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GENETIC EPIDEMIOLOGY

Sex-specific differences in effect size estimates at established complex trait loci

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Background Genetic differences between men and women may contribute to sex differences in prevalence and progression of many common complex diseases.

Using the WTCCC GWAS, we analysed whether there are sex-specific differences in effect size estimates at 142 established loci for seven complex diseases: rheumatoid arthritis, type 1 diabetes (T1D), Crohn's disease, type 2 diabetes (T2D), hypertension, coronary artery disease and bipolar disorder.

Methods For each Single nucleotide polymorphism (SNP), we calculated the per-allele odds ratio for each sex and the relative odds ratios (RORs; the effect size is higher in men with ROR greater than one). RORs were then meta-analysed across loci within each disease and across diseases.

Results For each disease, summary RORs were not different from one, but there was between-SNP heterogeneity in the RORs for T1D and T2D. Four loci in T1D, three in Crohn's disease and three in T2D showed differences in the genetic effect between men and women ($P < 0.05$). We probed these differences in additional independent replication samples for T1D and T2D. The differences remained for the T1D loci *CTSH*, 17q21 and 20p13 and the T2D locus *BCL11A,* when WTCCC data and replication data were meta-analysed. Only *CTSH* showed different genetic effect between men and women in the replication data alone.

Conclusion Our results exclude the presence of large and frequent differences in the effect size estimates between men and women for the established loci in the seven common diseases explored. Documenting small differences in genetic effects between men and women requires large studies and systematic evaluation.

Keywords Genetic Predisposition to Disease, Genome-Wide Association Study, Odds ratio, Sex

Introduction

The prevalence, course and severity of many common traits and diseases, including autoimmune diseases,[1] cardiovascular diseases[2] and asthma[3] differ between men and women. For example, the prevalence of type 1 diabetes (T1D) and type 2 diabetes (T2D) in women is 58% and 47%, respectively. Sex hormones are known to be important mediators of these differences. However, it is also speculated that differences in male and female genetic architecture and heritability, involving both sex chromosomes and autosomes, might also contribute to sex differences in prevalence rates and progression.[4] It has been proposed that genetic studies should incorporate sex-gene interaction effects in their design and interpretation to avoid missing a significant proportion of trait-associated loci.[4] Numerous studies have claimed sex-related differences in genetic associations in the past, but usually each of them has addressed only one or few genetic variants and one or a few phenotypes at a time. Moreover, an in-depth evaluation of the literature of sex-specific effects has shown that most of the reported differences were insufficiently documented or spurious, and replication in independent data sets was uncommon.[5] The availability of a large number of robustly replicated genetic loci from genome-wide association studies allows the evaluation of sex-specific effects in a large number of loci and phenotypes. Here, we explore the presence of sex-specific differences in effect size estimates at a large number of established loci for seven different complex traits.

Materials and methods

We used the Wellcome Trust Case Control Consortium 1 (WTCCC1) genome-wide association study (GWAS) data for seven common complex diseases, including rheumatoid arthritis (RA) (470 males and 1390 females), T1D (998 males and 965 females), Crohn's disease (CD) (680 males and 1068 females), T2D (1118 males and 806 females), hypertension (HT) (775 males and 1177 females), coronary artery disease (CAD) (1527 males and 399 females) and bipolar disorder (BD) (497 males and 1171 females), and 2938 control subjects (1446 males and 1492 females).[6]

For each disease, established associated loci, that is, those Single nucleotide polymorphisms (SNPs) reaching genome-wide significance levels ($P < 5 \times 10-^{8}$), were selected from recent publications (Supplementary Table 1, available as Supplementary data at *IJE* online).[6–26] A number of SNPs that have been robustly validated by replication in independent samples, but have not attained $P < 5 \times 10-^{8}$ in any single study were also included (marked with an asterisk in Supplementary Table 1, available as Supplementary data at *IJE* online). SNPs mapping to sex chromosomes were excluded from the analysis. Reported GWAS SNPs were analysed for each locus if they were included in the Affymetrix GeneChip 500 K Mapping Array Set. Otherwise, the best proxy ($r^2 > 0.80$) was selected from the chip using SNAP.[27] The SNPs selected for investigation were not in linkage disequilibrium with each other.

Patients and control subjects were stratified according to sex, and risk odds ratios (ORs) (OR per copy of the risk allele) were calculated for each locus in both subgroups using Plink.[28] For each SNP, the risk allele was denoted as the allele that increases the risk of the disease in the combined data of men and women across all populations tested in the literature. Relative odds ratios (RORs) were calculated as the ratio of the OR in males versus the OR in females, so that the effect size would be higher in men or women, if $\mathrm{ROR} > 1$ or $\mathrm{ROR} < 1$, respectively. The standard error (SE) of the logROR was calculated as the square root of the sum of the squares of the SE of the OR in males and the SE of the OR in females. For each locus, we tested whether ROR is different from one by performing fixed and random effects meta-analysis, equivalent to testing for an SNP-sex interaction effect. RORs were then meta-analysed across loci within each disease and across diseases. A test of whether the summary-effect measure is equal to one was performed, as well as a test for heterogeneity (i.e. whether the true effect in all tests is the same). Heterogeneity was also quantified using the I^2 measure, which shows the variation in effect size attributable to heterogeneity beyond chance.[29] We also report 95% CIs for this metric.[30] The analysis was repeated by synthesizing established loci ROR across all seven diseases. Moderate-size differences between the two sexes at each locus could be difficult to identify, given that the power to detect such differences is modest. Therefore, for each disease and across diseases, we tested whether the proportion of loci showing sex difference P values below different thresholds (0.05, 0.10, 0.20 and 0.25) were different from the expected proportion by means of a binomial probability test.

For two of the three disease phenotypes where genetic effect differences were seen for at least one gene locus between men and women, we were able to test for replication of these differences in additional larger data sets.

The T1D replication cohort consisted of 9541 British males (4420 cases and 5121 control subjects), 9301 British females (4089 cases and 5212 control subjects), 1837 Danish males (915 cases and 922 control subjects) and 1950 Danish females (874 cases and 1076 control subjects). The British T1D cases were recruited from paediatric and adult diabetes clinics at 150 National Health Service hospitals across the UK, as part of the Genetic Resource Investigating Diabetes collection of the Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory. The British control subjects consisted of subjects drawn from the British 1958 Birth Cohort

and the UK Blood Services Common Control Collection (UKBS-CC).[6,31] The Danish T1D cases were recruited from a nationwide registry, and the control subjects were randomly selected from the Inter99 study.[32]

For the replication of T2D results, we used data from the DIAGRAM consortium, excluding overlapping WTCCC samples.[25] A total of 16 222 males (3333 cases and 12 889 control subjects) and 26 034 females (2874 cases and 23 160 control subjects, all of European descent) were included in this replication experiment.

We present results based on the replication data alone, as well as results of the meta-analysis of all the available data (both the original WTCCC samples plus the replication data sets).

Meta-analyses and binomial probability tests were performed using Stata version 9.2 (College Station, TX).

Results

Overall, we considered 31 RA loci, 45 T1D loci, 69 CD loci, 36 T2D loci, six HT loci, six CAD loci and two BD loci. Of these 195 loci, we could evaluate sex-differences for 142 (26, 33, 50, 22, 5, 5 and 1 for the seven phenotypes, respectively) that had been directly genotyped or had proxy-SNPs directly genotyped in the WTCCC GWAS (Supplementary Table 1, available as Supplementary data at *IJE* online).[6] As previously described, some susceptibility loci were shared between different diseases.

We did not find differences in the genetic effect for men and women after adjusting for 142 comparisons. However, for 10 of the 142 loci (four in T1D, three in CD and three in T2D), we observed differences ($P < 0.05$ uncorrected for multiple comparisons) in the genetic effect between men and women (Supplementary Table 1, available as Supplementary data at *IJE* online). One would expect $0.05 \times 142 = 7.1$ to differ by chance at that level of significance. Binomial probability tests showed that the proportion of loci showing sex difference *P* values below different threshold values (0.05, 0.10, 0.20 and 0.25) was not different from the expected proportion when considering all diseases together. However, we found that the number of T1D sex-specific loci was inflated at $P < 0.10$, $P < 0.15$ and $P < 0.20$ (Supplementary Table 2, available as Supplementary data at *IJE* online). For 7 of the 10 loci with differences, the genetic effect was larger in women, and for three loci it was larger in men. Moreover, for each locus the OR point estimates in the two sexes did not differ substantially in absolute value, and only five loci had an ROR estimate (OR in males/OR in females) > 1.2, and one had an ROR estimate < 0.8 (Supplementary Table 1, available as Supplementary data at *IJE* online).

For each disease, summary RORs were not different from one, with estimates ranging from 0.975 to 1.014, indicating that there are no consistent differences in the effect size estimates between men and women with consistently larger effects in one or the other sex (Table 1). Moreover, we found no between-locus heterogeneity in the ROR estimates for five of the seven disease phenotypes. There was between-locus heterogeneity for T1D and T2D, and I^2 estimates were also consistent with moderate heterogeneity, suggesting that some estimates may differ from the pattern of ROR = 1.00.

We sought replication for the seven T1D and T2D loci with effect differences across sexes in consortial meta-analyses with much larger sample sizes. Sex differences at two of the four T1D loci were confirmed in the UK replication cohort (*CTSH* and 17q21), but not in the smaller Danish cohort (Table 2). There were sex differences only for *CTSH* when both replication data sets were combined. When all three cohorts were combined, three loci showed different effect sizes across sexes: *CTSH*, 17q21 and 20p13.

In the replication study of the T2D loci, ORs were similar in men and women for all three loci studied. However, when the non-overlapping DIAGRAM samples were combined with the WTCCC data set, there was still a sex-specific difference in effect size for the *BCL11A* locus (Table 2).

Discussion

Our assessment argues against the presence of frequent large sex-specific effects in established loci for complex disease. However, these data are also consistent with the occasional presence of small differences in sex-specific effects, although these did not stand after the highly conservative Bonferroni correction for multiple testing.

When gender differences are substantial, a gene locus may be much easier to detect in one gender rather than in analyses including the whole population. For example, if the per allele OR of a gene locus with risk allele frequency of 10% is 1.25 across both genders, then a study of N = 10 000 alleles would have only 22% power to detect it. However, if the OR is 1.5 in women but 1.0 in men, then the power to detect this gene locus in women with half the sample size would be 80%.

For each single locus, the power to detect moderate-size differences between the two sexes in the WTCCC data set at $P < 0.05$ is modest, and several such differences (e.g. ROR values in the range of 1.2 or 0.8) may have been missed. This is why we also evaluated more lenient significance thresholds, and tested the observed versus expected number of sex-specific differences that passed each significance threshold. An excess versus what is expected by chance was seen only for T1D, and even this excess was modest. Moreover, very few of the ROR estimates deviated from 1.0 by more than 20%; thus, it is likely that very few or even none of the sex-specific

Table 1 Summary RORs for each of seven diseases included in the WTCCC1 study, obtained by meta-analysis of RORs for all established disease loci

Disease	Loci tested	Loci with sex-difference $P < 0.05$	Fixed effects Summary ROR (95% CI)	Fixed effects Sex difference P value	Random effects Summary ROR (95% CI)	Random effects Sex difference P value	Heterogeneity P value	I^2 (%) (95% CI)
RA	26	0	1.006 (0.966–1.048)	0.775	1.006 (0.966–1.048)	0.775	0.503	0 (0–43)
T1D	33	4	0.972 (0.942–1.004)	0.087	0.975 (0.935–1.017)	0.245	0.010	40 (9–61)
CD	50	3	0.979 (0.953–1.006)	0.130	0.979 (0.953–1.006)	0.130	0.945	0 (0–33)
T2D	22	3	1.003 (0.963–1.045)	0.885	1.003 (0.953–1.055)	0.917	0.066	34 (0–61)
HT	5	0	1.014 (0.919–1.119)	0.779	1.014 (0.907–1.134)	0.811	0.282	21 (0–66)
CAD	5	0	0.981 (0.894–1.078)	0.692	0.981 (0.894–1.078)	0.692	0.679	0 (0–79)
BD	1	0	0.984 (0.676–1.431)	0.931	0.984 (0.676–1.431)	0.931	–	–
All	142	10	0.987 (0.971–1.003)	0.111	0.987 (0.970–1.004)	0.129	0.258	6.9 (0–25)

ROR, relative odds ratio (OR males/OR females); RA, rheumatoid arthritis; T1D, type 1 diabetes; CD, Crohn's disease; T2D, type 2 diabetes; HT, hypertension; CAD, coronary artery disease; BD, bipolar disorder.

differences represent moderately large deviations in effect size.

It is difficult to make conclusive inferences about smaller effect deviations. Small differences (e.g. differences in the OR scale of 1.1-fold or less) are not easy to detect and cannot be excluded for almost any of these associations. We documented four associations with sex-specific differences, when both the WTCCC and replication data were combined, and for all of them the ROR showed approximately a 10% deviation from 1.0. It is possible that not all of them are genuine sex-specific differences because only one of the four was present both in the WTCCC and in the replication data, when these were examined separately. These differences are not likely to be due to random differences in allele frequencies in male and female controls, as different loci appear to present different sex-specific differences in T1D and T2D.

Larger studies may document additional differences in sex-specific effects. It would be interesting to carry out a meta-analysis across multiple cohorts, as more data accumulate. To have 80% power to detect an ROR of 1.05 at $\alpha = 0.05$ for a variant with minor allele frequency of 10%, one needs a sample size of 42 213 cases and control subjects, and the numbers become larger when there is imbalance between the number of men and women. Moreover, it may be that for some phenotypes, sex-specific differences are more common than what we observed in the seven phenotypes that we analysed here. For example, a recent meta-analysis for waist-hip ratio comprising 77 167 participants found genome-wide significant association for 14 loci, and when these were subsequently analysed in men and women separately, half of them showed larger effect size estimates in women compared with men.[33] Some of these sex-specific differences were substantially large, in contrast to what we observed.

We should also acknowledge that individual studies and meta-analyses that have led to the discovery of the established loci for the seven diseases investigated here, have been sufficiently powered to detect associations across both sexes. Therefore, loci that have sex-specificity in their effects would have less power to be detected. Importantly, for most of the examined loci, truly causal variants within the region have not been identified to date and, hence, effect estimates are likely to be inaccurate and overall smaller than the effects of the causal variants. It is possible that by analogy, the sex-specific differences may be larger for the causal variants than for their linked markers. In this regard, rare variants, which may have stronger effect sizes than common variants, have not been captured in GWA studies.

Acknowledging these caveats, our findings suggest that estimates of risk conferred by currently known genetic markers for these seven phenotypes to date, are not much different in men and women. To avoid spurious claims and to enhance the detection of

Table 2 Replication of loci showing nominally statistically significant effect differences between sexes in WTCCC1

Locus	SNP	Gene[a]	RAF males	OR males (95% CI)	RAF females	OR females (95% CI)	ROR (95% CI)	*P* value ROR = 1
T1D								
WTCCC								
3p21	rs6441961[b]	*CCR5*	0.30	1.10 (0.98–1.25)	0.28	1.34 (1.18–1.51)	0.83 (0.69–0.98)	0.031
15q25	rs3825932	*CTSH*	0.67	1.27 (1.12–1.44)	0.69	1.06 (0.93–1.20)	1.20 (1.01–1.44)	0.040
17q21	rs7221109	*CCR7-SMARCE1*	0.67	1.06 (0.94–1.20)	0.63	1.37 (1.21–1.55)	0.77 (0.65–0.92)	0.003
20p13	rs2281808	*SIRPG*	0.65	1.01 (0.89–1.13)	0.64	1.22 (1.08–1.38)	0.82 (0.69–0.97)	0.024
UK T1D								
3p21	rs333[b]	*CCR5*	0.89	1.15 (1.04–1.26)	0.88	1.18 (1.08–1.30)	0.97 (0.85–1.11)	0.649
15q25	rs3825932	*CTSH*	0.68	1.24 (1.16–1.32)	0.69	1.10 (1.03–1.18)	1.12 (1.02–1.23)	0.014
17q21	rs7221109	*CCR7-SMARCE1*	0.65	1.05 (0.99–1.12)	0.64	1.18 (1.11–1.26)	0.89 (0.81–0.97)	0.011
20p13	rs2281808	*SIRPG*	0.64	1.10 (1.03–1.17)	0.63	1.19 (1.12–1.27)	0.92 (0.84–1.01)	0.067
Denmark T1D								
15q25	rs3825932	*CTSH*	0.69	1.04 (0.90–1.20)	0.68	1.03 (0.90–1.18)	1.01 (0.83–1.22)	0.964
17q21	rs7221109	*CCR7-SMARCE1*	0.64	1.14 (0.99–1.31)	0.65	0.99 (0.87–1.13)	1.15 (0.95–1.39)	0.162
20p13	rs2281808	*SIRPG*	0.64	1.13 (0.98–1.29)	0.65	1.07 (0.94–1.22)	1.05 (0.87–1.27)	0.600
T1D replication cohorts combined (UK + Denmark)								
15q25	rs3825932	*CTSH*		1.20 (1.13–1.27)		1.09 (1.03–1.15)	1.10 (1.01–1.20)	0.021
17q21	rs7221109	*CCR7-SMARCE1*		1.06 (1.01–1.13)		1.14 (1.08–1.21)	0.93 (0.86–1.01)	0.087
20p13	rs2281808	*SIRPG*		1.10 (1.04–1.17)		1.17 (1.10–1.24)	0.94 (0.87–1.02)	0.156
Meta-analysis of all data								
3p21	rs6441961[b]	*CCR5*					0.91 (0.82–1.02)	0.094
15q25	rs3825932	*CTSH*					1.12 (1.04–1.21)	0.004
17q21	rs7221109	*CCR7-SMARCE1*					0.90 (0.84–0.97)	0.005
20p13	rs2281808	*SIRPG*					0.92 (0.85–0.99)	0.024
T2D								
WTCCC								
2p16	rs243021	*BCL11A*	0.44	1.32 (1.18–1.47)	0.45	1.01 (0.90–1.14)	1.30 (1.11–1.54)	0.002
4p16	rs10010131	*WFS1*	0.59	1.18 (1.05–1.32)	0.60	0.99 (0.88–1.13)	1.19 (1.00–1.40)	0.046
7q32	rs972283	*KLF14*	0.53	1.02 (0.91–1.14)	0.50	1.22 (1.08–1.38)	0.83 (0.71–0.98)	0.028
T2D replication (DIAGRAM)								
2p16	rs243021	*BCL11A*	0.48	1.09 (1.02–1.16)	0.48	1.05 (0.98–1.11)	1.04 (0.95–1.13)	0.379
4p16	rs10010131	*WFS1*	0.68	1.14 (1.07–1.21)	0.68	1.09 (1.02–1.16)	1.04 (0.95–1.14)	0.335
7q32	rs972283	*KLF14*	0.55	1.10 (1.04–1.17)	0.55	1.12 (1.05–1.19)	0.99 (0.90–1.08)	0.761
Meta-analysis of all data								
2p16	rs243021	*BCL11A*					1.09 (1.01–1.18)	0.024
4p16	rs10010131	*WFS1*					1.07 (0.99–1.16)	0.081
7q32	rs972283	KLF14					0.95 (0.88–1.03)	0.187

[a]The Genes column denotes the nearest gene.
[b]LD = 1 with reported SNP (rs11711054).
CCR5 Genotype data were not available for the Danish population.
RAF, risk allele frequency in control subjects.

genuine sex-specific effects, it is important to evaluate and document them routinely and systematically in association studies for complex traits and to use extensive and robust replication practices.

Our findings overall lend little support to the hypothesis that differences in disease occurrence by sex at the studied loci are genetic and because of differences in effects conferred by common variants. Alternative possibilities of some genetic impact on sex differences of disease occurrence include gender differences confined to rare variation and sex differences that are driven by complex gene-by-environment interactions that cannot be captured by looking solely at the main effects for SNPs. The evaluation of these alternatives would require much larger studies with accurate data on environmental exposures and capturing the rare variants variability profile in these populations.

Supplementary Data

Supplementary Data are available at *IJE* online.

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Conflict of interest: None declared.

KEY MESSAGES

- The prevalence, course and severity of many common traits and diseases differ between men and women. Sex hormones and differences in male and female genetic architecture and heritability are thought to contribute to these differences in prevalence rates and progression.
- We explored the presence of sex-specific differences in effect size estimates at 142 established loci for seven different complex traits.
- Our results argue against the presence of frequent large sex-specific effects in established loci for complex disease.
- However, our results were also consistent with the occasional presence of small differences in sex-specific effects, as three loci in T1D and one in T2D showed differences in the genetic effect between men and women.

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