RE: Familial aggregation of clinical and neurocognitive features in sibling pairs with and without schizophrenia

Janice A. Husted,

Department of Health Studies and Gerontology, University of Waterloo, Waterloo, 200 University Avenue West, Waterloo, Ontario, Canada N2L 3G1. Tel.: +519 885 1211; fax: +519 746 2510

Celia Greenwood, and

Program in Genetics and Genomic Biology, Hospital for Sick Children, Research Institute, Toronto, Ontario, Canada

Anne S. Bassett

Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

The recent study by Chen et al. (2009) adds to the emerging body of research providing formal estimates of the heritability of neurocognitive traits. There are now at least seven published studies in the literature, using heterogeneous samples of schizophrenia and various neurocognitive tests, covariates and methods (Glahn et al., 2007; Greenwood et al., 2007; Gur et al., 2007a,b; Husted et al., 2009; Touloupoulou et al., 2007; Tuulio-Henriksson et al., 2002). Although the findings of Chen et al. (2009), using subjects aged 9–31 years, demonstrate many similarities with the existing evidence, they also reveal some of the challenges facing this research area. Using Sequential Oligogenic Linkage Analysis Routines (SOLAR), the reported heritability estimates for four neurocognitive domains were only modest to moderate in the schizophrenia proband-affected sibling pairs, ranging from 0.00 to 0.43, consistent with the results of other studies. Notably, this is significantly less than comparable heritability estimates for diagnosis of schizophrenia ($h^2=0.81$) (Touloupoulou et al., 2007). The magnitude of the Chen et al. (2009) heritability estimates for neurocognitive traits was altered by the presence of schizophrenia; an overall pattern of lower heritability estimates in the schizophrenia-sibling pairs relative to the control sibling pairs. In our recent study, using a familial form of schizophrenia associated with the NOSAP1 gene on chromosome 1 (Husted et al., 2009), we also reported modest to moderate heritability estimates ($h^2=0.05-0.49$) for 12 neurocognitive measures, after adjusting for age and sex. However, SOLAR analyses showed that when we included diagnosis of schizophrenia as a covariate, heritability estimates either increased or decreased, depending upon the specific neurocognitive measure examined. It is clear that the expression of schizophrenia has important effects on heritability estimates and should be taken into account in these studies.

Another factor that can affect these heritability estimates, not addressed by Chen et al. (2009), is general intellect. In a large sample of twin pairs, Touloupoulou et al. (2007) estimated the heritabilities of full-scale IQ and four neurocognitive domains. IQ was found to be the most highly heritable of the neurocognitive measures ($h^2=0.70$). Lowered IQ scores in monozygotic twins discordant for schizophrenia suggested that it is the genetic vulnerability to schizophrenia, rather than the expression of schizophrenia, that reduces IQ. The domain of working memory was also highly heritable ($h^2=0.65$). Shared genetic variance accounted for the majority of the covariance between schizophrenia and both IQ and working memory. Three other cognitive domains (processing speed, perceptual organization and verbal comprehension) were found to be moderately heritable, with a smaller portion of the observed covariance between each domain and schizophrenia genetically shared. In our recent study (Husted et al., 2009), we observed similar additive heritability for full-scale IQ, adjusting for age, sex and schizophrenia ($h^2=0.64$). Despite the fact that IQ is a composite construct comprised of several components that overlap with a number of cognitive domains, covarying for such a measure of overall intellect when examining the heritability of a neurocognitive test can reveal interesting relationships. Our results showed that there were noteworthy differences in heritability estimates of individual neurocognitive tests in SOLAR analyses that included IQ as a covariate compared with those that did not. We reported that these differences could in part be explained by the observed bivariate genetic correlations between IQ and the individual neurocognitive tests. The bivariate correlations between IQ and our measures of working, auditory and verbal memory were very high (0.84 to 1.00), whereas the bivariate correlations between IQ and measures of processing speed were negative (−0.10 to −0.34). Indeed, we found that accounting for IQ helped sort out the bivariate genetic correlations between the neurocognitive measures and helped to identify two heritable components: memory-IQ and visuomotor-processing speed. Our results further suggest that the relationships between the heritability of cognitive domains may differ from the relationships involved in test performance itself. Like Touloupoulou et al. (2007), we believe that considering general intellect in future studies may aid in the identification of heritable neurocognitive traits related to the expression of schizophrenia.

Finally, Chen et al. (2009) incorporated a correction for ascertainment bias in their SOLAR models. This ascertainment correction may be inadequate. If the shapes of the score distributions for schizophrenic probands and siblings are very different from the distributions for unaffected individuals, the heritability estimates could be affected in ways that are hard to predict. Ascertainment correction is a very difficult issue (Vieland and Hodge 1996).

References

- Chen LS, Rice TK, Thompson PA, Barch DM, Csernansky JG. Familial aggregation of clinical and neurocognitive features in sibling pairs with and without schizophrenia. *Schizophr Res.* 2009; 111:159–166. [PubMed: 19398304]
- Glahn DC, Almasy L, Blangero J, Burk GM, Estrada J, Peralta JM, Meyenberg N, Castro MP, Barrett J, Nicolini H, Raventos H, Escamilla MA. Adjudicating neurocognitive endophenotypes for schizophrenia. *Am J Med Genet B Neuropsychiatr Genet.* 2007; 144:242–249.

- Greenwood TA, Braff DL, Light GA, Cadenhead KS, Calkins ME, Dobie DJ, Freedman R, Green MF, Gur RE, Gur RC, Mintz J, Nuechterlein KH, Olincy A, Radant AD, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Schork NJ. Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. *Arch Gen Psychiatry*. 2007; 64:1242–1250. [PubMed: 17984393]
- Gur RE, Calkins ME, Gur RC, Horan WP, Nuechterlein KH, Seidman LJ, Stone WS. The consortium on the genetics of schizophrenia: neurocognitive endophenotypes. *Schizophr Bull*. 2007a; 33:49–68. [PubMed: 17101692]
- Gur RE, Nimgaonkar VL, Almasy L, Calkins ME, Ragland JD, Pogue-Geile MF, Kanes S, Blangero J, Gur RC. Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. *Am J Psychiatry*. 2007b; 164:813–819. [PubMed: 17475741]
- Husted J, Chow EWC, Bassett AS. Heritability of neurocognitive traits in familial schizophrenia. *Am J Med Genet (Neuropsychiatric Genet)*. 2009; 150B:845–853.
- Touloupoulou T, Picchioni M, Rijdsdijk F, Hua-Hall M, Ettinger U, Sham P, Murray R. Substantial genetic overlap between neurocognition and schizophrenia: genetic modeling in twin samples. *Arch Gen Psychiatry*. 2007; 64:1348–1355. [PubMed: 18056542]
- Tuulio-Henriksson A, Haukka J, Partonen T, Varilo T, Paunio T, Ekelund J, Cannon TD, Meyer JM, Lonnqvist J. Heritability and number of quantitative trait loci of neurocognitive functions in families with schizophrenia. *Am J Med Genet B Neuropsychiatr Genet*. 2002; 114:438–490.
- Vieland VJ, Hodge SE. The problem of ascertainment for linkage analysis. *Am J Hum Genet*. 1996; 58:1072–1084. [PubMed: 8651268]