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Replicated Linkage for Eye Color on 15q Using Comparative Ratings of Sibling Pairs

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The aim of the study was to perform a genetic linkage analysis for eye color, for comparative data. Similarity in eye color of mono- and dizygotic twins was rated by the twins' mother, their father and/or the twins themselves. For 4748 twin pairs the similarity in eye color was available on a three point scale ("*not at all alike*"—"*somewhat alike*"—"*completely alike*"), absolute eye color on individuals was not assessed. The probability that twins were alike for eye color was calculated as a weighted average of the different responses of all respondents on several different time points. The mean probability of being alike for eye color was 0.98 for MZ twins (2167 pairs), whereas the mean probability for DZ twins was 0.46 (2537 pairs), suggesting very high heritability for eye color. For 294 DZ twin pairs genome-wide marker data were available. The probability of being alike for eye color was regressed on the average amount of IBD sharing. We found a peak LOD-score of 2.9 at chromosome 15q, overlapping with the region recently implicated for absolute ratings of eye color in Australian twins [Zhu, G., Evans, D. M., Duffy, D. L., Montgomery, G. W., Medland, S. E., Gillespie, N. A., Ewen, K. R., Jewell, M., Liew, Y. W., Hayward, N. K., Sturm, R. A., Trent, J. M., and Martin, N. G. (2004). *Twin Res.* **7**:197–210] and containing the OCA2 gene, which is the major candidate gene for eye color [Sturm, R. A. Teasdale, R. D, and Box, N. F. (2001). *Gene* **277**:49–62]. Our results demonstrate that comparative measures on relatives can be used in genetic linkage analysis.

KEY WORDS: Comparative phenotypes; eye color; regression-based linkage.

INTRODUCTION

Genetic linkage analysis is based upon the co-segregation of phenotypes and genotypes within pedigrees. Phenotypes, such as disease status or quantitative traits, are usually measured in individuals that are informative for linkage, such as multigenerational families or pairs of siblings. For a number of proposed statistical analyses of linkage data, the genetic information is condensed into a measure of genetic similarity between relatives, essentially because linkage is about explaining within-family variation. For example, if sib pairs have been ascertained because both are affected with a disease, then a standard test for linkage is to compare the proportion of alleles shared identical-by-descent (IBD) at a particular locus with the expected value (of 0.5) under the null hypothesis of no linkage. Common methods for linkage assume that the trait of interest is measured on each individual, i.e. that two trait values are available per sib pair. For some traits, however, data may be best collected in terms of comparative ratings. Recently, Kirk *et al.* (2000) applied a method proposed by Eaves *et al.* (1991) to use comparative

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ratings of being bitten by mosquitoes in twin pairs to determine heritability. They found that the comparative rating ("*compared with your twin, who is bitten by mosquitoes more often?*") was more reliable than the individual self-ratings of how often each individual was bitten by mosquitoes. Kirk *et al.* (2000) hypothesized that whereas the ordinal scale in their study did not provide a widely recognized standard against which the personal experience of being bitten by mosquitoes can be compared, the comparison with one's co-twin does provide a convenient standard for comparison. Comparative ratings may therefore aid in assessing subjective experiences which may be difficult to quantify, but can easily be compared to others.

Many twin registries send out questionnaires that include items to determine the zygosity status of twins. These items are usually phrased in terms of the similarity between two siblings, for example: "*how alike are you and your twin for hair color, facial features, eye color, or body height?*". The traits used for these items are known for their high heritability. For example, eye color is one of the most heritable human traits with heritability estimates as high as 99% (Zhu *et al.*, 2004). Because of this high heritability, eye color has often been used as a model trait in genetic research. In fact, one of the first investigations into the concept of inheritance in humans was the consideration of eye color (Davenport and Davenport, 1907). In 1937, when Penrose first described how the relation between the similarity of a trait between pairs of sibs and the sibs' similarity in marker phenotypes provides information for linkage, he used eye color as an example (Penrose, 1937).

The physical basis of eye color lies in the distribution and content of the melanocyte cells in the uveal tract of the eye. Although the number of melanocytes does not differ between eye colors, the melanin pigment quantity, packaging and quality does vary, resulting in a range of different eye shades (Boissy, 1998; Imesch *et al.*, 1997; Prota *et al.*, 1998; Sturm and Frudakis, 2004). The apparently non-mendelian examples of eye color transmission from parents to offspring, combined with the quantitative nature of iris pigmentation indicate that the inheritance of eye color is influenced by several different genes (Badano and Katsanis, 2002; Sturm and Frudakis, 2004). In spite of its extremely high heritability and known physical basis, the underlying genetic polymorphisms that determine eye color diversity have not yet been identified.

Two recent investigations aimed at dissecting the genetic basis of human eye color. Frudakis *et al.* (2003) used a hypothesis-driven SNP screen, focusing on pigmentation candidate genes. They identified 61 SNPs that were associated with iris pigmentation. Most of these SNPs were in the leading candidate gene for eye color: the gene for oculo-cutaneous albinism type II (OCA2) on chromosome 15q.

Zhu *et al.* (2004) conducted the first genome-wide linkage scan for eye color using absolute ratings obtained by a research nurse in a sample of 502 families, consisting of 1205 individuals and 951 quasi-independent pairs. They found highly significant evidence for linkage on chromosome 15q (LOD-score 19.2) in the region containing OCA2.

We present a regression-based method for linkage that uses comparative ratings on sib pairs and apply this method to eye color.

METHOD

Sample and Trait Descriptives

Adolescent and adult twins from the Netherlands Twin Register and their parents participated in biannual longitudinal, survey based projects since 1991 (Boomsma *et al.*, 2002). Questionnaires have been completed by twins and their family members. All questionnaires included a question regarding the similarity in eye color for twins to determine zygosity status. In a subsample of same-sex twins, zygosity was available from DNA or blood group polymorphisms. Questionnaire and DNA/blood group zygosity was available for 869 pairs, showing an agreement of 97%. Based on DNA, questionnaire data, or on opposite sex status, 2167 were MZ twins, 2520 were DZ twins, and for 61 twin pairs zygosity was ambiguous.

Out of eight measurement occasions, the question on eye color of the twins was answered by the mother on four occasions, by the father on one occasion, and by the twins themselves on six occasions. Eye color similarity was rated on a three point scale ("*not at all alike*"—"*somewhat alike*"—"*completely alike*"). The probability that twins were alike for eye color (eye color similarity, s) was calculated from the response pattern on all questionnaires and all informants, by summing over the product of the three possible answer categories (where "*not at all alike*" was coded 0, "*somewhat alike*" was coded 0.5, and "*completely alike*" was coded 1) and their respective frequencies across all informants: P (alike for eye color) $= s = f$ (not at all alike) $\times 0 + f$(somewhat alike) $\times 0.5 + f$(completely alike) $\times 1$. For 4748 twin pairs eye color similarity was available.

Genotyping

For 294 DZ twin pairs genome-wide marker information as well as comparative phenotypic data were available. In 222 subjects, a 369 autosomal marker genome scan (9.44 cM spacing) was done by the Mammalian Genotyping Service, using microsatellite screening set 10 with few alternative markers. In 366 subjects, a 419 marker genome scan (8.34 cM spacing) was performed by the Molecular Epidemiology Section, Leiden University Medical Centre, The Netherlands (see Heijmans *et al.*, 2005). Fifty subjects were typed at both centers. For 38 pairs one parent was typed, while for 68 twin pairs both parents were typed. The number of typed markers for the 174 parents ranged between 344 and 392 (mean of 379 ± 8). For the 588 offspring, the number of typed markers ranged from 202 to 710, with an average of 406 (± 85) total markers.

Marker locations were taken from an integrated genetic map from the published DeCode and Marshfield maps (Kong *et al.*, 2002, 2004), with interpolated genetic map positions estimated via locally weighted linear regression (lo(w)ess) from the Build 34.3 (and 35.1) physical map positions. Mendelian errors were detected using PEDSTATS and unlikely double recombinants using MERLIN, which were both removed using PEDWIPE (Abecasis *et al.*, 2002). Pedigree relationships were checked with the GRR program (Abecasis *et al.*, 2001).

Statistical Analysis

The probabilities of sharing 0, 1 or 2 alleles IBD were computed for a 1 cM grid using the Lander-Green algorithm implemented in MERLIN (Abecasis *et al.*, 2002). This was then combined into an estimate of $\pi(\hat{\pi})$, where $\hat{\pi} = 0 \times p_{\mathrm{IBD}=0} + 1/2 \times p_{\mathrm{IBD}=1} + 1 \times p_{\mathrm{IBD}=2}$. A regression assuming a linear relationship between the probability that the twins are alike for eye color (similarity, s) and $\hat{\pi}$ was used to estimate genome wide evidence for linkage,

$$s_i = \alpha_j + \beta_j \hat{\pi}_{ij} + \varepsilon_{ij},$$

where s_i is the probability that the i-th twin pair is completely alike for eye color as defined earlier, α_j is the intercept, β_j is the regression coefficient of s on $\hat{\pi}_{ij}, \hat{\pi}_{ij}$ is the proportion of alleles shared IBD at location j for the i-th twin pair and ε_{ij} is the residual effect. The regression weight β denotes the difference in mean eye color similarity between sib pairs that are genetically dissimilar (IBD = 0) and sib pairs that are genetically similar (IBD = 2) at a certain position. Under the null hypothesis of no linkage, β is zero, whereas β is positive if there is linkage. Note that the test statistics for linkage are equivalent if the dependent and independent variables are swapped.

Evidence for linkage was evaluated for all genome-wide positions, by least squares linear regression analysis. The (F) test statistic was calculated as the ratio of the regression and the residual mean squares, which is equivalent to the ratio of the squared estimate of the regression coefficient and its estimated sampling variance. When the estimate of the regression was negative the test statistic was set to zero, that is, we performed a one-sided test of significance. This is commonly done in Haseman–Elston regression methods (Haseman and Elston, 1972) implicitly assumed in variance components linkage methods that require estimated variance components to be non-negative. Corresponding genome-wide p-values were determined through 100,000 permutation tests under the null hypothesis of no linkage.

RESULTS

The mean probability of being alike for eye color was 0.98 for MZ twins (2167 pairs), whereas the mean similarity for DZ twins was about 1/2 that for MZ twins at 0.46, suggesting very high heritability for eye color. For the 294 DZ twins included in the scan, the mean probability of being alike was 0.44 (Table I) The distribution of eye color similarity was non-normal showing three clear peaks. (see Figure 1).

The mean and variance of the test statistic over all positions from all 100,000 permuted samples (i.e., under the null hypothesis of no linkage) are 0.503 and 1.28, respectively. These are very close to the expected values (0.50 and 1.25, respectively) under normality, showing that the test statistic is approximately distributed as zero with a probability of 0.5 and a χ^2 distribution with 1 degree of freedom with a probability of 0.5 (e.g., Visscher and Hopper, 2001). The

Table I. Mean Similarity for Eye Color in MZ and DZ twins in the Dutch Twin Registry and for DZ twins Included in the Present Scan

	In genome scan	N pairs	Mean	SD
MZ	No	2167	0.98	0.09
DZ	No	2243	0.46	0.37
DZ	Yes	294	0.44	0.34

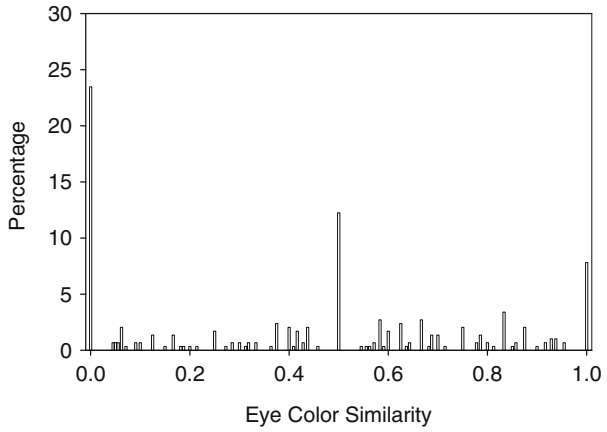

Fig. 1. Distribution of eye color similarity in the 294 twins included in the linkage scan.

genome-wide 5% significance threshold was a LOD of 2.81.

As the test statistic approximated a χ^2 distribution with 1 degree of freedom, we divided the genome-wide F test statistics by 2ln10 to obtain approximate genome-wide LOD scores. The peak LOD score was observed at chromosome 15 (LOD = 2.9), peaking at 7 cM at marker D15S128. The one LOD drop area is from 0 to 24 cM, between markers D15S817 and D15S1007, which includes the peak marker as reported by Zhu *et al.* (2004) (Figs. 2 & 3). The empirical chromosome-wide and genome-wide p-values were 0.0023 and 0.058, respectively. The 5% significance threshold for chromosome 15 was a LOD of 1.52.

Comparison with Zhu et al.

To compare our results based on comparative ratings with the results obtained using absolute ratings by Zhu *et al.* (2004), using 951 quasi-independent sib pairs, we reanalyzed their chromosome 15 data. Zhu *et al.* (2004) assessed eye color on a three point scale for each individual in the sample, rated by a research nurse. We converted this to a comparative rating by assigning 1 to pairs with the same rating on the 3-point scale and 0 to pairs with different ratings. The original LOD score of 19.2 dropped to 7.4 using the comparative rating method. A LOD score of 7.4 relative to our peak LOD score of 2.9 is approximately proportional to the sample sizes in both studies.

DISCUSSION

We presented a linkage approach based on a simple regression analysis that uses comparative phenotypes, assessed in pairs of relatives. Our peak LOD score of 2.9 on 15q was above the empirically derived genomewide threshold for significant linkage, and replicated the linkage result reported by Zhu *et al.* (2004). When we adjusted the data for the locus on chromosome 15q and performed a new genome-scan (data not shown), the next largest test statistics were LODs of 1.7 and 1.5, on chromosomes 12 and 11, respectively, which were slightly higher LOD scores than seen in the scan unadjusted for the 15q locus. Although these were not significant at the genome-wide level, the chromosome 11 peak is interesting as it is in a region that contains the tyrosinase gene (TYR, aka OCA1A on 11q14-11q21) which plays a role in melanine formation in the eye (Frudakis *et al.*, 2003; Oetting and King, 1993). The same regions on 11 and 12 showed modest peaks in the analysis of Zhu *et al.*, 2004.

The regression method is robust and because it is extremely fast it lends itself to computer-intensive resampling methods such as permutation testing to obtain significance and for example bootstrapping to estimate the confidence region of the trait locus. By performing a permutation test to assess significance, no explicit assumption is made about the distribution of the errors. Nevertheless, the average mean and

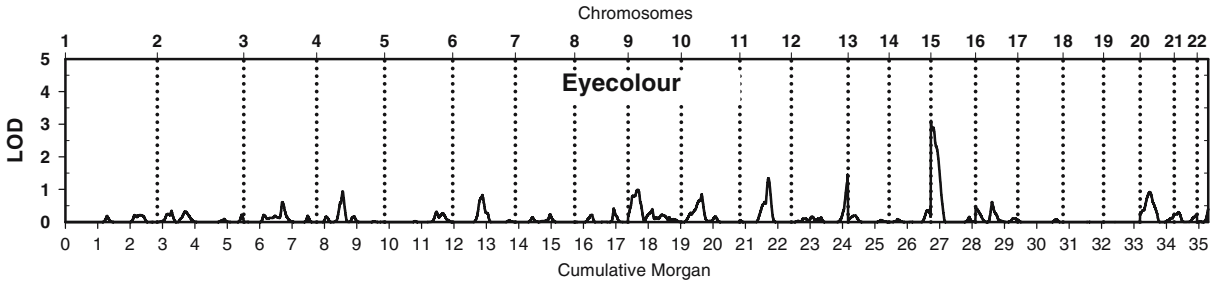

Fig. 2. Full autosomal genome scan for eye color using a regression based linkage methods for comparative ratings on 294 Dutch twins.

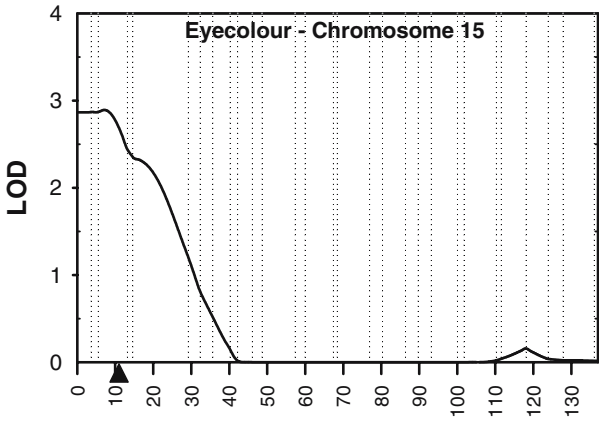

Fig. 3. Chromosome 15 region of significant linkage for eye color. The triangle marks the location of the linkage peak from Zhu *et al.* (2004) on 15q. Dotted lines represent the positions of the markers. The *x*-axis is in centiMorgan.

variance of the test statistic from permuted samples was close to values that were expected if the test statistic was distributed as zero with a probability of 0.5 and a χ^2 with 1 degree of freedom with a probability of 0.5. This is perhaps not surprising, because the test statistic of the original Haseman–Elston regression method, for which the dependent traits are squared differences, is also approximately distributed as a standard statistical distribution (e.g., Visscher and Hopper, 2001). Hence, regression methods appear to be robust with respect to the distribution of the data.

If we only had two classes of comparative scores, "alike" and "not alike", then our method is analogous to testing the difference in mean IBD scores between "concordant" (alike) and "discordant" (not alike) pairs, with weights proportional to the number of pairs in the two groups. Depending on the allelic spectrum and gene action of the 15q locus there could be more efficient weighting schemes to maximize power. For example, if variation in eye color were due to a single bi-allelic locus with a rare dominant allele, then most information on linkage would come from discordant pairs because they would not share the dominant allele from one of their parents. At the chromosome 15q locus, the mean IBD sharing of 69 pairs with a similarity score of exactly 0.0 was 0.399 (SE 0.035) and the mean IBD sharing of 23 pairs with a similarity score of exactly 1.0 was 0.542 (SE 0.052). When compared to the expected value of 0.5, using a one-sided test, these sharing statistics have *p*-values of 0.003 and 0.214, respectively.

In principle, an analysis of the full distribution of responses could be done using, for example, logistic regression, and this might improve power. Such an analysis should take account of two sources of heterogeneous variances in our data, namely (i) that the similarity scores close to zero and one are likely to have lower variance (assuming an underlying binomial distribution) and (ii) that mean similarity scores based upon more raters are likely to have lower variance. A weighted least squares linear regression analysis, using the number of raters as weight, resulted in a slightly lower maximum test statistic (results not shown) and was not pursued.

Although a method based on comparative ratings is less powerful than a method that uses absolute ratings—as illustrated by the drop in LOD score when reanalyzing the data from Zhu *et al.* (2004), comparative ratings of phenotypes may sometimes be more reliable to obtain than "absolute" measures on ordinal or interval scales (e.g. Kirk *et al.*, 2000; Swerdlow *et al.*, 2002). For example, in studies of late-onset disease, or in studies of elderly samples, self-report data of phenotypes such as birth-weight, age of onset of menarche, or age at first cigarette, may show low reliabilities. However, comparative ratings of twins (e.g. which sister, regardless of absolute age, entered menopause first) may show higher reliability. This was demonstrated in a study of Swerdlow *et al.* (2002) who looked at the relation of breast cancer in female twins and childhood characteristics such as height and weight at age 10. Absolute values for height and weight for a particular age during childhood are nearly impossible to obtain by self-report, but comparative ratings from twins show good inter-rater reliability. In addition, when two parents rate the behavior of their children they may easily disagree on the absolute scale of e.g. aggressive behavior (Hudziak *et al.*, 2003), whereas they do show strong agreement on which child is more aggressive than the other.

At least as important, comparative ratings can be used in longitudinal studies of ageing, in which DNA/marker data are available for twin pairs, but in which there is only one surviving twin to report on phenotypic traits (e.g. Christensen *et al.*, 2003). Comparative ratings provided by the surviving twin will in that case be the only source of information.

In summary, comparative phenotypes may sometimes be preferred over absolute phenotypes. We propose a simple regression method based on comparative ratings that is robust to non-normality and extremely fast. Applying this method to comparative ratings of eye color in a sample of 294 twins replicated the 15q region previously implicated in eye color.

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