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'Racial' differences in genetic effects for complex diseases

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'Racial' differences are frequently debated in clinical, epidemiological and molecular research and beyond[1,2]. In particular, there is considerable controversy regarding the existence and importance of 'racial' differences in genetic effects for complex diseases[3–6] influenced by a large number of genes[7]. An important question is whether ancestry influences the impact of each gene variant on the disease risk. Here, we addressed this question by examining the genetic effects for 43 validated gene-disease associations across 697 study populations of various descents. The frequencies of the genetic marker of interest in the control populations often (58%) showed large heterogeneity (statistical variability) between 'races'. Conversely, we saw large heterogeneity in the genetic effects (odds ratios) between 'races' in only 14% of cases. Genetic markers for proposed gene-disease associations vary in frequency across populations, but their biological impact on the risk for common diseases may usually be consistent across traditional 'racial' boundaries.

'Race' is difficult to define[8–11] and inconsistently reported in the literature[12]. Thus we focused on major, distinct 'racial' groups that are unlikely to be influenced by reporting and in which most gene-disease association research has been done so far. We compared frequencies of genetic markers of interest and their genetic effects across European, East Asian, African and other populations. We screened 134 meta-analyses of genetic association studies for various diseases (**Supplementary Note** and **Supplementary Table 1** online) compiled by updating a previous database[13,14]. Of those, 12 were covered by another more comprehensive meta-analysis, 36 had no sufficient data from at least two 'racial' groups, and in 3, <80% of the available studies could be classified by 'race'. Of the remaining 83 studies, 40 had no statistically significant results either overall or for any of the included 'racial' groups. We analyzed the remaining 43 gene-disease associations for which either the overall meta-analysis showed statistically significant results ($P < 0.05$; $n = 32$) or there were statistically significant results for at least one 'racial' group without the overall meta-analysis reaching formal significance ($n = 11$). We included the latter group, even though their validity is somewhat less certain, to try to avoid biasing the results towards our null hypothesis of no 'racial' differences in genetic effects. If anything, these gene-disease associations may show larger differences in genetic effects between 'racial' groups than truly exist.

The 43 eligible meta-analyses (**Table 1**) included 'race'-specific data on 697 gene-disease association studies (European, $n = 479$; East Asian, $n = 139$; African, $n = 47$; other, $n = 32$) with total sample size of 297,411. All meta-analyses included data on individuals of European descent, and 34, 24 and 18 also had data on subjects of East Asian, African and other descent (Jewish, $n = 12$; Turkish, $n = 7$; Arabic, $n = 3$; Hindu, $n = 8$; Native Indian, $n = 1$; Hawaiian, $n = 1$), respectively.

Heterogeneity between studies was almost ubiquitous for the frequencies of the genetic markers of interest in the control populations and relatively common for the magnitude of the genetic effects (odds ratios) when all studies were considered (**Table 2**). Thirty-six (84%; 95% binomial confidence interval (c.i.) = 69–93%) meta-analyses had statistically significant heterogeneity (based on χ^2 or Fisher's exact test, as appropriate) in the frequencies of the genetic markers of interest in the control populations across all studies. Seven (16%) meta-analyses had statistically significant between-study heterogeneity across all studies, but not within any of the descent groups. Significant between-study heterogeneity in one descent group, but not across all studies, was never seen (**Table 2**). Twenty-two (51%; 95% c.i. = 35–67%) meta-analyses had statistically significant heterogeneity in the odds ratios across all studies based on the χ^2-based Q statistic. Only two meta-analyses had statistically significant between-study heterogeneity across all studies, but not within any descent groups; another two meta-analyses had statistically significant between-study heterogeneity in some descent groups but not across all studies (**Table 2**).

'Racial' group–specific frequencies of the genetic markers of interest in control populations are shown in **Figure 1** (ref. 15). The between-group variance was larger than the within-group variance in 24 meta-analyses, and the opposite was true in 19 cases (**Supplementary Table 2** online). In pairwise comparisons (**Supplementary Table 3** online), we observed statistically significant differences in 20 of 34 (59%) comparisons of European versus East Asian descent, 12 of 19 (63%) comparisons of European versus African descent and 10 of 21 (48%) comparisons of East Asian versus African descent. Heterogeneity may be influenced by the number of available studies in each assessment. Therefore, we also evaluated the I^2 statistic,

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which is not affected by the number of available studies and provides an estimate of how much of the heterogeneity is unlikely to be due to chance[16]. There was large heterogeneity (defined as $I^2 \geq 75\%$) between the various groups in 25 of 43 (58%; 95% c.i. = 42–73%) meta-analyses (**Fig. 1**).

Although these selected genetic markers showed prominent frequency variation between different populations, the genetic effects were usually similar between 'racial' groups. Group-specific odds ratios are shown in **Figure 2**. For some meta-analyses with relatively limited data, modest differences between 'race'-specific

Table 1 Evaluated gene-disease associations

ID	Disease or outcome	Gene (polymorphism); genetic contrast	Available sample size (available studies)					
			All analyzed	European	East Asian	African	Other	NS
1	Lung cancer	*CYP2D6* (deficient oxidation); poor vs. others	4,091 (14)	4,003 (13)	0	88 (1)	0	1,071 (1)
2	Lung cancer	*GSTM1* (gene deletion); –/– vs. others	9,620 (22)	7,485 (18)	1,486 (2)	649 (2)	0	104 (1)
3*	Lung cancer	*CYP1A1* (4889A→G); GG vs. AA+AG	2,392 (7)	1,479 (4)	155 (1)	658 (2)	0	0
4*	Lung cancer	*CYP1A1* (*MspI*); +/+ vs. others	4,263 (15)	3,338 (10)	172 (1)	753 (4)	0	0
5	Bladder cancer	*NAT2* (slow acetylation alleles); slow/slow vs. others	5,836 (21)	5,174 (16)	635 (4)	27 (1)	0	0
6	ICVD	*APOE* (epsilon 2/3/4); allele 4 vs. others	3,632 (9)	2,920 (7)	712 (2)	0	0	0
7	Nonsyndromic cleft lip	*TGFA* (*TaqI*); allele 2 vs. allele 1	5,836 (14)	4,654 (8)	906 (3)	276 (3)	0	0
8	Ischemic stroke	*ACE* (insertion/deletion); DD vs. DI + II	2,160 (6)	1,918 (5)	242 (1)	0	0	0
9	Diabetic nephropathy	*ACE* (insertion/deletion); II vs. DI + DD	5,289 (19)	4,527 (14)	762 (5)	0	0	104 (1)
10	NTD	*MTHFR* (677C→T); TT vs. CT + CC	3,730 (12)	3,588 (11)	0	0	142 (1 T)	150 (1)
11	NTD, mothers	*MTHFR* (677C→T) mother; TT vs. CT + CC	1,955 (8)	1,822 (7)	0	0	133 (1 T)	0
12	IHD	*APOE* (epsilon 2/3/4); 4/3+4/2+4/4 vs. 3/3	8,962 (9)	7,875 (7)	1,087 (2)	0	0	0
13	CAD	*ITGB3* (L33P); A2A2 + A1A2 vs. A1A1	17,029 (31)	16,500 (29)	0	259 (2)	0	268 (1)
14	Bladder cancer	*GSTM1* (gene deletion); –/– vs. others	4,723 (18)	3,701 (10)	660 (3)	127 (2)	235 (3 Ar)	0
15	SLE nephritis	*FCGR2A* (R131H); RR vs. RH + HH	2,801 (21)	1,641 (11)	709 (6)	451 (4)	0	0
16	Alzheimer disease	*LRP1* exon3 (766C→T); CC vs. CT + TT	4,097 (8)	3,751 (7)	346 (1)	0	0	0
17	SLE nephritis	*FCGR3A* (F158V); F allele vs. V allele	4,830 (16)	2,512 (7)	1,500 (5)	818 (4)	0	0
18	Parkinson disease	*UCHL1* (S18Y); Y/Y + Y/S vs. S/S	4,194 (11)	2,894 (7)	1,300 (4)	0	0	0
19	APS	*FCGR2A* (R131H); RR vs. RH + HH	2,134 (10)	1,371 (6)	614 (3)	149 (1)	0	0
20*	Prostate cancer	*CYP17A1* (promoter T→C); A2A2 + A1A2 vs. A1A1	5,159 (12)	4,026 (7)	886 (2)	247 (3)	0	0
21*	Prostate cancer	*SRD5A2* (A49T); AT + TT vs. AA	3,731 (8)	2,567 (5)	687 (2)	477 (1)	0	0
22	Pre-eclampsia	*F5* (Leiden mutation); V vs. v allele	9,876 (18)	9,210 (16)	0	0	662 (2 J)	414 (1)
23	Pre-eclampsia	*MTHFR* (677C→T); TT vs. CT + CC	6,008 (22)	4,557 (15)	549 (3)	569 (2)	333 (2 J)	205 (1)
24	Essential HTN	*AGT* (M235T); TT vs. MM	14,148 (40)	9,688 (22)	3,586 (12)	874 (6)	0	0
25	IHD	*AGT* (M235T); TT vs. TM + MM	20,060 (21)	17,225 (14)	2,835 (7)	0	0	0
26	Ischemic stroke	*MTHFR* (677C→T); TT vs. CT + CC	4,319 (12)	3,593 (10)	581 (1)	145 (1)	0	0
27*	MI	*MTHFR* (677C→T); TT vs. CT + CC	7,402 (13)	6,907 (11)	0	0	495 (1 J, 1 T)	378 (1)
28	MI	*F2* (20210G→A); AA + AG vs. GG	12,217 (19)	11,909 (18)	0	308 (1)	0	513 (1)
29	Schizophrenia	*DRD4* (–521C→T); C allele vs. T allele	2,918 (3)	1,040 (1)	1,878 (2)	0	0	0
30	Schizophrenia	*DRD3* (S9G); SS vs. SG + GG	8,653 (39)	6,082 (26)	2,067 (9)	203 (1)	301 (2 J, 1 Hi)	108 (1)
31	Schizophrenia	*DRD2* (S311C); C allele vs. S allele	18,704 (26)	12,480 (16)	5,352 (9)	0	872 (1 N Ind)	0
32*	Retinal arterial occlusive disease	*MTHFR* (677C→T); TT vs. CT+CC	587 (3)	323 (2)	0	0	264 (1 J)	0
33*	Retinal venous occlusive disease	*MTHFR* (677C→T); TT vs. CT+CC	3,444 (9)	1,305 (7)	0	0	2,139 (2 J)	0
34*	Schizophrenia	*APOE* (epsilon 2/3/4); allele 4 vs. others	4,303 (16)	3,250 (12)	985 (3)	68 (1)	0	0
35	MI	*PON1* (Q192R); RR vs. QQ	13,786 (19)	10,103 (15)	3,683 (4)	0	0	0
36	Coronary stenosis	*PON1* (Q192R); RR + QR vs. QQ	11,928 (26)	7,783 (14)	3,457 (9)	0	688 (1 T, 2 Hi)	0
37*	CHD	*PON2* (S311C); S allele vs. C allele	7,196 (7)	1,422 (2)	5,138 (4)	0	636 (1 Hi)	0
38	Alzheimer disease	*ACE* (insertion/deletion); DI + II vs. DD	6,439 (20)	4,827 (14)	1,263 (3)	196 (1)	153 (1 J, 1 T)	356 (1)
39	Venous thromboembolism	*MTHFR* (677C→T); TT vs. CT+CC	11,242 (28)	7,650 (18)	2,552 (6)	278 (1)	762 (1 J, 2 T)	697 (2)
40*	Lung cancer	*TP53* (P72R); PP vs. RP + RR	7,389 (16)	5,206 (9)	1,829 (4)	166 (2)	188 (1 Haw)	150 (1)
41	Head and neck cancer	*GSTM1* (gene deletion); –/– vs. other	9,230 (28)	6,020 (16)	2,217 (9)	88 (1)	905 (2 Hi)	530 (3)
42*	Head and neck cancer	*CYP1A1* (3801T→C); VV +VI vs. II	3,388 (12)	2,059 (6)	1,084 (4)	87 (1)	158 (1 Hi)	262 (1)
43	Schizophrenia	*KCNN3* (exon 1 CAG-repeat); alleles >19 vs. others	5,803 (11)	4,161 (7)	1,324 (3)	0	318 (1 Hi)	0

*These associations are formally statistically significant only for specific 'racial' groups and not in the overall meta-analysis.
APS, antiphospholipid syndrome; Ar, Arabic; CAD, coronary artery disease; CHD, coronary heart disease; Haw, Hawaiian; Hi, Hindu; HTN, hypertension; ICVD, ischemic cerebrovascular disease; ID, identification number; IHD, ischemic heart disease; J, Jewish; MI, myocardial infarction; N Ind, Native Indian; NS, descent not stated or data not possible to separate by 'race'; NTD, neural tube defect; SLE, systemic lupus erythematosus; T, Turkish.

genetic effects might have been missed owing to low statistical power. Nevertheless, the observed variability between group-specific estimates was limited, and between-group variance was larger than within-group variance in only 10 meta-analyses, whereas the opposite was true in 31 cases (between-group and within-group variance were equal in two cases; **Supplementary Table 4** online). In pair-wise comparisons (**Supplementary Table 5** online), statistically significant differences were seen in 5 of 34 (15%) comparisons of European versus East Asian descent, 2 of 24 (8%) comparisons of European versus African descent and in none of 21 comparisons of East Asian versus African descent. These discrepancy rates are not much different from what would be expected by chance (5%). Moreover, there was large heterogeneity ($I^2 \geq 75\%$) between the various groups in only 6 of 43 (14%; 95% CI = 5–30%) meta-analyses (**Fig. 2**). This included 4 of the 32 meta-analyses (13%) that had a formally statistically significant association overall, and not in only a single 'racial' group. The median I^2 of these overall-validated gene-disease associations was 0% (interquartile range = 0–51%, **Supplementary Fig. 1** online), whereas the median I^2 in the other 11 cases that had an association in only one 'racial' group was as much as 61% (interquartile range = 4–67%; $P = 0.007$ for the comparison by Mann-Whitney U test).

Table 2 Statistical significance of the observed between-study heterogeneity

	Significant heterogeneity in frequencies of genetic marker in control groups				Significant heterogeneity in odds ratios associated with the genetic marker			
ID	All studies	European	East Asian	African	All studies	European	East Asian	African
1	–	–	NS	NS	+	+	NS	NS
2	+	+	–	–	+	+	–	–
3	+	+	NS	–	–	–	NS	–
4	+	+	NS	–	–	–	NS	–
5	+	+	+	NS	+	+	+	NS
6	+	–	–	NS	–	–	–	NS
7	–	–	–	–	+	+	–	–
8	+	+	NS	NS	+	–	NS	NS
9	+	–	–	NS	+	+	–	NS
10	+	+	NS	NS	–	–	NS	NS
11	–	–	NS	NS	–	–	NS	NS
12	+	+	–	NS	+	+	–	NS
13	+	+	NS	–	+	+	NS	+
14[a]	+	–	–	–	+	+	–	–
15	+	+	+	+	–	–	–	+
16	+	+	NS	NS	+	+	NS	NS
17	+	+	+	–	–	–	–	–
18	+	–	–	NS	–	–	–	NS
19	+	–	–	NS	–	–	–	NS
20	+	+	–	–	+	+	+	–
21	+	+	–	NS	–	–	–	NS
22[a]	+	+	NS	NS	+	+	NS	NS
23[a]	+	+	+	–	+	+	–	–
24	+	+	+	+	+	+	–	–
25	+	+	+	NS	+	+	–	NS
26	+	+	NS	NS	–	–	NS	NS
27	+	+	NS	NS	+	–	NS	NS
28	+	+	NS	NS	–	–	NS	NS
29	–	NS	–	NS	–	NS	–	NS
30[a]	–	–	–	NS	–	–	–	NS
31	+	–	–	NS	–	–	–	NS
32	–	–	NS	NS	–	–	NS	NS
33[a]	–	–	NS	NS	–	–	NS	NS
34	+	+	–	NS	–	–	–	NS
35	+	+	+	NS	–	–	–	NS
36[a,b]	+	–	+	NS	+	+	+	NS
37	+	–	+	NS	+	–	+	NS
38	+	+	+	NS	+	+	–	NS
39[a]	+	+	+	NS	–	–	–	NS
40	+	+	–	–	–	+	–	–
41[a]	+	–	–	NS	+	–	+	NS
42	+	+	+	NS	+	–	+	NS
43	+	–	+	NS	+	+	–	NS

[a]More than one study in each of the other 'racial' groups were available.
[b]Heterogeneity was significant for only two studies in subjects from India (for both metrics). ID, identification number (as in Table 1); NS, no studies or only one study available.

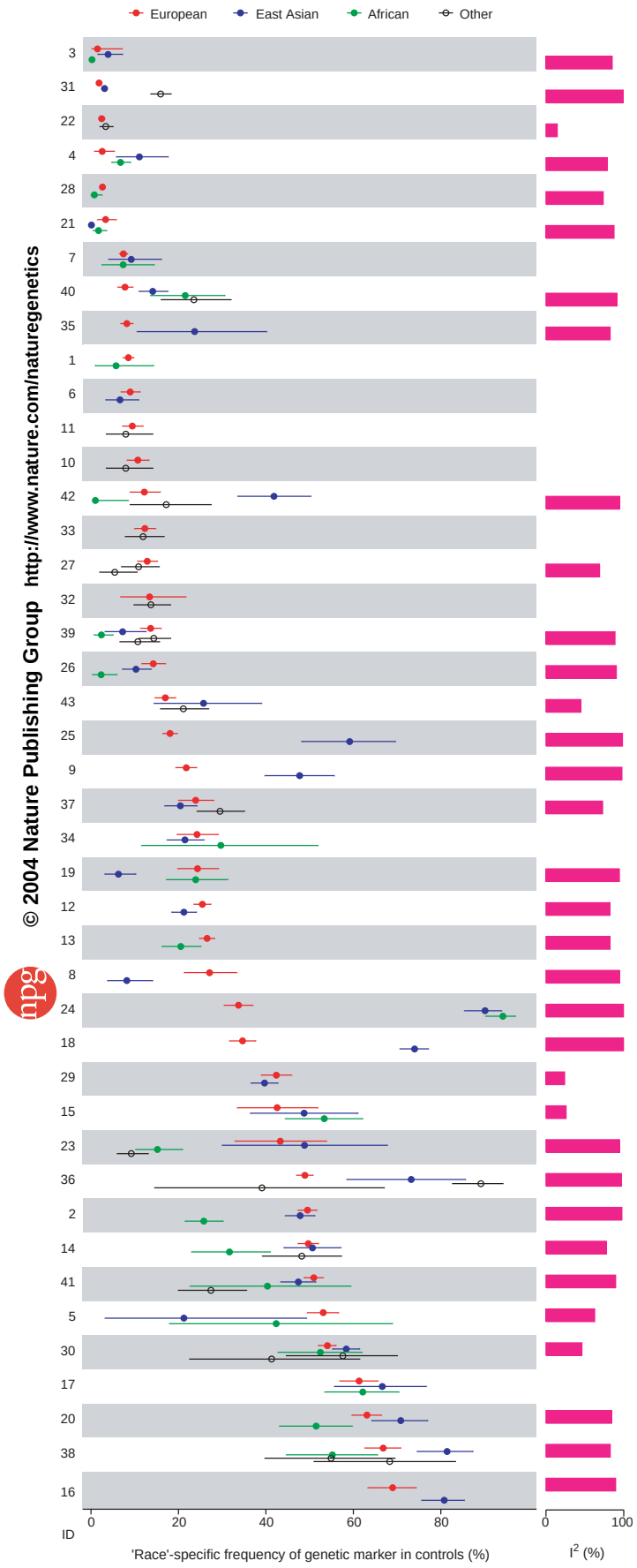

Figure 1 Frequencies of the allele(s) or genotype(s) of interest in control populations of various descents in each meta-analysis of gene-disease associations. For each group with available data, random effects summary estimates are shown (dots) along with the respective 95% confidence intervals (extending lines). Different racial descents are shown with different colors. The identification numbers (ID) on the left side correspond to those in **Table 1**. The meta-analyses are ordered according to increasing frequency of the genetic variant of interest in the subjects of European descent. On the right side, the graded horizontal bars show the I^2 values for the observed heterogeneity between the frequency estimates of the groups in each meta-analysis. Values $\geq 75\%$ are considered characteristic of large heterogeneity.

In 32 meta-analyses (74%), all the 'race'-specific odds ratio estimates either suggested genetic susceptibility (all odds ratios >1) or suggested genetic protection (all odds ratios <1; **Fig. 2**). In the remaining 11 meta-analyses, some 'race'-specific odds ratio estimates were in opposite directions, but we never observed statistically significant gene-disease associations in opposite directions in different groups.

We evaluated whether the associations with large heterogeneity ($I^2 \geq 75\%$) in the genetic effects (odds ratios) between the various 'racial' groups were different from those without such large heterogeneity. There was no suggestion that the available sample size, number of studies, type of disease phenotype, type of genetic contrast, frequency of the genetic marker of interest in the subjects of European descent, or presence of large heterogeneity in the control frequencies across groups differed in these two types of associations (**Table 3**). But modest differences could have been missed, given the small number of associations with large 'racial' heterogeneity.

We specifically addressed the possibility that low levels of observed between-'race' heterogeneity in the genetic effects may be due to relatively limited amount of data for some gene-disease associations. In 15 meta-analyses (284 studies), there were sufficient data to reach formal statistical significance for the association (the 95% c.i. excluded 1) in two different 'racial' groups. In all 15 cases, the significant 'race'-specific effects were in the same direction. In 11 of 15 cases, all available 'racial' point estimates (significant or not) were in the same direction. We also found evidence that meta-analyses with more data were likely to show higher between-'race' heterogeneity in the control group frequencies ($P = 0.03$, **Fig. 3a**). On the contrary, there was absolutely no evidence that the availability of more data increased the observed between-'race' heterogeneity in the odds ratios; we observed the opposite trend (**Fig. 3b**). None of the eight meta-analyses (210 studies) with a sample size exceeding 10,000 showed large heterogeneity in the odds ratios between groups, and heterogeneity typically was minimal in these cases (**Fig. 3b**). Only 2 of 19 meta-analyses (383 studies) with a sample size exceeding 1,000 in at least two different groups showed large heterogeneity in the odds ratios.

Variation in genotype frequencies across diverse populations may affect the number of individuals at increased risk for a disease, and population substructure imbalances may create spurious differences in genotype frequencies of the compared groups in gene-disease association studies[4]. Our data are compatible with the hypothesis that genetic effects are consistent across traditionally defined 'racial' groups. The existing evidence does not necessarily prove that 'race'-specific genetic effects are exactly the same. In gene-disease associations with limited data, one cannot exclude large differences in effect size or even effects in opposite direction across different 'racial' groups. Moreover, unrealistically large sample sizes are required to have

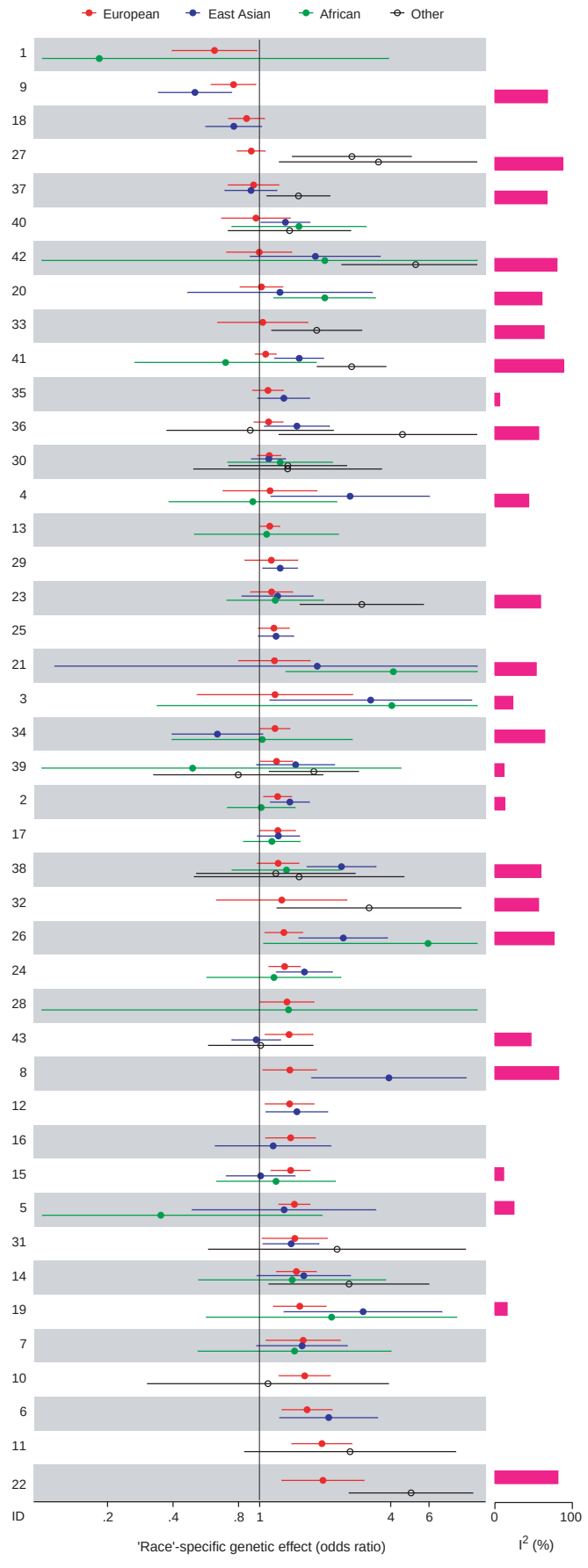

Figure 2 Odds ratios for the observed genetic association in studies of groups of various descents in each meta-analysis of gene-disease associations. Odds ratios >1 suggest susceptibility to the disease, and values <1 suggest protection from the disease. For each group with available data, random effects summary estimates are shown (dots) along with the respective 95% confidence intervals (extending lines). Different 'racial' descents are shown with different colors. The identification numbers (ID) on the left side correspond to those in **Table 1**. The meta-analyses are ordered according to increasing odds ratio in the subjects of European descent. On the right side, the graded horizontal bars show the I^2 values for the observed heterogeneity between the odds ratio estimates of the groups in each meta-analysis. Values $\geq 75\%$ are considered characteristic of large heterogeneity.

sufficient power to exclude very small 'racial' differences. Even the proposed extremely large US prospective cohort study[17] would probably be underpowered to distinguish between odds ratios of 1.40 and 1.50. Here, we observed a 14% rate of large disagreements in the genetic effects between 'racial' groups. The exact clinical importance of such disagreements may also be examined and debated on a case-by-case basis. The data analyzed here may help inform a field where strong opposing opinions have been common.

A consistent genetic effect across racial descent groups means that genetic variants eventually reflect a common, consistent, final biological effect on individuals. Theoretically, the final biological effect may be modified by both environmental exposures and the overall genetic mix-up of each population (the influence of other genes on the gene variant of interest). There is good evidence that the overall genetic makeup of people from different 'races' is similar[8]. Depending on the marker system and the exact population used, at least 85% of genetic variation is accounted for by within-population interindividual differences, not by differences between groups[8]. This evidence is consistent with the lack of significant modification of the genetic effects that we observed across 'racial' groups. Important environmental risk exposures may also vary across subjects of different geographic and 'racial' origin. But these risk factors probably also show larger variation within populations than between populations and largely reflect personal lifestyle rather than geographically or 'racially' determined exposures[18,19].

Alternatively, genetic and environmental factors may have mostly independent effects on the development of complex diseases. Synergistic effects (such that one risk factor has an effect only in the presence of another) may not be very important. The expectation that all different genes and polymorphisms will have similar parameters of effect across the world is implausible. But most of the genetic effects may be multiplicative, and the odds ratios for an individual may be independent products of component odds ratios of all of that individual's genetic risk factors. Moreover, some of the studied alleles may not be associated with disease themselves, but instead may be in linkage disequilibrium with the disease-associated allele. If so, and because linkage disequilibrium breaks down differently in different populations, variations in the estimated odds ratios may reflect variable linkage disequilibrium rather than variation in the true genetic effect. This suggests that the differences between 'racial' groups in the genetic effects of the true disease-associated alleles may be even smaller than we observed here.

Literature claims for 'racial' differences in genetic risks should be scrutinized cautiously. Some of them may be spurious interpretations of the data. The available evidence is compatible with the hypothesis that genetic effects are usually consistent across human populations. Small sample size, study design flaws or other biases[13,14,20] may be

Table 3 Comparison of associations with or without large racial heterogeneity in the genetic effects (odds ratios)

Characteristic	Between-group heterogeneity in the genetic effect		*P* value*
	$I^2 \geq 75\%$ ($n = 6$)	$I^2 < 75\%$ ($n = 37$)	
Total sample size, median (IQR)	5,861 (3,388–9,230)	5,289 (4,091–8,962)	0.83
Number of studies, median (IQR)	13 (12–18)	16 (9–21)	0.70
Disease or outcome:			
Cancer	2	9	0.32
Vascular, including hypertension	4	13	
Neurodegenerative and psychiatric	0	8	
Other	0	7	
Genetic contrast:			
Allele-based	1	8	1.00
Genotype-based	5	29	
Genetic marker frequency in controls of European descent, median (IQR)	13.6% (12.2–27.0%)	23.9% (8.9–13.3%)	0.60
Large between-group heterogeneity in control frequencies:			
Yes	4	21	1.00
No	2	16	

*Based on Fisher's exact and Mann-Whitney U tests, as appropriate. IQR, interquartile range.

more common reasons than true 'racial' heterogeneity for the observed discrepancies between studies addressing genetic risks.

METHODS

'Racial' descent. The categorization was done *a priori*. 'European descent' includes native populations of Europe and subjects of European descent from Oceania, North America and South America, including Hispanics. 'African descent' includes populations of sub-Saharan Africa and African Americans. 'East Asian descent' includes native populations of China, Japan, Korea, Indochina and the Philippines. When available, subjects of other ethnic descent (not included in the groups above) were considered separately.

Gene-disease associations. We updated a previously developed database of meta-analyses of associations of binary disease outcomes with genetic markers other than HLA alleles. Selection criteria and search strategies were as previously described[13,14]. We updated our database by adding recently published, potentially eligible genetic meta-analyses (last MEDLINE search May 2004) and meta-analyses from our team that are currently in press. We also communicated with investigators of potentially eligible, published meta-analyses to obtain pertinent study-level data, whenever these were not available in their publication. We separated data on subjects of different 'racial' descent. Whenever a study reported to have a population admixture without providing the exact genotype and disease frequencies per 'racial' group, we retained it if >80% of the subjects belonged to one group as defined above. When only the country where a study took place was stated, we retained the data if >80% of the general population of that country belonged to one of these groups. We carried out quantitative analyses on the meta-analyses in which the data from >80% of the studies could be assigned to the predefined 'racial groups' and for which data were available for at least two groups.

Data synthesis. For each 'racial' group, we obtained weighted frequencies of the genetic marker of interest in the control group with random effects calculations, which allow for and incorporate between-study variability[15]. We used the Freeman and Tukey arcsin transform to stabilize variances. We estimated summary odds ratios (the metrics showing the strength of the genetic effects) for each entire meta-analysis, as well as for each 'racial' group, according to the DerSimonian and Laird random effects model[15]. For both frequencies and odds ratios, we report the point estimates and 95% confidence intervals.

Extent of heterogeneity. I^2 is provided by the ratio of (Q – df)/Q, where df is the degrees of freedom and Q is the χ^2-based statistic of between-study heterogeneity[15]. I^2 gives a measure of the extent to which this heterogeneity is not due to chance and takes values from 0–100%. Large heterogeneity is defined typically as $I^2 \geq 75\%$ (ref. 16).

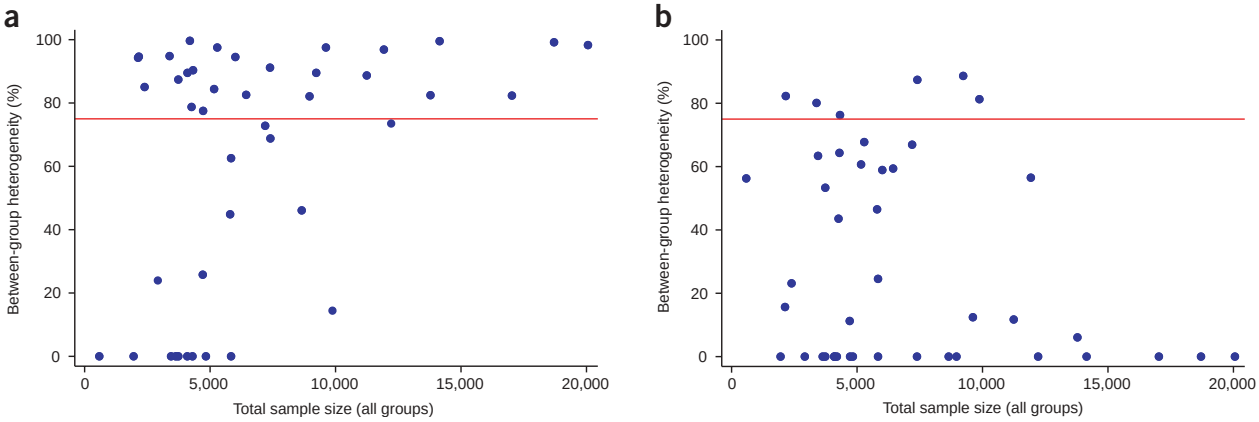

Figure 3 Correlation between the available total sample size and the I^2 for the observed heterogeneity between the frequency estimates (**a**) and between the odds ratios (**b**) of the 'racial' groups in each meta-analysis. Spearman's correlation coefficients were 0.34 ($P = 0.03$) and –0.11 ($P = 0.47$), respectively.

Note: Supplementary information is available on the Nature Genetics website.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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