Smooth Pursuit Ocular Motor Dysfunction in Schizophrenia: Evidence for a Major Gene

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Objective: Evidence suggests that poor eye tracking relates to genetically transmitted vulnerability for schizophrenia. The authors tested competing models for the genetic transmission of poor eye tracking in a search for major gene effects. Method: Samples from three studies (conducted in Minneapolis, New York, and Vancouver, B.C.) were pooled. Probands (N=92) were diagnosed as schizophrenic by DSM-III criteria. Of the comparison subjects (N=171), Vancouver patients were an epidemiologic first-episode group; at other sites selected admitted patients were studied. First-degree relatives (N=146) of 65 probands were also studied. Eye tracking was measured while subjects followed a horizontally moving, sinusoidally driven (0.4 Hz) spot of light on a screen. Performance was quantified by root mean square error. Data analysis was by complex segregation analysis (Bonney's class D regressive models). Results: A single major gene is needed to account for poor eye tracking in schizophrenic patients and their relatives. This gene alone can explain about two-thirds of the variance in eye tracking performance. A single gene alone (regardless of dominance) will, however, not account for the data; polygenic factors are also required. Conclusions: Results support postulation of a single gene for ocular motor dysfunction, which may be a risk factor for schizophrenia. Eye tracking may be useful as a genetic test in genetic studies of schizophrenia.

(AM J Psychiatry 1992; 149:1362-1368)

Well-conducted family, twin, and adoption studies support the role of genetics in the transmission of schizophrenia (1–3), although risks to relatives vary among studies (2, 4). The literature justifies the conclusion that a single gene alone cannot account for transmission of schizophrenia (3, 5). It is nonetheless possible that a single gene contributes strongly to risk. A chromosome 5 translocation family (7) and an English-Icelandic linkage study (8) suggest a role for a gene on chromosome 5. However, replication attempts have failed (9, 10).

It may be the case that a major gene, in addition to numerous other genes that are individually not very influential, accounts for risk. Gottesman and McGue (11) recently demonstrated that a moderately common allele of relatively modest effect on risk (10% risk for schizophrenia), together with polygenic factors, can account for the data (12). Two, three, or more genes can also be used to account for the empiric risks (13).

One reason it may be hard to find a gene for schizophrenia is low penetrance (probability of manifesting schizophrenia given a susceptible genotype). For example, if a dominant gene accounted for the transmission of schizophrenia, half of parents and siblings would be carriers. Since roughly 6%–10% of these develop schizophrenia in pre-DSM-III studies (2) versus less than 6% under DSM-III (4), risk to carriers would lie in the range of 12%–20%. This would make it hard to decide whether a nonschizophrenic relative was a gene carrier (14). Prospects of finding a major gene could improve if one had a good carrier test. With suitable carrier tests, and given a strong effect of a putative gene on schizophrenia risk, one could sort relatives by risk category.

Perhaps the currently most promising way to detect putative gene carriers for schizophrenia is eye tracking dysfunction (15, 16). This abnormality has a low base rate (4%–5%) in normal subjects and their relatives (17), is temporally stable (18), and is found in a specific subset of schizophrenic patients and their relatives (17, 19). Eye tracking dysfunction also correlates with schizotypal personality features in relatives of schizophrenic patients (20, 21).
Recent research has demonstrated that measures of eye tracking dysfunction are bimodally distributed in patients with schizophrenia and in their relatives (17, 22). Further, lacono et al. (23) studied eye movements in Bassett et al.'s (7) trisomy 5 family and showed that the two schizophrenic, partially trisomic members had eye tracking dysfunction while the three non schizophrenic, nontrisomic members did not. This suggested an association between eye tracking dysfunction and a genetic abnormality conjecturally tied to schizophrenia.

Two published studies of the familial distribution of schizophrenia and smooth pursuit eye movement dysfunction by Matthysse, Holzman, and colleagues (24, 25) used a "Mendelian latent structure analysis" model, which presumes that the only genetic cause common to schizophrenia and eye tracking dysfunction (in schizophrenic patients' families) is a dominant gene. Neither of these studies tested for a major gene effect against models incorporating only polygenic factors, as needs to be done (26). Further, family and twin data show that a single gene cannot account for the transmission of schizophrenia (12, 13, 27). The data of Matthysse, Holzman, and colleagues, as presented, therefore, neither compel nor uniquely favor a single-gene hypothesis (27-29).

The Mendelian latent structure model makes predictions about familial resemblance for schizophrenia and/or eye tracking dysfunction. If a major gene affects risks for schizophrenia and ocular motor dysfunction, it follows that the gene affects the risk for each trait alone. Therefore, one can test the theory of Matthysse, Holzman, and colleagues by looking at ocular motor dysfunction alone.

In this report we improve on previous efforts to identify single-gene influences on schizophrenia in three ways. First, instead of examining diagnosed schizophrenia, we use a presumably simpler trait, ocular motor dysfunction, specifically related to schizophrenia risk. Second, unlike Matthysse, Holzman, and colleagues (24, 25), we use a quantitative indicator of ocular motor dysfunction rather than dichotomous ratings of eye tracking dysfunction. Maclean et al. (30) showed that using quantitative traits improves the power of genetic analyses. Third, we directly test whether single-gene models fit the data by using standard statistical tests.

METHOD

Subjects

Subjects came from three separate studies in Minneapolis (21), New York (22), and Vancouver, B.C. (17). Probands were recruited from consecutive hospital admissions (Minneapolis, New York) or patients with consecutively reported first onsets of psychosis in a community network (hospitals, clinics, private practitioners, and counseling bureaus in Vancouver). All met DSM-III criteria for schizophrenia on the basis of structured interview. Details of subject selection and diagnosis are given in the cited reports.

Lists of first-degree relatives were compiled from patients and informant relatives. Relatives over age 15 years who lived in specified areas around study centers (e.g., 250-mile radius in Minneapolis) were invited to participate. Informed consent was obtained. Relatives were evaluated by structured interview (Diagnostic Interview Schedule [31] in Vancouver; Structured Clinical Interview for DSM-III [32] for other sites) for DSM-III schizophrenia. At two sites (Minneapolis and New York) relatives were also evaluated for schizophrenia-related personality disorders (with the Schedule for Schizotypal Personalities [33]). Last, subjects' eye movements were studied. The reader should note that our sampling scheme did not select for or against families that had multiple individuals with schizophrenia.

Community comparison subjects were obtained in Minneapolis and Vancouver. Recruitment involved screening family practice clinic visitors (Minneapolis) or by soliciting volunteers from community institutions (Young Men's Christian Association, union halls, family practices, and community colleges in Vancouver). Normal subjects were screened to exclude those with a personal or family history of psychotic disorders. These comparison subjects were used only for preliminary analyses (discussed later), not for genetic analyses.

Assessment of Eye Tracking Dysfunction

Details of stimulus presentation, response recording, and scoring are given elsewhere (17, 20, 21). Procedures were quite similar across sites. Briefly, a 0.4-Hz sinusoidally driven electronic target oscillated horizontally across a display screen. The target simulates the motion of a pendulum, but rather than transcribing an arc, its movement was restricted to one dimension. The stimulus traverse subtended 20° of visual arc. Eye tracking was recorded for 12 cycles of target motion. For two samples (Minneapolis and Vancouver), eye movements were recorded by electro-oculogram (EOG), while the New York study used infrared recording, digitized at 128 samples. These two types of recording yield measures that correlate very highly (18). Nevertheless, to ensure similarity across samples, all ocular motor recordings were filtered with a 30-Hz low-pass Blackman filter, preserving actual eye movements while reducing non-eye movement signals often found in the EOG.

Eye movements were scored by using a method developed by Iacono and Lykken (34). Each cycle of tracking and target motion was centered and normalized to eliminate amplitude differences between recordings of eye and target movements. When eye position lags behind the target (as it usually does), a phase difference occurs that can artifically inflate eye tracking dysfunction scores. Therefore, target and eye channels were aligned so as to produce maximal cross-correlation between eye and target channels, minimizing this artifact. The squared difference between target and eye
position was then computed for each digitized sample, and for each cycle the square root of the mean of these squared differences was computed. The median of these cycle-by-cycle error measures constitutes the root-mean-square-error measure of eye tracking dysfunction analyzed in this report. Root mean square error thus provides an estimate of the degree to which a subject’s eye movements resemble the motion of the target. All scoring was done in a manner that was blind to subject status and diagnosis.

The root-mean-square-error measure is a relatively global one, which indicates how bad eye tracking is without specifying how it is deficient. We chose it nonetheless because previous work has shown that it has desirable properties for behavior genetic analyses. It has high test-retest reliability (18), shows heritability in twins (34), is bimodally distributed in schizophrenic patients and in their relatives (17), and correlates highly with neuro-ophthalmologic measures of eye tracking dysfunction (e.g., oculomotor gain; reference 22).

**Statistical Analyses**

We compared samples before pooling them, using one-way analysis of variance. We also looked for age effects (by correlation) and sex effects (by t test) on eye tracking.

We then corrected for distributional skewness in root mean square error. Skewed variables cause problems because skewing can lead to simulation of major gene action (35). One remedy is to fit a skewness-reducing transformation along with the genetic model, but this often leads to trouble with parameter estimation. Therefore, we instead estimated a standardized Box-Cox power transform (36) to the comparison subjects’ data. The Box-Cox method is flexible, allowing for sophisticated transformations. Logarithmic, square root, and other commonly used transformations occur as special cases of the Box-Cox transform. We estimated a Box-Cox transformation that essentially abolished skewness of root mean square error in our comparison group and applied this same transformation to our patients’ families. Because almost all comparison subjects should be free of a relatively uncommon schizophrenia-proneness gene, it is unnecessary to consider major gene effects in this sample. Schizophrenic patients’ family data were then transformed (using comparison subjects’ transformation) before genetic analysis.

We carried out segregation analyses on transformed root mean square error in schizophrenic patients’ families. Segregation analysis is a statistical methodology used to determine the mode of inheritance of a trait from family data. This procedure provides for the evaluation of goodness of fit between an inclusive model and a series of nested models in an effort to refute nested models of interest. Each model yields a likelihood statistic that indicates the probability of observing the data, given that the model is correct. The model fit is evaluated by calculating likelihood ratio $\chi^2$ tests that indicate whether the nested model can be rejected.

That is, if the $\chi^2$ test is significant, the data do not fit the nested model. A nonsignificant $\chi^2$ indicates that the nested model cannot be rejected.

We used the Statistical Analysis for Genetic Epidemiology program REGC (version 3.0) (presented by R.C. Elston et al. at a conference in 1986), which computes Bonney’s class D regressive models (37), making three main assumptions. First, there are just three familial influences on eye tracking dysfunction: major genotype, regression on parental eye tracking dysfunction values, and residual sibling resemblance in eye tracking. Second, the gene is a two-allele autosomal locus. Third, within major genotypes, siblings share a common regression on parental values and also share a common correlation with other siblings.

The following is a conceptual outline of the regressive segregation analysis models we used. The models are regression (i.e., prediction) models. They predict offspring genotype from parental genotype according to definite transmission rules, and they predict all the phenotypes (here, eye tracking scores) from the genotypes. These models incorporate both transmission due to major genes (i.e., following Mendel’s laws of segregation) and transmission from parent to offspring such as occurs with polygenic inheritance (as when the average height of offspring lies midway between the parents’ heights).

The models test the data for consistency with the following predictions, which are derived directly from genetic theory: 1) presence of parent-offspring (vertical) transmission, 2) tendency of eye tracking dysfunction scores to sort into distinct classes of dysfunction (i.e., multimodality or distribution admixture), 3) resemblance between parents and offspring, and among siblings, on eye tracking dysfunction scores that follow Mendelian ratios, and 4) resemblance between siblings over and above that found between parents and offspring. Placing the first test is, of course, required by any genetic model. The second tests whether “segregation” (tendency either to get or not get abnormal eye tracking, without in between cases) is occurring. The third test assesses whether any ostensible segregation is of a kind consistent with genetic, as opposed to, for example, environmental, transmission from parent to offspring. The fourth and final test tells us whether polygenic factors, in addition to a major gene, may be at work.

To capture all these phenomena requires a complex model. The models fit had the following parameters: $q$ (frequency of genetic allele $A$ causing eye tracking dysfunction); $\mu_{AA}$, $\mu_{AB}$, and $\mu_{BB}$ (transformed root mean square errors for major genotypes $AA$, $AB$, and $BB$); $\sigma^2$ (the within-genotype variance); $\rho$ (the result of equating $\rho_{AA}$, the regression of offspring on parent, and $\rho_{AA}$, the residual sibling correlation—see later discussion); and $\tau_{AA}$, $\tau_{AB}$, and $\tau_{BB}$ (probability of transmitting an “allele” $A$ for major genotypes). We assumed random mating with respect to eye tracking dysfunction, Hardy-Weinberg genotype proportions, no sex effect on root mean square error, and that mother-off-
TABLE 1. Characteristics of Schizophrenic Patients, First-Degree Relatives, and Normal Comparison Subjects in a Study of Genetics of Ocular Motor Dysfunction

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Women</th>
<th>Age (years)</th>
<th>Root Mean Square Error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
</tr>
<tr>
<td>Proband</td>
<td>92</td>
<td>26</td>
<td>25.6 7.3</td>
<td>189.0 144.9</td>
</tr>
<tr>
<td>Relatives</td>
<td>146</td>
<td>80</td>
<td>42.4 15.3</td>
<td>176.6 151.9</td>
</tr>
<tr>
<td>Comparison subjects</td>
<td>171</td>
<td>91</td>
<td>33.6 14.6</td>
<td>141.4 107.7</td>
</tr>
</tbody>
</table>

spring, father-offspring, and sibling-sibling correlations were all equal. These assumptions appeared justified by our data (see later discussion). In contrast to other computer programs for segregation analysis, to test for no polygenic contribution to a trait, one fits a model that constrains correlations between biological relatives all to be zero.

Parameters were estimated by maximum likelihood, using direct search of the likelihood surface (starting from various initial parameter values), followed by Newton-Raphson iterations. Differences in log-likelihoods for various models yielded likelihood ratio χ² tests of model adequacy (see later discussion).

Since families were sampled by virtue of having a schizophrenic proband, an ascertainment correction needs to be made. We adopted a suggestion made by Elston (personal communication), namely, that one correct for ascertainment by conditioning on the proband's exact root mean square error score.

RESULTS

Subject Participation and Description

We recruited 92 schizophrenic patients; no family contained two probands. There were 146 participating first-degree relatives of 65 of these probands. We also studied 137 normal comparison subjects and 34 of their relatives. Sixty percent of all eligible relatives (i.e., over age 15 and living within specified geographical radii of our study centers) were studied in the laboratory. Table 1 shows descriptive statistics for subjects. Table 2 breaks down the numbers of families according to how many and what kind of relatives were tested. A large number of schizophrenic patients (N=27) had no evaluated relatives. These subjects were retained in data analyses because they help estimate the rate of eye tracking dysfunction in probands. This in turn improves our estimated frequency of the genetic allele influencing eye tracking dysfunction.

Among relatives, there were five schizophrenic patients (Weinberg short method morbidity risk=4.3%, risk period=15–45 years) in five different families. Eye tracking data were available for four of these. For the two samples in which schizotypal personality was evaluated, 11.8% of relatives qualified for a definite DSM-III diagnosis. These values are close to those observed by Baron et al. in a similar family study (38). Since analyses with and without the schizophrenic relatives yield similar conclusions, we kept schizophrenic relatives in the sample.

Preliminary Analyses

Our three samples of probands did not differ significantly on root mean square error (F=0.94, df=2, 86, p<0.40). However, relatives did differ (F=14.23, df=3, 142, p<0.001). This difference was entirely due to the Minneapolis sample relatives' lower root mean square errors. Three considerations led us, nevertheless, to pool all samples for this report. First, bimodality (confirmed by skewness-correcting admixture analysis) was found in both pooled New York–Minneapolis and Vancouver samples (17, 22). Second, results of genetic analyses were similar when all three samples were used or the Minneapolis sample was excluded. Third, the same significance test results for model adequacy occurred from including or excluding the Minneapolis sample. Therefore, sample heterogeneity does not account for our findings. We would have tested genetic models for the Minneapolis sample alone to check this further, but the sample was too small.

There were no significant sex differences on root mean square error for members of schizophrenic patients' families. While the age effect was significant, it accounted for just 4% of the variance. Analyses of age- and sex-adjusted data were completely consistent with those from raw data, so only raw data are used here.

Root mean square error was positively skewed (coefficient of excess=2.72). The estimated parameters required to eliminate skewness in comparison subjects were λ₁=−0.24 (power parameter) and λ₂=-36.50 (offset parameter). This means that the lower the transformed score, the worse the eye tracking performance.

We looked for evidence of assortative mating. The estimated spousal correlation (after allowing for genetic transmission) was −0.36 (SD=0.34, not significantly different from zero (χ²=0.93, df=1, p<0.40). We also tested whether parent-offspring and sibling-sibling correlations differed. If they did, then we would need to fit these correlations separately. They were estimated as 0.29 and 0.32, respectively, not significantly different (χ²=0.16, df=1, p<0.70). Therefore, in further analyses

TABLE 2. Number of Families in a Study of Genetics of Ocular Motor Dysfunction, by Number of Relatives Evaluated

<table>
<thead>
<tr>
<th>Number of Siblings Evaluated</th>
<th>0 Parents Evaluated</th>
<th>1 Parent Evaluated</th>
<th>2 Parents Evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Includes one family in which both the proband and an offspring were evaluated.*
we assumed that assortative mating was absent and that there was only one distinct correlation rho to be estimated, to which parent-offspring and sibling-sibling correlations were equal.

**Segregation Analyses**

Results appear in table 3. Column heads denote genetic parameters (see earlier discussion). In the three columns headed "\( \tau_{AA} / \tau_{AB} / \tau_{BB} \)" each row specifies a different model. A significant \( \chi^2 \) means that a model can be rejected.

Before we can test the genetic hypotheses of interest, we need a null hypothesis model to serve as a yardstick. This model should be one that fits the data parsimoniously. It must include parameters corresponding to all the genetic models that we wish to test. If it does not, differences between log-likelihoods for the models being compared will not generally be distributed as \( \chi^2 \) and we cannot compute significance levels.

Therefore, the first lines of table 3 compare two candidate null models, the free tau and mixed models. Both models are very general, having a major gene as well as polygenic-like effects. The free tau model differs from the mixed model in that the former allows the "gene" not to act like a real gene. That is, its segregation is not required to be Mendelian. We illustrate this difference with an example: in the mixed model, the offspring of an AB genotype × AB genotype mating are required by Mendel's laws to have genotypes AA, AB, and BB in proportions \( 1/4 \), \( 1/2 \), and \( 1/4 \) (ignoring sampling variation), which proportions are generated by the assumption that \( \tau_{AB} = 0.5 \). Also in the mixed model, an AAXA mating can produce only AA offspring because each parent transmits the allele A to all its offspring (symbolized \( \tau_{AA} = 1 \)); similarly, \( \tau_{BB} = 0 \) under the mixed model. By contrast, in the free tau model, the ts may lie anywhere between zero and one. Therefore, the comparison between the first two tables lines tests whether the major "gene" acts like a real gene and follows Mendel's laws.

In fact, the mixed model fits as well as the free tau model. Furthermore, the estimated \( \tau_{AB} \) (first line) lies within 1 SE (0.38, SE=0.39) of its theoretical value, 0.5. Therefore, the inference that the major gene shows true Mendelian segregation is supported. This implies that the mixed model is the best standard against which to test the nonenvironmental models below it.

The next line, "Environmental," tests for presence of vertical (parent-offspring) transmission. In this model, there are three potentially distinct grades of eye tracking performance, but parental performance is not required to predict offspring performance. This is concretely modeled by assuming that, no matter what the parental "genotype," the probability of transmitting the tendency to have high root mean square error is the same, i.e., \( \tau_{AA} = \tau_{AB} = \tau_{BB} \). (The actual value estimated, 0.1, is immaterial here.) Therefore, rejecting this model amounts to affirming parent-offspring resemblance. Because the environmental model contains free parameters (three ts) that are constrained in the mixed model, the environmental model has, for technical reasons, to be tested against the free tau model rather than against the mixed model. (Since these two models have nearly equal likelihoods, here this makes little difference.) From the p value, we see that there is clearly significant vertical transmission. Therefore, the data are consistent with genetic transmission as opposed to, for example, sibling "contagion."

The next lines test specific genetic models of interest. The first two lines in the third part of the table test models in which all transmission occurs by a single gene. Whether one assumes that the allele A is dominant ("Dominant") or that heterozygotes can lie anywhere...
with respect to homozygotes ("Generalized single major locus" model), single-gene models are rejected. Therefore, the hypothesis of Matthysse, Holzman, and colleagues of strictly dominant major gene action is not supported.

The line labeled "Residual genetic" tests whether non-major-gene (quasi-polygenic) factors alone can account for the data. This model is concretely specified by requiring that the three major genotype groups have the same mean, i.e., by requiring $\mu_{AA} = \mu_{AB} = \mu_{BB}$. Again, the actual estimated value for these $\mu$s, 560.5, is immaterial here. This no-major-gene model is decisively rejected. Therefore, at least one major gene is required to account for the data; the polygenic model advanced by Gottesman et al. (2) for schizophrenia does not fit these eye tracking data. The major gene in the mixed model accounts for 68% of the variance in root mean square error.

In untabulated analyses, we also tested variants on the mixed model (second line) to see whether simple Mendelian patterns occurred. Purely dominant, exactly additive, and purely recessive patterns (working in concert with residual genetic influences) do not fit these data ($\chi^2 = 19.83$, df = 1, p < 0.001; $\chi^2 = 23.83$, df = 1, p < 0.001; and $\chi^2 = 23.83$, df = 1, p < 0.04, respectively). However, the favored mixed model, in the second line, is rather close to recessive ($\mu_{AB}$ is approximately equal to $\mu_{BB}$).

**DISCUSSION**

To our knowledge, these data provide the first rigorous evidence for a major gene affecting eye tracking dysfunction in fact, we believe that this is the first such demonstration for any schizophrenia-related biological trait. (Previously reported linkage of schizophrenia to chromosome 5 markers has not replicated.) Our results imply that schizophrenia itself may be influenced in some families by at least one single major gene (despite the inconsistent linkage data). Eye movement dysfunction may help detect gene carriers, potentially improving prospects for genetic analysis. This gene would presumably affect the risk of schizophrenia, but we decline at present to speculate how this might occur.

Matthysse, Holzman, and colleagues' dominant gene theory for eye tracking dysfunction and schizophrenia does not adequately fit our data in that their model proposes dominant gene action alone, while we find recessive action in addition to polygenic-like transmission. However, our results clearly and strongly support their central tenet, namely, a single major gene that influences eye tracking.

Our data do not prove that a single gene is at work. First, replication is needed. Second, other causes of apparent Mendelian segregation need to be considered. For example, McGuffin and Huckle (39) recently facetiously reported finding "the recessive gene for attending medical school." They "showed" that a major gene accounts for the familial nature of becoming a doctor. This example, while sobering, does not cast serious doubt on our results. Attending medical school is clearly a function of many influential life events, while eye tracking dysfunction is not subject to social selection or influence as far as we know. It is implausible that nongenetic factors happen to mimic a major gene for eye tracking dysfunction.

The potential role of platykurtosis (flattening of the distribution of eye tracking dysfunction scores) also needs to be considered. Eaves (40) gave examples in which correct/incorrect psychological test item scores are cumulated into a total score. If items are very good at discriminating whether individuals possess more or less than a specific (arbitrary) amount of the underlying ability measured by the test, then grossly platykurtotic scores can be found because the test has a distorted measurement scale. If the tested ability is heritable and if such a variable is subjected to segregation analysis, Mendelian segregation could be simulated. However, this is also not a major threat to our conclusions. Our data show not just platykurtosis but replicated outright bimodality (17, 22). This is hard to account for by deficiencies in scaling of the eye tracking dysfunction measure.

Objections might be raised that we should not have transformed our data before segregation analysis. Deciding whether to transform data can be a difficult problem. As pointed out earlier, analysis of untransformed but skewed scores can lead to false positive findings of major gene action. However, it is also true that transforming data to reduce skewness could lead to false negative results, at least when a very common gene of relatively modest effect is at work. Since the effect of transformation, then, is to lower power to detect a single major gene (without raising the risk of falsely finding a gene), and since our results strongly favor a major gene hypothesis, the problem of whether to transform the data does not vitiate our conclusions.

Our data also do not prove that only one major gene accounts for eye tracking dysfunction. Our models allow for heterogeneity only in having both polygenic and major gene causes of eye tracking dysfunction. We were not able to evaluate models that postulate two- or three-gene action. Study of such possibilities awaits general availability of more sophisticated computer programs.

An eye tracking gene may not account for most of the variance in schizophrenia risk. We have shown elsewhere (22) that eye tracking dysfunction accounts for approximately 25% of the variance in risk for a spectrum diagnosis (schizophrenia in addition to schizotypal personality) in schizophrenic patients' families. Any gene discovered here is probably only one cause of schizophrenia.

The analysis of eye tracking and other biological traits related to familial risk for schizophrenia may serve two useful functions. First, it may help us account for more of the risk for this disorder. Second, it may help break down the complex clinical presentation of schizophrenia into more simply inherited biological abnormalities.
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Am J Psychiatry 149:10, October 1992

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