</td>
<td>FOXP2</td>
<td>440</td>
<td>2</td>
<td></td>
<td>rs1378769 0.104/0.021/0.028/0.018/0.069</td>
<td>46.50</td>
</tr>
<tr>
<td>Chr11: 70.81–70.90</td>
<td>NAD</td>
<td>DHCR7, NADSYN1</td>
<td>70.78–70.93</td>
<td>90</td>
<td>10</td>
<td>rs2276360 0.353/0.160/0.190/0.338/0.372</td>
<td>71.22</td>
</tr>
<tr>
<td>Chr15: 25.69–26.20</td>
<td>Skin, hair, eye color</td>
<td>OCA2, HERC2</td>
<td>26.20</td>
<td>510</td>
<td>12</td>
<td>rs8041209 0.139/0.035/0.042/0.015/0.160</td>
<td>70.51</td>
</tr>
<tr>
<td>Chr20: 33.00–33.31</td>
<td>Glutathione synthetase; protection of cells from oxidative damage</td>
<td>GSS, MYH7B, TRPC4AP, EDEM2, PROC, MMP24</td>
<td>310</td>
<td>9</td>
<td></td>
<td>rs619865 0.035/0.149/0.138/0.086/0.051</td>
<td>48.08</td>
</tr>
</tbody>
</table>

The genes discussed in the present study are printed in bold. * = regions overlapping with those in [3]. Note the absence of LCT in [3].
of the same length (p = 0.024 and p = 0.005, respectively). Several of the categories are related to the MHC region onChr6, which is known to exhibit considerable long-rangeLD. It is therefore possible that the significance ofimmunity-related categories is inflated. We therefore removedall SNPs and genes in the MHC region and repeated theanalysis (results not presented). The excess number ofover-represented categories was not solely due to theMHC region, and the top-ranking GO categories re-mained largely unchanged.

Regions containing the most significantly differenti-ated SNPs (at least one SNP at \( p < 10^{-45} \) and the boundarydefined with lack of p value \( < 10^{-30} \) for an interval of >500kb, see Materials and Methods) and the genes within theseintervals are shown in table 2. The relevance of these genesand comparisons with previous findings follow in theDiscussion. Figure 2 shows the significance of SNPs andthe positions of genes in one of these intervals, which isone of the best-known stratified regions: around the \( LCT \)gene on Chr 2. Similar figures for the 11 top-ranked lociare presented in online supplementary figure 3.

**Discussion**

A trend for a NW/SE gradient for genetic differencesbetween European populations was observed over 30years ago using a limited number of genetic markers [10].The recent GWA studies provided a much more detailedpicture of these differences and have shown a remarkablyclose relationship between genetic similarity and place ofbirth in the European continent (see Introduction). Inthis paper we confirmed the genetic relationship betweenpopulations and their geographic distribution in Europe[1, 3–5]. This is demonstrated by the magnitude of differ-ences between the five populations (online suppl. fig. 1)and the results of the Principal Component analysis (on-line suppl. fig. 2).

The main aim of this paper was, however, to identifythe most highly stratified genes and the mechanisms thatmight have contributed to these differences. The large sample size and availability of populations from four cor-ners of Europe allowed us to obtain extremely high sig-nificance levels to confidently identify the top hits. Someof the genes within these regions have already been iden-tified in previous research (e.g. [3, 6], indicated in a sepa-rate column in table 2) and have plausible biological ef-fects on selection, while others have not been within thetop hits in these studies, and for some genes we are notaware of any obvious effects on selection within Europe.

Most differences are likely to have been caused by ancientdifferences between formerly isolated groups during thepopulation of Europe [10]. The largest differences aremore likely to have been caused by selective forces operat-ing differently in different parts of the continent, e.g. byepidemics and nutritional factors. We now discuss themain groups of genes within our top 11 regions from ta-ble 2 and online supplementary figure 3.
Genes Involved in Hair, Skin, and Eye Color

Our GO categories analysis placed the genes for pigmentation at the top of our results. The region on Chr6: 0.33–0.49 Mb, including IRF4 and EXOC2, was previously associated with hair color, freckles, and skin sensitivity in a GWA study in 2,986 Icelanders and replicated in samples of 2,718 Icelanders and 1,214 Dutch people [16]. Another group [17] showed that rs12203592 within the IRF4 gene is associated with hair, skin and eye color and tanning ability. The association between IRF4 genotypes at rs12203592 with eye and particularly with hair color was confirmed in a US cohort [18]. Our best SNP in this region is rs6920655 (p = 3.7 × 10^{-50}), ~30 kb away from IRF4 and ~45 kb from EXOC2. IRF4 is expressed in melanocytes and is suggested as a sensitive marker for metastatic melanomas and benign melanocytic nevi [19], making it the more plausible candidate.

The gene for oclocutaneous albinism II (OCA2), and HERC2 on Chr15: 25.69–26.20 Mb are also implicated in skin, hair, and eye color [17] and are within our most significant regions. Association of eye and hair color with SNPs in OCA2 (rs7495174, rs6497268, rs11855019) and HERC2 (rs1667394) was found by Sulem et al. [16]. These authors argue that since the link between OCA2 and pigmentation is quite well established, the association with the HERC2 gene is due to LD. However, rs12913832 in HERC2 remained significant after adjusting for OCA2 SNPs [17]. Our best SNP in this region also lies within HERC2: rs8041209 (p = 3.1 × 10^{-71}). It is of course possible that the responsible gene is still OCA2, but there are regulatory elements for it nearby.

Some genes implicated before in the genetics of hair and skin color did not reach our 11 most significant hits, but were also strongly stratified: TYR (tyrosinase precursor) [20] at Chr11: 88.55–88.67 Mb reached a best p value of 10^{-39} and SLCA52A2 (MATP) on Chr11: 33.98–34.02 Mb, implicated in hair color formation [16, 19, 21], reached p = 3.1 × 10^{-36}.

Immunity Genes

These are well-known factors for selection in Europe, and GO categories related to immunity dominated our top GO findings together with those related to pigmentation (online suppl. table 2). Among our most significant regions (table 2) is the HLA region on Chr6, and the cluster of Toll-like receptors TLR10, TLR1, TLR6 on Chr4: 38.38–38.59 Mb. Toll-like receptors play a role in pathogen recognition and activation of innate immunity in, for example, defense against tuberculosis. Both regions were stratified in the WTCCC study [6]. HLA was the top region identified in our GWA study paper as conferring risk for schizophrenia [9]. That result is, however, not caused by population stratification as it was derived by the Cochran-Mantel-Haenszel test, which accounts for population differences, and we did not reach similar results for the other top hits in the current study, such as TLR10 or LCT.

Genes Involved in NAD Metabolism

This mechanism was proposed in the WTCCC study [6] which found the NAD synthetase 1 gene (NADSYN1) to be stratified. A role in prevention of pellagra was postulated. Pellagra is caused by a lack of niacin (Vitamin B3) and can result from nutritional deficit of niacin or tryptophan. It is possible that genetic variation in the genes involved in its metabolism can contribute to the development of the illness among populations with limited amounts of niacin or tryptophan in their diet. We also find this gene among our top hits, with the associated region overlapping that in the WTCCC study, thus strengthening the initial observation. Interestingly, another gene (ACMSD) that plays a role in NAD metabolism is also within our top regions: close to the lactase gene (LCT). ACMSD is an intermediate in the de novo synthesis pathway of NAD from tryptophan. It is possible that the presence of ACMSD within this locus has increased the strength of the signal around LCT. The effect from NAD metabolism is further supported by the GO analysis (but only if we repeated the analysis with a relaxed cutoff of p < 10^{-20}, data not presented), as the category ‘oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor’ reached 12th place on the list, with 8 genes in this category reaching that cut-off.

Lactase Gene

Lactase gene (LCT) is one of the best-known genes that have provided selective advantage around the world, because of the ability of farming communities to consume the milk of domesticated animals [22, 23]. It is also among our top hits.

Overlap with Previous Studies

As shown in table 2, five of the 11 top loci coincide with those identified in the WTCCC study [6] as stratified within the UK. The boundaries of the loci also overlap closely, indicating that the same factors have operated within the UK and within Europe. Three of the loci also coincide with those identified by McEvoy et al. [3]. That work was conducted on populations of Northern Euro-
Most stratified. Most intriguingly, we also find SNPs lig-

2 Lao O, Lu TT, Nothnagel M, Junge O, Frei-

5 Novembre J, Johnson T, Bryc K, Kutalik Z,

are compared

4 Price AL, Helgason A, Palsson S, Stefansson

Bauchet et al. [7] suggested a list of 20 best Euro-

pean ancestry informative markers, which are not among

our top hits. One possible explanation is the small sample

size in that study (a total of 297 individuals).

New Findings

There were several stratified loci that included genes

for which there is no obvious mechanism for a role in se-

lection in these populations. Of those, the zinc finger

genes ZSCAN3, ZSCAN12 and ZSCAN23 on Chr6 were

most stratified. Most intriguingly, we also find SNPs ly-
ing within 20 kb from FOXP2 among our top hits. This
gene has been implicated in the development of language

in humans [24]. There is evidence that it has been subject
to positive selection when human and primate genomes are

compared [21]; however, the two human-specific ami-

no-acid changes are likely to have occurred more than

300,000 years ago [25]. It should be pointed out that the

signal in FOXP2 just reached our inclusion criteria and
did not involve many SNPs. The true relevance of this

finding will therefore have to be tested in other studies,

preferably including more populations. Another finding

involves three genes of the glutathione peroxidase sys-
tem: glutathione peroxidase 5 and 6 (GPX5, GPX6) in the

Chr6: 28.43–28.64 Mb locus, and glutathione synthetase

(GSS) within the Chr20: 33.00–33.31 Mb locus. Glutathi-
one is part of the hydrogen peroxide scavenging system
and is important for the protection of cells from oxidative
damage by free radicals. The effect may be coming in-
stead from other genes in these loci, e.g. the zinc finger
genes ZSCAN3 and ZSCAN23 on Chr6.

Our paper focuses on the top 11 loci and suggests plau-
sible mechanisms for most of them. However, the total

number of genome-wide significant SNPs is >50,000 and

the top hits clustered in several GO categories. We cannot

judge which ones are due to the effects of selection or to

other mechanisms. We present a full list of genes with the

best and median p values for SNPs within them (sepa-

rately for the full sample and for controls only), so that

others can make use of this information in future studies

(online suppl. table 1).

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