Behavior Genetics, Vol. 36, No. 1, January 2006 (© 2006)
DOI: 10.1007/s10519-005-9010-2

Introduction to the Special Issue: Human Linkage Studies for Behavioral Traits

D. Posthuma,[1,3] S. S. Cherny,[2] and D. I. Boomsma[1]

In the post Genome era, the aim of behavior genetics has shifted from estimating the relative contributions of genes and environmental factors to (co-)variation in human complex traits, to localization of genes and identification of functional genetic variants. This special issue reflects this transition and presents fifteen papers that report on genome-wide linkage scans for complex traits in humans and on methodological tools and innovations. Six papers focus on cognition and report overlapping linkage peaks on chromosomes 6p and 14p. Papers on addictive behavior, i.e. smoking and alcohol dependence and its endophenotypes, find moderate LOD scores on chromosomes 6p, 5q, 4p and 7q, respectively. Three papers concentrate on emotionality, depression and loneliness and examine chromosomes 2q and 12q. The papers in this issue represent a summary of the first large scale linkage enterprises of human behavioral traits.

KEY WORDS: Addiction; depression; empirical *p*-value; intelligence; linkage methods; whole genome scan.

The past 5 years have seen a major shift in the aim of behavioral genetic research in humans. Whereas previously research in the field of behavior genetics was mainly concerned with unraveling the *nature* of the causes of complex trait (co-)variation, we are now aiming at detection of the actual genes and environmental factors. This special issue is concerned with detecting genes for complex, behavioral traits through whole genome linkage scans, and reflects the ongoing transition in our field, where we are moving "beyond heritability".

Whole genome linkage analysis provides a first step in gene finding by identifying genomic regions that contain quantitative trait loci—QTLs. The current special issue presents thirteen genome-wide linkage scans for behavioral traits from several domains, a technical note on two software applets that can aid in linkage analysis, as well as a contribution describing an integrated genetic map for linkage analysis. These fifteen papers centre around four main themes: Methods, Cognition, Addiction, and Depression/Anxiety.

Methods: Several studies in this issue have used the internet accessible database containing genetic map positions for over 12,000 loci, described by Duffy. Such an integrated map with publicly available map positions is indispensable to researchers using different marker sets that wish to compare their results or pool their data. The methodological note by Beeby *et al.* presents two Java utilities that aid in the interpretation of linkage results by providing a graphical representation of these results. It allows rapid detection of outliers as well as rapid comparison of univariate versus multivariate linkage results. The paper by Posthuma *et al.* reports on a novel regression based method for linkage that uses comparative ratings on sib pairs. The method is applied to comparative ratings of eye color as a model trait.

[1] Department of Biological Psychology, Vrije Universiteit, Amsterdam, The Netherlands.
[2] Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford, United Kingdom.
[3] To whom correspondence should be addressed at Department of Biological Psychology, Vrije Universiteit, Van der Boechorststraat 1, 1081 BT, Amsterdam, The Netherlands. Tel.: 31-20-5988814; Fax: 31-20-5988832; e-mail: danielle@psy.vu.nl

Although the use of comparative ratings compromises statistical power, the method is extremely fast and allows the calculation of empirical *p*-values through 100,000 permutations on a single processor within a day. A previously reported large LOD score for absolute ratings of eye color on 15q was replicated.

Cognition: Six papers in the current issue are concerned with intelligence and cognition in a broader sense. The papers by Hansell *et al.* and Singer *et al.* focus on memory functioning, a major component of cognitive functioning. Hansell *et al.* look at working memory as indexed by event related potentials (ERP) induced in a working memory task. After a stringent correction for multiple testing, their most promising finding lies on chromosome 10. Singer *et al.* looked at self reported prospective and retrospective memory, which is quite distinct from the concept of working memory, and found evidence for linkage on 12q and 18q but not on chromosome 10. The papers by Luciano *et al.*, Buyske *et al.* and Dick *et al.* report on linkage for intelligence, assessed with psychometric IQ tests. Both Luciano *et al.* and Dick *et al.* find evidence for linkage on 6p, replicating one of two earlier reported regions of interest (6p and 2q; Posthuma *et al.*, 2005). Most notably, all three papers report on (near) significant linkage on chromosome 14p, in an area spanning 32 cM. The two studies that use data from the COGA study report LOD scores in this area which range from 1.5 (Dick *et al.*) to 6.0 (Buyske *et al.*). The regional overlap from these studies strengthens the evidence for 14p. The paper by Wainwright *et al.* focuses on academic skills, which are correlated with intelligence. They find evidence for linkage on both 6p and 2q, but also on 18q, 10 cM away from the second highest LOD score for retro- and prospective memory functioning reported by Singer *et al.* These papers therefore clearly converge on several QTLs for cognition, although they also suggest the presence of at least some specific QTLs for different aspects of cognition.

Addiction: Three groups of researchers have scanned the genome for QTLs for addictive behavior. Vink *et al.* and Morley *et al.* focused on nicotine dependence. Vink *et al.* used the age at which the first cigarette was smoked, whereas Morley *et al.* used smoking vs. non-smoking. Although their highest LOD scores were reported in distinct areas, both Vink *et al.* and Morley *et al.* report (near) significant linkage on 6p and 5q.

In a review of the COGA study, Dick *et al.* show how endophenotypes can aid in the detection of linkage for alcohol abuse, and report on the GABRA2 and CHRM2 genes on chromosomes 4 and 7. These areas also show evidence for linkage in the study by Morley *et al.* confirming their role in addictive behavior. Dick *et al.* describe how both alcohol dependence and quantitative electroencephalographic (EEG) measures of brain functioning (beta power, P300) show significant linkage on chromosomes 4 and 7. The linkage peaks for the EEG measures were right on top of two candidate genes on chromosomes 4 and 7: the GABRA2 and CHRM2 genes. They further show a significant association between these genes and alcohol dependency. The use of EEG measures as endophenotypes for alcohol dependency is justified as a vast body of literature exists in which disturbances in EEG measures are related to alcohol abuse (e.g. Porjesz and Begleiter, 2003). EEG measures are generally used as a representation of the brain's *cognitive* functioning, implying that its relation to alcohol dependency or susceptibility to addiction might be mediated through cognitive disturbances. This is confirmed by the observation that at almost exactly the same region, the chromosome 7 QTL showed linkage both to the ERP induced in a working memory task (Hansell *et al.*) as well as to IQ in the study of Luciano *et al.* Moreover, the CHRM2 gene at 7q has previously been associated with IQ and years of education (Comings *et al.*, 2003). Gosso *et al.* (in press) have recently tested three single nucleotide polymorphisms in the CHRM2 gene and confirmed a strong association with IQ. This suggests that the CHRM2 gene may play a more general role in cognition and that its relation to alcohol dependency is mediated by cognitive (dys)functioning.

Depression/Anxiety: Beem *et al.* adapted a combined linkage and association approach in an attempt to replicate a previously reported association of a chromosome 2 marker and major depression in females. In spite of a relatively large sample size, they failed to replicate this association in females. However, they did find a weak association in males, but this was unsupported by significant linkage in this area. They conclude that the association of the chromosome 2 marker with major depression may not be so robust after all. Boomsma *et al.* focused on loneliness, which is an important component of many psychiatric disorders. Treating loneliness as an ordinal trait, they find suggestive evidence for linkage on 12q. This area has been implicated previously in psychiatric disorders such as schizophrenia, bipolar disorder and major depression, suggesting that this

region may contains genes that induce a general vulnerability to psychiatric disorders.

Using their well-known results for anxiety related traits, Fullerton *et al.* show how cross-species genetic information can be used to progress from a QTL to a quantitative trait nucleotide (QTN). Whereas linkage studies in human subjects will usually identify relatively large genomic regions containing hundreds of genes, complementary use of mouse models enables to reduce these intervals to areas containing a dozen genes.

All papers have used empirically derived thresholds to determine the significance of a linkage signal. These thresholds turned out to be lower than the guidelines provided by Lander and Kruglyak (1995), where a LOD $\geqslant 2.2$ stands for suggestive linkage and a LOD $\geqslant 3.6$ represents significant linkage. The guidelines provided by Lander and Kruglyak assume a quantitative trait, dense marker genotyping and near complete extraction of inheritance information. Experimental factors that influence the amount of information extracted from the data set such as pedigree structure, the completeness and accuracy of genotype data, and marker density are expected to have substantial effects, both on the power of a study to detect true linkage and on the significance of any linkage finding. Most papers in this issue—except those by Luciano *et al.* and Buyske *et al.*—do not find significant linkage according to the Lander and Kruglyak guidelines. However, as is evident from the six studies on cognition, lower LOD scores that are not labeled "significant" in a single scan, may see replication in independent scans, confirming that even if a LOD score is below the threshold for significance, it may still represent "true" linkage.

Ultimately, replication must be the key in separating false positives from true positives. Therefore, representing full genome scans and describing not only significant LOD scores, but also smaller LOD scores is essential. Although these may be difficult to interpret in a single study, especially if sample size is small, providing them to other researchers will enable meta-analytic studies and will facilitate comparison across independent scans and render them more interesting when replicated. For the purpose of meta-analyses on published scans it is crucial to provide not only the most significant LOD scores.

This special issue reflects the expanding goal of behavior genetics, namely the inclusion of vast amounts of *measured* genetic markers in statistical models to ultimately find the genes that determine interindividual variation in complex traits. Due to lowered costs and the growing availability of high-throughput genotyping facilities, many twin registries have begun the collection of DNA in their large and well-phenotyped samples. Soon, this may lead to an explosive increase in published genome-wide scans for human complex traits, of which this special issue is merely the beginning.

REFERENCES

Comings, D. E., Wu, S., Rostamkhani, M., McGue, M., Lacono, W. G., and Cheng, L. S. (2003). Role of the cholinergic muscarinic 2 receptor (CHRM2) gene in cognition. *Mol. Psychiatry* **8**:10–11.

Gosso, M. F., van Belzen, M., de Geus, E. J. C., Polderman, J. C., Heutink, P., Boomsma, D. I. and Posthuma, D. Family based association testing provides further evidence for a role of the CHRM2 gene in cognition. *Genes Brain Behav.*, in press

Lander, E., and Kruglyak, L. (1995). Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nat. Genet.* **11**:241–247.

Porjesz, B., and Begleiter, H. (2003). Alcoholism and human electrophysiology. *Alcohol Res. Health* **27**(2):153–160.

Posthuma, D., Luciano, M., Geus, E. J. C., Wright, M. J., Slagboom, P. E., Montgomery, G. W., Boomsma, D. I., and Martin, N. G. (2005). A Genomewide Scan for Intelligence Identifies Quantitative Trait Loci on 2q and 6p. *Am. J. Hum. Genet.* **77**:318–326.