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ARTICLE

The *SETDB2* locus: evidence for a genetic link between handedness and atopic disease

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Abstract

The gene *SETDB2*, which mediates aspects of laterality in animal model systems, has recently been linked with human handedness as measured continuously on a scale from strong left to strong right. By contrast, it was marginally associated with a left-right dichotomous measure, and it showed no evidence of association with absolute handedness strength independent of direction. We genotyped the *SETDB2* handedness-associated single nucleotide polymorphism, rs4942830, in a large healthy population likewise phenotyped for continuous, absolute, and dichotomous handedness variables. Our results demonstrated significant effects of rs4942830 genotype on continuous handedness, and weaker, marginal effects on dichotomous handedness, but no effects on absolute handedness. These results help to establish the locus marked by the SNP rs4942830 as a strong candidate for mediating human handedness. Intriguingly, rs4942830 is also in complete linkage disequilibrium with rs386770867, a polymorphism recently shown to affect human serum levels of IgE production and other atopic phenotypes. These findings implicate this locus in the longstanding links of handedness with asthma and other atopic diseases.

Introduction

Human handedness exhibits substantial heritability, on the order of 0.3–0.7 depending on how it is measured (Lien et al. 2015). However, identification of specific genes that underlie variation in handedness has been challenging. Three genes, *AR* (Androgen Receptor), *LRRTM1* (Leucine Rich Repeat Transmembrane Neuronal 1), and *PCSK6* (Proprotein Convertase Subtilisin/Kexin Type 6) stand out as strong candidates (Medland et al. 2005; Francks et al. 2007; Scerri et al. 2010; Hampson and Sankar 2012; Arning et al. 2013; Leach et al. 2014; Robinson et al. 2016). Even for these genes, however, replications have been inconsistent with regard to the specific markers implicated, the populations demonstrating associations (e. g., typical or with dyslexia), and the specific metrics of handedness associated with genetic or epigenetic variation. As a result, studies of the molecular and developmental genetic bases of human handedness have been hindered by a lack of validated markers and candidate loci.

The gene *SETDB2* (SET Domain Bifurcated 2) was recently associated with human handedness variation by Ocklenburg et al. 2016, in a Caucasian population. This gene represents a strong *a priori* functional candidate given that its gene product regulates left-right asymmetries in the central nervous system, at least in part though effects on expression of the growth factor fgf8 (fibroblast growth factor 8) (Xu et al. 2010). Ocklenburg et al. 2016 demonstrated that the SNP rs4942830 was significantly associated with a continuous measure of handedness from strong left to strong right, but not associated with strength of handedness, and associated only nominally (not after multiple-comparison adjustment) with handedness categorized as left vs. right.

The *SETDB2* locus is also of notable interest because its chromosomal location at 13q14 represents a well-validated genomic region for association with risk of atopic diseases (mainly asthma, eczema, and hay fever) and with serum levels of the immune molecule, IgE, that mediates atopic hypersensitivities (Wills-Karp and Ewart 2004; Jones and Stewart 2010; Holt et al. 2011, 2015). These findings suggest that genetic variation in this region may underlie, to some degree, the epidemiological connections of atopic disease with handedness (Geschwind and Behan 1982, 1984; Smith 1987; Weinstein and Pieper 1988; Tonnessen

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et al. 1993; Andreou et al. 2000; Kaynar and Dane 2003; Krommydas et al. 2003, 2004; Peters et al. 2006; Preti et al. 2008) that trace back to seminal work by Geschwind and Galaburda (1985). By the Geschwind-Galaburda hypothesis, which has remained controversial since its inception due to inconsistencies in evidence and ignorance of causal mechanisms (e.g., Bryden et al. 1994), handedness and immune disorders are associated due in part to their shared mediation by fetal testosterone levels. Testosterone has indeed been associated with aspects of atopic immune disorders (e.g., Shaheen et al. 2007), and measures of handedness (Hampson and Sankar 2012), but specific molecular and developmental bases for associations have yet to be identified. Discovery and analysis of such causal factors is important because they will provide novel insights into the workings of the human neuroimmune system, and its genetic, epigenetic and environmental underpinnings, and provide for robust tests and extensions of Geschwind and Galaburda′s (1985) influential ideas.

This study has two goals. First, we set out to replicate the results of Ocklenburg et al. 2016, by genotyping rs4942830 for a population that was phenotyped for the same three measures of handedness (continuous left to right, strength, and dichotomous direction) and conducting the same analyses. Second, we used publicly-available human genetic data, and salient literature, to evaluate the hypothesis that the locus marked by rs4942830 mediates pleiotropy of handedness with risks and phenotypes of atopic disease.

Methods

Study population

The study population was a sample of Caucasian undergraduate students from both University of Alberta (Edmonton, Canada) and Simon Fraser University (Burnaby, Canada) ($N = 808$, 275 males, 533 females, mean age of 19 with SD = 2). The data collection was approved by Human Research Ethics at University of Alberta and the Simon Fraser University Research Ethics Board, and subjects provided written informed consent prior to participation.

Handedness data

Participants filled out the Waterloo Handedness Questionnaire (WHQ) (Steenhuis et al. 1990). Scores for each of 32 WHQ items ranging from +2 for strong right, +1 for weak right, 0 for ambidextrous, −1 for weak left and −2 for strong left, giving a total scale range from −64 to +64. Our metrics of handedness were constructed to match those of Ocklenburg et al. 2016: Laterality Quotient (LQ), a continuous measure from −64 to +64 that thus incorporates both direction and strength of handedness; Strength of Handedness (ST), the absolute value of LQ; and Left-Right (LR), a dichotomous measure whereby −1 to −64 is designated left and +1 to +64 is right. We also analyzed the handedness data using statistical protocols corresponding to those in Ocklenburg et al. 2016, with χ^2 tests (3 by 2 contingency tables) used for analyzing the LR data in relation to genotype, for directness of interpretation.

Genetic data

DNA was extracted from saliva using standard phenol-chloroform protocols. Fluorophore-labeled primers for *SETDB2* rs4942830 were used for TaqMan® genotyping on a Roche LightCycler® 96 Real-Time PCR machine. VIC and FAM fluorescence data were analyzed under Endpoint Genotyping using LightCycler® 96 software, version 1.1.0.1320. Genotypes were in Hardy-Weinberg equilibrium ($\chi^2 = 0.94$, $P = 0.33$).

Results

Handedness

The average LQ was 36 (SD = 24) and average ST was 41 (SD = 15). Overall, 9.3% of participants were classified as left handed and 90.7% as right handed, by the LR measure. The three handedness variables were all significantly correlated with one another (LQ-ST, $r = 0.652$, $P < 0.0001$; LQ-LR, $r = 0.808$, $P < 0.0001$; LR-ST, $r = 0.328$, $P < 0.0001$).

Main effects of sex, and sex by rs4942830 genotype, were both non-significant ($P = 0.083$ and 0.56 respectively), in analysis of LQ scores as a function of genotype and sex, so the sexes were pooled for analysis, as in Ocklenburg et al. 2016. LQ differed significantly between the three genotype groups (Table 1) with low η^2 values indicating small magnitudes of effect; essentially the same significance values were also obtained under dominant ($P = 0.036$) and recessive ($P = 0.034$) models. The genotypic effects thus appeared to be linear, with the genotypes AA, AT, and TT each separated by about a three point decrease in right shift of LQ (Table 1). In contrast to Ocklenburg et al. (2016), the T allele was associated with lower levels of LQ.

Handedness categorized as LR showed an apparent pattern of increasing percent left-handedness with numbers of T alleles (AA, 6.8%; AT, 9.1%; TT, 13.8%), but these differences were marginally non-significant (Table 1). The measure ST, in contrast to LQ and LR, showed no evidence of any differences between genotypes (Table 1).

Table 1 Tests for association of the three handedness metrics with *SETDB2* rs4942830 genotype

rs4942830 (*N*)						
Handedness Metric	AA (265)	AT (384)	TT (159)	ANOVA *F* value	ANOVA *P* value	Effect Size η^2
LQ (±SD) Laterality Quotient	38.6 ± 21.6	35.8 ± 23.6	32.4 ± 29.6	3.32	0.037	0.0082
ST (±SD) Handedness Strength	41.5 ± 15.4	40.1 ± 14.9	41.0 ± 15.6	0.67	0.51	0.0017
LR Left-Right (counts)				χ^2 value	*P* value	
Left handed	18	35	22	5.87 (2 d.f.)	0.053	
Right handed	247	348	137			

One individual had an WHQ score of zero and could not be categorized into left or right

SETDB2 locus

We used publically-available 1000 genomes phase 3 data to evaluate the hypothesis that the *SETDB2* SNP rs4942830 marks a functional haplotype that mediates not just handedness, but also serum IgE and risks and phenotypes of atopic disease, given previous evidence of a QTL for serum IgE and asthma in this immediate region (Zhang et al. 2003; Wills-Karp and Ewart 2004).

The SNP rs4942830 is located in the first intron of the *SETDB2* gene, about 6 kb from the start of its coding sequence. Multiple transcripts are produced from this region, including some that encompass just *SETDB2*, and one that extends to also include the gene *PHF11* (PHD Finger Protein 11) (Zhang et al. 2003); this extended transcript is referred to as *SETDB2-PHF11* (NCBI gene ID 107303344).

The two SNP markers in this region most strongly and directly linked with human IgE levels, and with risks and phenotypes of atopic disease, are rs386770867 (an AT/G indel polymorphism in the 5′ untranslated region of the *SETDB2* gene) and rs1046295 (an A/G polymorphism in the 3′ untranslated region of the gene *PHF11*) (Holt et al. 2011, 2015).

In the CEU Caucasian population, rs386770867 (and its overlapping proxy SNP rs71307668) are in complete linkage disequilibrium (LD) ($D' = 1$ and $R^2 = 1$) with rs4942830, and the two SNPs are separated by only 536 base pairs. LD values were virtually the same as in CEU in East Asian (CHB, JPT, CHS, CDX, KHV) and South Asian (GIH, PJL, BEB, STU, ITU) populations ($D' = 0.99–1$, $R^2 = 0.97–1$), as well as in the other Caucasian groups (TSI, FIN, GBR, IBS) (see Machiela and Chanock 2015, and https://analysistools.nci.nih.gov/LDlink for population codes). For the CEU data, rs386770867, rs71307668 and rs4942830 are all within the same haplotype block of about 9 kb in size (by Haploview), which comprises four haplotypes with frequencies of 0.58, 0.26, 0.10 and 0.06. In contrast to these populations, among Africans (YRI, LWK, GWD, MSL, ESN), the markers rs386770867 and rs4942830 were not in linkage disequilibrium, with $D' = 1$ but $R^2 = 0.09–0.10$, apparently due to low frequency of the rs386770867 G allele in these populations (and the corresponding high frequency of AT). These results indicate that rs386770867 marks the same haplotype as rs4942830 among non-African human populations, rendering them essentially the same locus.

The IgE and atopy-linked SNP rs1046295, located within the *PHF11* gene (and the *SETDB2-PHF11* gene), is about 83 kb from rs4942830. Despite this distance, the two SNPs are in strong to moderate LD in the five European populations (overall, $D' = 0.85$, $R^2 = 0.68$), with lower LD in South Asians ($D' = 0.84$, $R^2 = 0.54$), East Asians ($D' = 0.62$, $R^2 = 0.33$), and Africans ($D' = 0.80$, $R^2 = 0.20$)(populations same as above, and results are equivalent using rs386770867 instead of rs4942830). These results provide evidence that alleles of the SNPs rs4942830 and rs1046295 are notably associated with one another, especially for the European populations that have provided the bulk of the evidence regarding associations of the markers with IgE and atopic disease.

Ocklenburg et al. (2016) analyzed three *SETDB2* SNPs in addition to rs4942830, none of which showed significant associations with handedness. If rs4942830 shows the strongest association with both handedness and IgE/atopy, such that it marks a haplotype pleiotropically associated with both sets of phenotypes, then none of these other SNPs should be strongly linked with rs4942830 or rs1046295. As expected, none of these SNPs are in strong LD with rs4942830 or rs1046295, in Europeans (CEU): rs4942830: highest LD with rs7998427, $D' = 1$, $R^2 = 0.56$; rs1046295: highest LD with rs7998427, $D' = 0.97$, $R^2 = 0.43$. The SNP rs7998427 also shows the strongest non-significant association with LQ in Ocklenburg et al. (2016), as expected given these patterns of LD.

Taken together, these results indicate that the handedness-associated SNP rs4942830 and the IgE/atopic disease-associated SNP rs386770867 mark the same genetic variation, providing evidence for pleiotropic effects on these

two sets of phenotypes. Moreover, their substantial LD with the *PHF11* SNP rs1046295 suggests the hypothesis that an extended haplotype, from the 5′ UTR of *SETDB2* at least to the 3′ end of *PHF11*, may mediate both handedness and IgE/atopy risk variation. This hypothesis is consistent with the location of rs4942830 and rs386770867 5′ upstream of *SETDB2* and *PHF11*, the presence of a transcript that extends across the two genes in humans and mice (Zhang et al. 2003, 2014), and the documented effects of rs386770867 allelic variation on transcriptional activity as mediated by the transcription factors YY1 and SRY (Holt et al. 2015). The hypothesis requires direct testing, however, as multiple loci within these genes may certainly affect their expression or functional activity.

Discussion

This study contributes to the literature on the genetics of handedness and laterality in two main ways. First, the data analyzed here generally corroborates the results from Ocklenburg et al. (2016), in demonstrating significant association of allelic variation in the *SETDB2* SNP rs4942830 with human handedness measured continuously from strong left to strong right (LQ). We also demonstrated, as did Ocklenburg et al. (2016), a complete lack of association of rs4942830 with handedness strength (ST) (independent of direction), and a marginally non-significant association with handedness dichotomized to left vs. right (LR). This latter, marginally non-significant result should, notwithstanding, be interpreted in the context of the close relationship between LQ and LR, and the loss of information and statistical power caused by pooling all individuals with LQ values above, or below, the midpoint. These findings establish the gene and haplotype marked by rs4942830 as a strong functional candidate for a 'handedness gene', as well as providing evidence for a genetic basis to the relationship of continuous handedness directionality with non-directional handedness strength (Prichard et al. 2013; Ocklenburg et al. 2014). Additional studies of the *SETDB2* in relation to handedness measures are required to evaluate the direction of the allelic association, which differed between Ocklenburg et al. (2016) and our results; such findings are not uncommon in association studies and may be attributable to unobserved multilocus effects or other causes (Lin et al. 2007).

The results reported here are consistent with a polygenic basis for human handedness effects (Medland et al. 2009; McManus et al. 2013) involving direction and strength (Ocklenburg et al. 2016). Many previous physiological and behavioral studies have demonstrated effects of handedness strength independent of direction (e.g., Luders et al. 2010; Lyle et al. 2012), which makes these results for *SETDB2* of interest in their clear absence of any effect on handedness strength. Additional effects from interacting, or independent, environmental factors such as testosterone (e.g., Hampson and Sankar 2012; Hollier et al. 2014) and other impacts, working through epigenetic effects (Ocklenburg et al. 2017), have yet to be evaluated for *SETDB2*. Further analysis of the nature of effects from handedness-related genes, which will allow more robust tests of alternative models, also requires validation of additional such genes beyond the small number recognized thus far.

The second main contribution of this study is the demonstration that the handedness-associated SNP rs4942830 is in complete or virtually-complete linkage disequilibrium (in non-Africans) with a SNP, rs386770867, that has been strongly associated with atopic disease and serum levels of IgE, from both genetic-association and functional-genetic studies (Holt et al. 2011, 2015). In particular, the rs386770867 indel alleles AT and G differentially regulate expression of *SETDB2* (and, apparently, *PHF11*), through their effects on binding of the transcription factors YY1 and SRY (Holt et al. 2015). The SNPs rs4942830 and rs386770867 are also in substantial LD (especially among Caucasians) with a locus in the downstream gene *PHF11*, rs1046295, that has also been shown to strongly affect risk of atopic disease and levels of IgE (Holt et al. 2011, 2015).

The complete linkage disequilibrium of rs4942830 with rs386770867 provides the first evidence indicative of pleiotropy between handedness and atopic disease, such that the same locus appears to affect both. This result is notable given the well-established epidemiological associations of left or mixed handedness with asthma and other atopic diseases (cited above), that have hitherto lacked evidence regarding clear functional or genetic bases. Thus far, these associations have been considered mainly in the context of the classical Geschwind-Galaburda hypothesis, whereby, as noted above, levels of testosterone during brain development influence both handedness and functioning of the immune system (Geschwind and Galaburda 1985). Any role for testosterone in effects of the *SETDB2-PHF11* locus remains conjectural at this point, although Holt et al. (2015) detected significant sex differences in *SETDB2* expression due to rs386770867 allelic variation, apparently due to the male-limited expression of the transcription factor SRY. Although neither we, nor Ocklenburg et al. (2016), detected significant main effects of sex or sex by genotype interactions on handedness, in our analyses these effects were only marginally non-significant ($P = 0.083$ for a sex effect), and rs4942830 associations with LQ and LR appeared to be stronger among females than males. These results suggest that this locus exerts sex-differential effects, although how testosterone might be involved remains unclear.

As noted above, *SETDB2* codes for a methyltransferase that influences expression of *FGF8*, whose gene product has been demonstrated to modulate left-right structural

asymmetries in vertebrates (Xu et al. 2010); this gene is also involved in chromosomal segregation (Falandry et al. 2010). The function of *PHF11* is less well characterized, although it has demonstrated roles in T-cell activation and viability (Rahman et al. 2010) and DNA repair (Gong et al. 2017). The different functions of these genes suggest the possibility that, across an extended haplotype of *SETDB2-PHF11*, different SNPs may independently influence handedness and IgE/atopy. Although this hypothesis is worth considering, it can provide no explanation for the epidemiological evidence, given that both handedness and atopy are each underlain by many genes of relatively small effect (Armour et al. 2014; Ober 2016).

The primary significance of these results taken together is that they provide a functional-genetic window into deciphering apparent pleiotropic effects in the development of human handedness, laterality, and immunity with special reference to atopic disease. As such, studies that collect detailed haplotype data on the *SETDB2-PHF11* locus, in conjunction with measurements of handedness, brain laterality, immune functioning, serum IgE, and atopic disorders, should generate novel insights into both human development and disease. Of particular importance will be sequencing across the haplotype containing rs4942830 and rs386770867 (a SNP whose local region shows high levels of polymorphisms), and conducing haplotype-based tests of associations with atopic disease and handedness, which should help to identify the presence and nature of specific functional variation in this region and provide more-precise tests for pleiotropy and effects from specific alleles. More generally, other GWAS loci underlying serum IgE and atopic disease risks might also usefully be investigated for links with handedness, to test for pleiotropic effects from other regions of the human genome.

DATA archiving

Data available from the Dryad Digital Repository: http://dx.doi.org/10.5061/dryad.vb769

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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