

Suggestive Association With Ocular Phoria at Chromosome 6p22

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PURPOSE. We conducted a genome-wide association study to identify genetic factors that contribute to the etiology of heterophoria.

METHODS. We measured near and far vertical and horizontal phorias in 988 healthy adults aged 16 to 40 using the Keystone telebinocular with plates 5218 and 5219. We regressed degree of phoria against genotype at 642758 genetic loci. To control for false positives, we applied the conservative genome-wide permutation test to our data.

RESULTS. A locus at 6p22.2 was found to be associated with the degree of near horizontal phoria ($P = 2.3 \times 10^{-8}$). The P value resulting from a genome-wide permutation test was 0.014.

CONCLUSIONS. The strongest association signal arose from an intronic region of the gene *ALDH5A1*, which encodes the mitochondrial enzyme succinic semialdehyde dehydrogenase (SSADH), an enzyme involved in γ -aminobutyric acid metabolism. Succinic semialdehyde dehydrogenase deficiency, resulting from mutations of *ALDH5A1*, causes a variety of neural and behavioral abnormalities, including strabismus. Variation in *ALDH5A1* is likely to contribute to degree of horizontal phoria.

Keywords: phoria, strabismus, GWAS, *ALDH5A1*, SSADH

Heterophoria (phoria) is the degree to which the visual axes of the eyes deviate from concomitant alignment when there is no stimulus for binocular fusion. It reveals itself if binocular fusion is broken by covering one of the eyes or by presenting different stimuli to the two eyes. When a binocular target is present, heterophoria is overcome by vergence: the directions of gaze of the two eyes converge at the point of fixation. Heterophoria is distinguished from heterotropia, or strabismus, which is a manifest phoria, a persistent deviation of the axes of the eyes that cannot be eliminated by vergence. Though heterophorias and heterotropias are often discussed separately, they may share an underlying etiology. A popular idea is that heterotropia appears when, for some reason, the fusional mechanism fails.¹

The etiology of phorias is complex.¹ They are thought to depend on a variety of anatomical and neural factors, including the anatomy of the bones, muscles, and ligaments of the orbit, as well as neural signals sent to or from the extraocular muscles. Thus, individual variability in phorias may plausibly arise from genetic differences that affect anatomical or neural factors.

It has long been known that there are genetic factors in the etiology of strabismus.^{2,3} Twin studies report heritabilities between about 50% and 100%.¹ Wilmer and Backus⁴ conducted a meta-analysis of twin studies of strabismus, and concluded that concordance for strabismus in monozygotic (MZ) twins is at least three times higher than in dizygotic (DZ) twins (53.8%

vs. 13.8%). They estimated the heritability of strabismus to be 92%. The heritability of phorias has not been so often studied. Wilmer and Backus⁴ found high concordance for phoria in MZ twins ($r = 0.58$), but also found high concordance for DZ twins ($r = 0.67$). They concluded that variability in phorias, in contrast to strabismus, is not attributable to genetic factors, and that the concordance between twins can be completely explained by shared environment. In a later study, combining measurements of phoria and strabismus in 1462 twin pairs, Sanfillippo et al.⁵ found that esodeviation (either esotropia or esophoria, a nasal deviation) is heritable at 64%, while exodeviation (a temporal deviation) is not. Though no genetic associations have been reported for phorias, several susceptibility loci^{6–8} and candidate genes^{9,10} have been suggested for strabismus.

Most adults have a measurable phoria, a small exophoria on average.¹¹ Orthophoria (where the visual axes are concomitantly aligned), is a minority phenotype. Because phoria is not pathological, it has not often been measured in clinical populations. However, manifest phoria (strabismus) has been reported to co-occur with many clinical conditions including schizophrenia,^{12,13} mental retardation,^{14–16} Williams syndrome,¹⁷ Down's Syndrome,^{18,19} cerebral palsy,²⁰ craniofacial dysostoses,^{21,22} aniridia,²³ and congenital heart defects.²⁴ Strabismus is also associated with prenatal environment: prevalence is increased in children with fetal alcohol syndrome,^{25,26} or where the mother smoked during pregnancy.²⁷

Since phoria is a common trait among healthy adults, and since possible genetic influences on phorias are unknown, we included measurements of phorias in the PERGENIC genome-wide association study (GWAS). The PERGENIC study examined a range of sensory, perceptual and motor characteristics in a population of healthy adults aged 16 to 40.^{28,29}

MATERIALS AND METHODS

Participants

One thousand sixty (647 female) participants recruited from the Cambridge area were each paid £25 to take part in our battery of 2.5 hours of psychophysical tests. A randomly selected 105 participants returned for a second session at least one week after the first session, allowing us to measure test-retest reliability. To guard against population stratification in our sample, participants were all of self-reported European origin, and this was checked in the genomic analysis. Participants had a minimum visual acuity of 0.0 logMAR in at least one eye when corrected.

The study was approved by the Cambridge Psychology Research Ethics Committee, and adhered to the tenets of the Declaration of Helsinki. All participants gave written informed consent before taking part.

Measurement of Phorias

We used the commercially available Keystone telebinocular (Mast Concepts, Reno, NV) with plates 5218 and 5219 to measure near (equivalent to 40 cm) and far (equivalent to 6 m) phorias, respectively. These are combined plates for measuring both horizontal and vertical phorias, where a target consisting of a red vertical and a green horizontal line is presented to the left eye, and an oblique scale of numbered points is presented to the right eye. On these Keystone combined plates a score of 3.5 indicates orthophoria. One unit corresponds to one prism diopter for vertical phorias, and one unit corresponds to half a prism diopter for horizontal phorias.

The red and green lines appear to intersect the scale at different places depending on the degree of phoria. On first viewing, the target lines often appeared to move relative to the scale. Participants were asked to report the numbered point of intersection for each target line, at the place where the target lines appeared to come to rest. The telebinocular test was administered by an experimenter about 30 minutes after the start of our 2.5-hour test battery.

The Keystone telebinocular (Mast Concepts) test of phorias is a quick and reliable method of measurement. It has been found to have comparable reliability to the clinical Maddox rod method of measuring phorias.³⁰ The test does not distinguish phoria from manifest phoria (strabismus).

Genetic Methods

Participants each provided 2 mL of saliva using Oragene OG-500 kits (DNA Genotek Inc., Ottawa, Canada). The saliva samples were stored at room temperature until data collection was complete. DNA was extracted from the saliva samples according to DNA Genotek protocols, and 1008 samples were genotyped by Cambridge Genomic Services (University of Cambridge, UK) using the HumanOmniExpress BeadChip (Illumina, San Diego, CA). The Illumina array characterized 733,202 single nucleotide polymorphisms (SNPs) from each sample. Genotype calling was by custom clustering, using Illumina GenomeStudio software.

We excluded 20 individuals from our genetic data set. Three were excluded owing to sex anomalies, one owing to a low call

rate, fifteen owing to relatedness or sample duplication, and one for being a population outlier. The genetic data from 988 participants were used in the GWAS.

Genotyped SNPs were excluded from the analysis if genotypes were missing for more than 2% of individuals (12,706 SNPs), or if the minor allele frequency was below 1% (77,738 SNPs). After excluding these 12.3% of the characterized SNPs, 642,758 remained in the analysis.

For each SNP we ran a linear regression model with our quantitative phenotype using the software PLINK.³¹ To control for any population stratification that remained in our sample, we used EIGENSOFT³² to extract the top three principal components (PC) accounting for genetic variation. The three PCs were entered, along with sex, as covariates in the regression. We performed genetic association analyses on four variables: near and far vertical and horizontal phorias.

Since our variables are not normally distributed, permutation analyses were run to control for type 1 errors. Phenotype-genotype correspondence in our data was randomly shuffled 10,000 times, and genetic associations were run for all SNPs in each permutation. To control for population stratification in the permutation analysis, we allowed shuffling of phenotypic data only within genetic clusters of participants. We identified clusters of genetically related individuals using PLINK's clustering model with identity-by-state (IBS) as the distance metric.

We carried out the permutation analyses using PLINK. The permuted *P* value for each SNP is the proportion of permutations on which the test statistic for any SNP exceeds the test statistic found in the standard (unpermuted) association analysis for that particular SNP. These permutation analyses control for type 1 errors, because the null distribution of test statistics is accurately defined for the particular phenotypic data gathered.

Loci that achieved a *P* value of less than 0.05 in the permutation analyses were imputed over a region of 2.5 Mb surrounding the SNP of interest. We performed the imputation using the software IMPUTE2^{33,34} with the 1000 genomes phased haplotypes.³⁵ Association analyses of the imputed regions were carried out on the genotype probabilities using the dosage association function of PLINK. The three PCs and sex were added into the analysis as covariates as in the initial stage.

Finally, we performed a clumping analysis on our region of interest. We used PLINK's clumping function, with a significance threshold for index SNPs of 0.00001, a significance threshold for clumped SNPs of 0.01, a linkage disequilibrium (LD) threshold for clumping of 0.1, and a physical distance threshold of 1250 kb. Clumping analysis defines a region that is in linkage disequilibrium with the significantly associated SNP, and which contains other SNPs also associated with the trait with a specified *P* value. This region is therefore likely to contain the locus of interest, where the polymorphism causing the variation in phenotype lies.

RESULTS

Test–Retest Reliabilities

Test–retest reliabilities were based on 104 participants (data were unavailable for one returning participant). Reliabilities were high for the horizontal phorias (For far $\rho = 0.71$, $P < 10^{-16}$; for near $\rho = 0.68$, $P = 2 \times 10^{-15}$), and moderate for the vertical phorias (For far $\rho = 0.56$, $P = 8 \times 10^{-10}$; for near $\rho = 0.54$, $P = 4 \times 10^{-9}$). Figure 1 shows plots of data from session 1 against data from session 2 for our 104 returning participants, for each of the four phorias we measured. The Table gives the

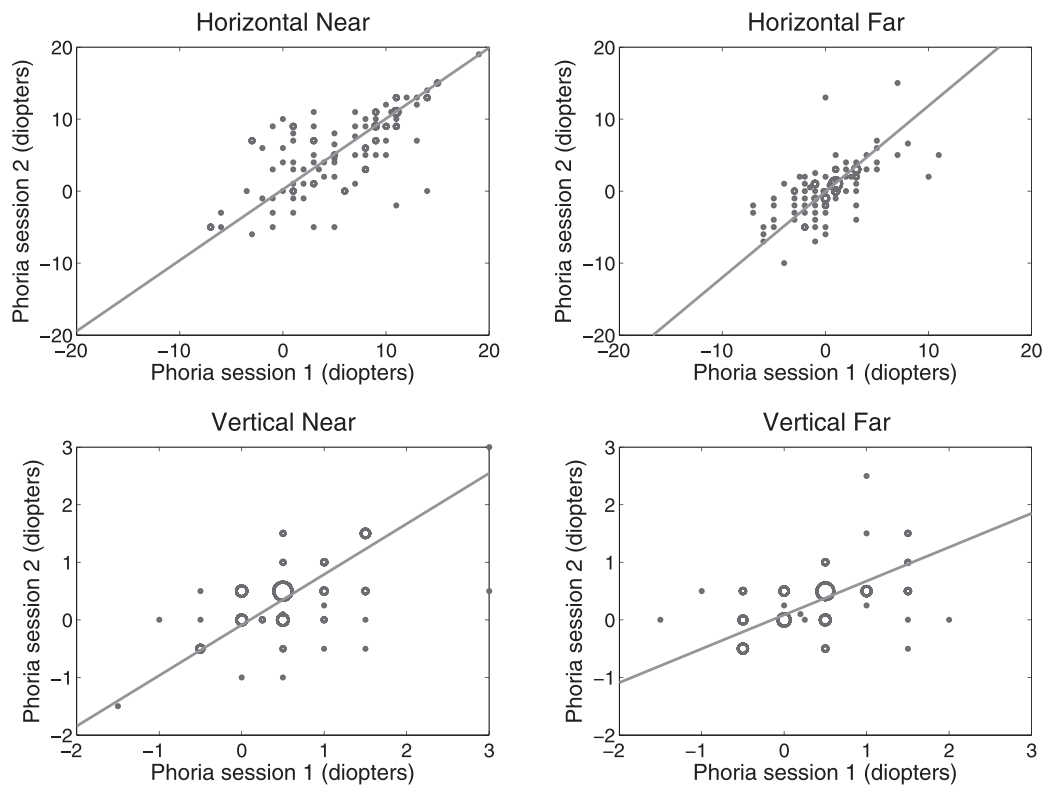


FIGURE 1. Scatter plots showing the test-retest reliabilities for horizontal and vertical near and far phorias. For each data point, the area of the marker is proportional to the number of participants sharing that point. The *grey line* is the orthogonal linear regression to the data. The Spearman coefficients for the correlation between session 1 phorias and session 2 phorias are 0.71 for far horizontal, 0.68 for near horizontal, 0.56 for far vertical, and 0.54 for near vertical.

alternative statistics of intraclass (C, 1) correlation coefficients and Pearson's correlation coefficients.

Phenotypic Distributions

Distributions of phorias for our whole sample are shown in Figure 2. Data for 1057 of our 1060 participants were available. Standard deviations (in prism diopters) were 5.32 for near horizontal phoria, 3.42 for far horizontal phoria, 0.791 for near vertical phoria, and 0.698 for far vertical phoria.

GWAS Results

Our criterion for deciding whether a SNP achieved genome-wide significance was that it should have a permuted P value of less than 0.05. One locus reached genome-wide significance for an association with near horizontal phoria. The locus contained three significantly associated SNPs: rs1569579, rs2744572, and rs807513, with unadjusted P values of 2.3×10^{-8} , 8.5×10^{-8} , and 8.6×10^{-8} , respectively. The permuted P values were 0.014, 0.048, and 0.046. The P value of the association with rs1569579 meets the currently accepted threshold for modern assays³⁶ ($P < 5 \times 10^{-8}$), and also survives a strict Bonferroni correction ($\alpha = 7.8 \times 10^{-8}$).

The linkage disequilibrium between rs1569579 and rs2744572 in our sample is $r^2 = 0.88$, calculated using PLINK, and the linkage disequilibrium between rs1569579 and rs807513 is $r^2 = 0.97$. Figure 3 shows a whole-genome Manhattan diagram for near horizontal phorias. The significantly associated locus is in chromosomal region 6p22, and rs1569579 lies in the fifth intron of the gene *ALDH5A1*. There were 27 further SNPs associated with near horizontal phoria to a level of $P < 10^{-7}$ in the region 1.25 MB on either side of

rs1569579. Figure 4 shows the associations between near horizontal phoria and genotyped and imputed SNPs in this region.

The minor allele frequency of the lead SNP rs1569579 was 9% in our sample. Each additional copy of the C allele was associated with a shift in phoria of 0.45 SDs in the direction of esophoria. Variation at rs1569579 explains 3.2% of the total variance in near horizontal phoria. Figure 5 shows distributions of near horizontal phoria for participants homozygous for the major allele (TT), and for heterozygous participants (CT). Since there were only six participants homozygous for the minor allele (CC), they are not represented in this figure.

Clumping analysis revealed a region spanning 159 kB associated with near horizontal phoria. This region contains the genes *GPLD1*, *ALDH5A1*, the last 10 exons of the gene *MRS2* and the last four exons of the gene *KIAA0319*.

Though no locus reached genome-wide significance for our three other measures of phoria (near and far vertical and far horizontal), the association between rs1569579 and far horizontal phoria has a P value of 8.1×10^{-5} . This is to be expected, since near and far horizontal phorias are related: they are significantly correlated in our sample ($\rho = 0.584$, $P < 0.001$). Because the two variables are significantly correlated, we also ran a multivariate genetic analysis including both horizontal and vertical phenotypes using TATES.³⁷ The probability returned by TATES that rs1569579 is associated with horizontal phoria was 4.1×10^{-8} . Since near and far vertical phorias were also significantly correlated in our sample, we also conducted a multivariate analysis using TATES with these two phenotypes. No loci significantly associated with vertical phoria were identified by the TATES analysis.

The association between rs1569579 and vertical phorias is very low ($P = 0.76$ for far vertical phoria, and $P = 0.59$ for near

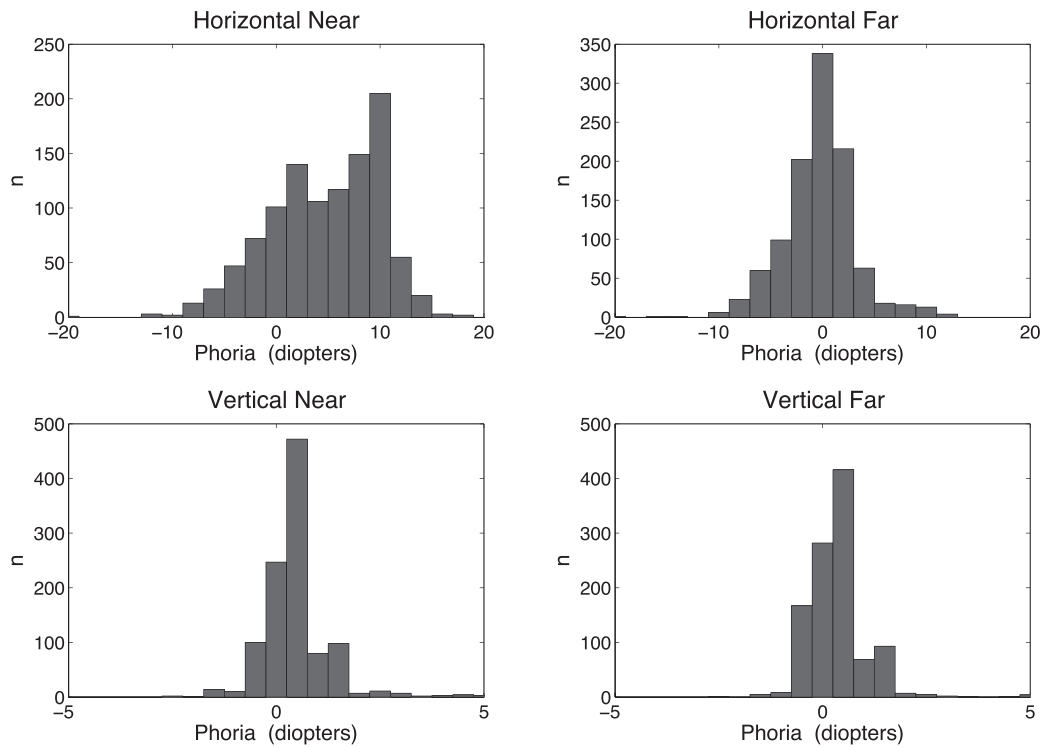


FIGURE 2. Distributions of near and far vertical and horizontal phorias for our 1057 participants.

vertical phoria). Again, this is not unexpected since the association between vertical and horizontal phorias is weak: in our sample, the correlations between vertical and horizontal phorias range from $\rho = 0.089$ ($P = 0.004$) between far vertical and far horizontal phoria, to $\rho = 0.01$ ($P = 0.75$) between near vertical and near horizontal phoria.

Interpupillary Distance

As part of the PERGENIC test battery we measured interpupillary distance by taking a photograph of the participants' eyes using a digital camera (DS126191; Canon, Tokyo, Japan) mounted at a distance of 105 cm. The mean interpupillary distance was 59.1 mm (SD: 3.2 mm; distance to point of fixation 100 cm). The test-retest reliability was 0.98, ($P << 0.001$). There was a weak but significant correlation between near horizontal phoria and interpupillary distance ($\rho = 0.089$, $P = 0.0035$). The association between our lead SNP for near horizontal phoria, rs1569579, and interpupillary distance had a P value of 0.0007. These relationships are not unexpected, since manifest phoria (strabismus) must contribute some of the variance in interpupillary distance, and may thus contribute to the variance shared between our measure of near horizontal phoria and rs1569579.

DISCUSSION

In a GWAS of phorias, we have identified one locus strongly associated with near horizontal phoria ($P = 2.3 \times 10^{-8}$; $P_{\text{permuted}} = 0.014$). The region containing the strongest association signal lies in the gene *ALDH5A1*. Independently, this gene is a very plausible candidate for being a source of variation in heterophoria and heterotropia.

ALDH5A1 encodes the mitochondrial aldehyde dehydrogenase (NAD⁺)-dependent enzyme succinic semialdehyde dehydrogenase (SSADH). This enzyme catalyzes the oxidation of succinic semialdehyde to succinate, the last operation in degradation of γ -aminobutyric acid (GABA). *ALDH5A1*, has two major alternative transcripts, and a single promoter region.³⁸ Blasi and colleagues³⁸ have suggested that various missense mutations in *ALDH5A1* may contribute to individual variability in SSADH activity.

Mutations of *ALDH5A1* cause the rare (and probably under-reported³⁹) recessively inherited disorder succinic semialdehyde dehydrogenase deficiency, otherwise known as gamma-hydroxybutyric aciduria.⁴⁰⁻⁴⁴ In GABA degradation, without SSADH, transamination of GABA to succinic semialdehyde is followed by reduction to the neuropharmacologically active compound 4-hydroxybutyric acid (GHB). GHB is found

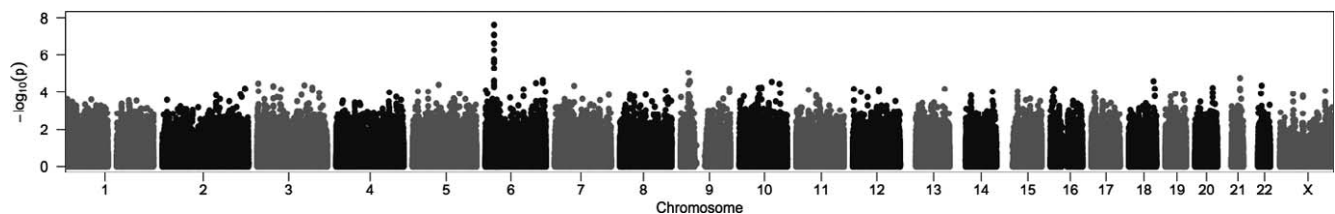


FIGURE 3. Manhattan diagram for near horizontal phorias. A locus on chromosome six reached genome-wide significance. The figure shows genotyped SNPs only, not imputed SNPs.

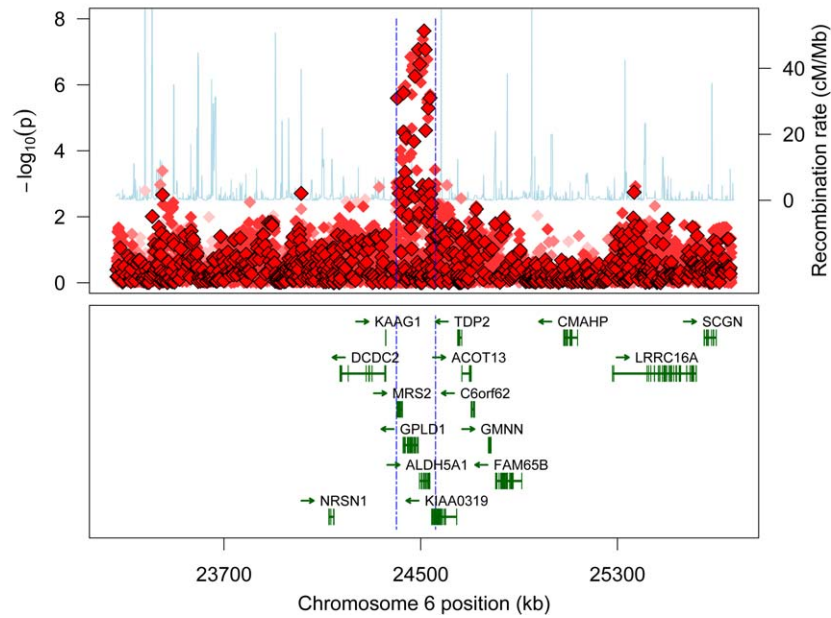


FIGURE 4. Manhattan diagram for the region around rs1569579. (Top) Association results for genotyped SNPs (red diamonds with black borders) and imputed SNPs (red diamonds with saturation corresponding to imputation quality). Recombination rate is plotted with a solid blue line. (Bottom) The genomic context of the region. Vertical rectangles indicate exons. (Both) Vertical blue dashed lines illustrate the region identified by clustering in which the underlying genetic polymorphism is likely to lie.

normally as a minor metabolite of GABA, but builds up, with GABA, in the brains of those suffering from SSADH deficiency.

The clinical features of SSADH deficiency include mental retardation, delayed language and motor development, hypotonia, seizures, behavioral problems, ataxia, and hyporeflexia.^{45,46} Especially pertinent to the present study is the fact that SSADH deficiency has been associated with strabismus.^{45,46} However, owing to the rarity of SSADH deficiency (only a few hundred cases worldwide), most reports are of single cases or of a small number of cases. It is therefore difficult to assess accurately the incidence of strabismus in SSADH deficiency, especially since it may be omitted from case reports to give precedence to the more debilitating clinical features of the disorder.

Also linking *ALDH5A1* to strabismus is valproic acid. Valproic acid is used as a drug to increase levels of GABA, probably by inhibiting SSADH.^{47,48} Exposure to valproic acid in utero causes fetal valproate syndrome, associated with a number of abnormalities, which include strabismus.^{49,50}

ALDH5A1 knockout mice have been studied as a model for SSADH deficiency. The mice show ataxia, seizures, and failure to thrive. Seizures are lethal around postnatal day 25.⁵¹ The brains of the knockout mice have increased levels of GABA and decreased levels of glutamine,⁵² and show reduced expression and impaired function of GABA(A) and GABA(B) receptors,⁵³ myelin abnormalities,⁵⁴ and lipid abnormalities.⁵⁵ *ALDH5A1* knockout mice can be partially rescued by administration of vigabatrin, NCS382 (a GHB receptor antagonist), CHP 25348 (a GABA[B] receptor antagonist), taurine, and a ketogenic diet.⁵⁶

Variation in *ALDH5A1* has been associated with clinical conditions other than SSADH deficiency, including schizophrenia,^{57,58} mild developmental delay accompanied by increased SSADH activity,⁵⁹ and epilepsy.^{60,61} Variations in the gene *ALDH5A1* in normal, healthy adults have been associated with intelligence,^{62,63} and with cognitive functioning and survival in old age.⁶⁴

Though the pathway by which *ALDH5A1* might influence ocular alignment is unclear, we can suggest one possibility. It

has been suggested that one factor in the etiology of strabismus might be delayed myelination, causing early disturbance of oculomotor reflexes.^{65,66} Variation in *ALDH5A1* may cause variation in myelination, since knockout mice have myelin abnormalities.

The three other genes present in the region identified by clustering are *MRS2*, *GPLD1*, and *KIAA0319*. *MRS2* encodes a magnesium transporter protein thought to mediate the influx of magnesium ions into the mitochondrial matrix.⁶⁷ *GPLD1* encodes a phospholipase that leads to the release of proteins anchored by phosphatidylinositol glycans from attachment to plasma membranes.⁶⁸ Neither is an obvious candidate for variation in phorias. *KIAA0319* encodes a transmembrane protein involved in neuronal migration during brain development.⁶⁹ Its association with dyslexia has given it the alias

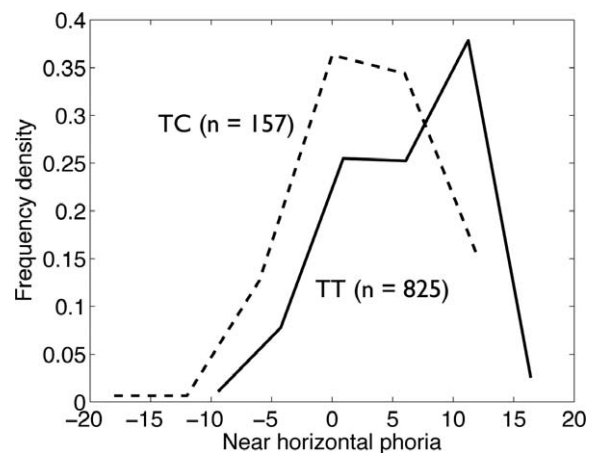


FIGURE 5. Distributions of near horizontal phorias for participants with different genotypes at rs1569579. Heterozygotes (TC) are indicated by the dashed line and homozygotes (TT) are indicated by the solid line. Each additional copy of the C allele shifts phoria by 0.45 SDs in the direction of esophoria.

TABLE. Test-Retest Reliabilities for the Four Measures of Phoria

	Spearman's rho; <i>P</i>	Pearson's <i>r</i> ; <i>P</i>	ICC (C,1); <i>P</i>
Near horizontal	0.68; 2.2×10^{-15}	0.70; 2.4×10^{-16}	0.7; 1.1×10^{-16}
Far horizontal	0.71; $<1 \times 10^{-16}$	0.65; 1.1×10^{-13}	0.64; 6.7×10^{-14}
Near vertical	0.54; 3.8×10^{-9}	0.59; 2.9×10^{-11}	0.59; 1.4×10^{-11}
Far vertical	0.56; 8.4×10^{-10}	0.47; 5.6×10^{-7}	0.45; 6.3×10^{-7}

ICC, intraclass correlation coefficient.

We consider Spearman's rho to be the most suitable measure of reliability since the distributions of phorias in our sample are not normal. *N* = 104.

Dyslexia Susceptibility 2 (DYLX2). *KIAA0319* is associated with alterations in white matter: knockdown mice have a reduction in the midsagittal area of the corpus callosum,⁷⁰ and variation in *KIAA0319* in humans is associated with variation in white matter volume in the temporoparietal region.⁷¹ Since the innervation of ocular muscles might be a factor in the etiology of phorias, *KIAA0319* is also a plausible candidate for causing variation in phorias. We note that phoria and strabismus have sometimes been associated with dyslexia,⁷² and dyslexia has been controversially treated using prisms.⁷³ However, there are also reports that dyslexia is not associated with the presence of binocular abnormalities.^{74,75}

Phoria and Strabismus

Combining their own measurements of phorias in twins with a meta-analysis of previous studies of strabismus in twins, Wilmer and Backus⁴ made the interesting suggestion that phorias are not heritable whereas strabismus is. Could the presence of a small number of strabismics in our population be driving the association we report here? We think this is unlikely for two reasons. First, Figure 5 shows that the difference in phoria by genotype does not depend upon a few outliers, but reveals itself in a shift of the entire distribution. Second, following Wilmer and Backus,⁴ we took failure on the TNO test (16th edition, Laméris Ootech B.V., Nieuwegein, The Netherlands; stereo-acuity worse than 480 arc seconds) as an (over-conservative) surrogate indicator of strabismus, and re-analyzed our data eliminating such participants (*n* = 94). We found only a modest increase in the *P* value for the association between near horizontal phoria and rs1569579 to 7.7×10^{-8} , an increase consistent with the reduction in the number of participants entered into the analysis.

In fact, our genetic association is not incompatible with Wilmer and Backus⁴ negative finding in their twin study of heritability of phoria. The confidence intervals on their correlation coefficients for the concordance of MZ twin pairs and of DZ twin pairs are compatible with the 3.2% genetic effect that we find here.

CONCLUSIONS

In conclusion, our results indicate that a locus in 6p22.2 is associated with near horizontal phoria. The most strongly associated variant is in the gene *ALDH5A1*. Though the effect size is large by GWAS standards, it is likely to be inflated to some degree by the winner's curse,⁷⁶ and this should be considered for future replication designs. Independent replication would be a vital next step, with exploration of the biological pathway by which *ALDH5A1* may exert its effect on phoria.

Given the occurrence of ocular deviation in a range of neuropsychiatric conditions, phorias may prove useful as a relatively easily measured endophenotype: elucidating their genetic basis may provide a clue to the basis of more complex phenotypes.

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