Published in final edited form as:
Psychol Med. 2008 December ; 38(12): 1693–1820. doi:10.1017/S003329170800367X.

THE DICE ARE ROLLING FOR SCHIZOPHRENIA GENETICS; COMMENTARY ON CROW

Patrick F. Sullivan, MD, FRANZCP[1,2]

[1]Departments of Genetics, Psychiatry, & Epidemiology, University of North Carolina at Chapel Hill

[2]Department of Medical Epidemiology & Biostatistics, Karolinska Institutet, Stockholm, Sweden

Keywords

meta-analysis; schizophrenia; genome-wide association; genome-wide linkage; evidence

Professor Tim Crow's impassioned review (Crow, In press) addresses the question at the heart of schizophrenia (SCZ) genetics: a decade into the genomic era and after at least 28 genomewide linkage studies (Konneker et al., Submitted), ~1300 association studies of ~700 candidate genes (Allen et al., In press), and three published genomewide association studies (GWAS) (Lencz et al., 2007, Shifman et al., 2008, Sullivan et al., In press), what do we truly know about the genetics of SCZ?

The initial portion of Crow's review is reasonable, but the latter portion is premature. As GWAS data for ~12,000 subjects with SCZ and ~14,000 controls will become available for meta-analysis by the end of 2008, it is far preferable for these data to be interpreted within a logical and systematic framework (Psychiatric GWAS Consortium, Submitted). It is crucial that this passionately debated area regain an element of dispassionate logic instead of serving as a projective canvas for belief, pet theories, and musings about the nature of SCZ. In effect, the GWAS dice are rolling and dice are famously disinterested in the cogitations of punters.

I agree with Crow that the current short answer about what we know for certain about the genetics of SCZ is "not much". (I would take exception with some of Crow's scholarship – some reviews cited as examples of hype are more balanced and careful than indicated.) At present, based on published data, there are no genomic regions implicated by linkage or association with clean, clear, and cogent replication evidence for SCZ (particularly when negative results for 14 prominent SCZ candidate genes are included) (Sanders et al., In press). The only sure way to make the existing SCZ association results consistent across studies is to invoke more complex models of disease. It is possible that empirical evidence will eventually demonstrate that such models are operative for SCZ. However, these more complex models are hardly parsimonious and are inconsistent with over 100 findings in

Correspond with Dr. Sullivan in the Department of Genetics, CB#7264, 4109D Neurosciences Research Building, University of North Carolina, Chapel Hill, NC, 27599-7264, USA. Voice: +919-966-3358, FAX: +919-966-3630. pfsulliv@med.unc.edu.

human complex trait genetics where simple models were confirmed. The possibility that all reported associations for SCZ are false has not been excluded.

I agree with Crow the evidential standard used by many in the field of SCZ genetics is inadequate: the all-too-common use of lax standards of evidence has led to confusion rather than clarity. A standard for “replication” has been defined for association studies (Chanock et al., 2007, Box 3) and appears to be widely used in human genetics. The poster child for replication in human genetics is the *FTO*-body mass index association in which replication was reported in 13 cohorts with 38,759 participants, all in the same paper (Frayling et al., 2007). Obviously, the standard for replication in SCZ genetics should conform to that used in human genetics. The definition of replication in human genetic association studies (Chanock et al., 2007) is akin to the definition of guilt in a criminal trial in US jurisprudence (“proof beyond a reasonable doubt”, PBARD). The definition often applied in psychiatric genetics (and by some of the reviewers Crow pillories) is lesser, and akin that used in a civil case (“preponderance of evidence”, POE). This distinction resolves the “OJ Paradox” – the US gridiron star Orenthal James Simpson was found not guilty of the murder of his wife and her lover but liable for wrongful death because the POE standard was met but not PBARD.

Researchers who apply POE-like standards of evidence often have the best of intentions. The rationale usually has two components: (a) due to inadequate sample sizes, signals that do not quite meet a PBARD-like standard must be taken seriously to avoid erroneous rejection of true positive signals, or (b) the informal Bayesian argument that signals that do not meet a PBARD-like standard but which have *a priori* evidence of involvement in SCZ (e.g., via neuroscience or molecular biology) should be elevated in importance. A straightforward simulation study has highlighted the perils of these strategies (Sullivan, 2007). For SCZ genetics to move forward, genomic regions associated with SCZ must be “convicted” at a PBARD-like level of evidence. Use of POE-like standards simply has not worked. For example, the initial descriptions of the associations of *DTNBP1* (Straub et al., 2002) and *NRG1* (Stefansson et al., 2002) with schizophrenia were published six years ago – it is highly disappointing that neither association has been compellingly proven or disproved and that belief-influenced arguments are required rather than reliance on empirical data.

Two of Crow’s conclusions are unquestionably premature. First, based on a small number of talks given at the World Congress of Psychiatric Genetics meeting in 10/2007, Crow appears to conclude that GWAS has not and will not work for SCZ. This conclusion is difficult to understand given that GWAS have yielded over 100 confirmed findings in cardiology, endocrinology, gastroenterology, hepatology, infectious disease, oncology, ophthalmology, neurology, pulmonology, and rheumatology (usually at PBARD-like levels of evidence). GWAS unquestionably can identify confirmed associations for human complex traits; the question is will GWAS “work” for psychiatry.

The disease that arguably has benefited most in the GWAS era is type 2 diabetes mellitus (T2DM) where there are now around 15 confirmed associations (up from three such associations in 2006). Two of the initial T2DM GWAS were completely unremarkable (Saxena et al., 2007, Scott et al., 2007), and only with meta-analysis did numerous positive findings emerge (indeed, multiple associations that ultimately replicated well were not in the

top 1000 signals in the initial study) (Frayling, 2007). Crow's conclusion is premature until meta-analyses have been done.

The Psychiatric GWAS Consortium (PGC) (Psychiatric GWAS Consortium, Submitted) was formed in early 2007 to conduct GWAS meta-analyses and now has 101 investigators from 48 institutions in 11 countries. There are 47 GWA samples that, taken together, constitute the largest biological experiment ever conducted in psychiatry – over 80,000 subjects (59,000 independent cases/controls and over 7700 family trios), ~500,000 SNP genotypes per subject, and ~40 billion total genotypes. The overall philosophy of the PGC is to be as inclusive, democratic, and rapid as possible. The PGC is well-underway with a coordinating committee, five disease working groups, a cross-disorder group, a statistical analysis and computation group, and a cluster computer for data warehousing and statistical analysis. There are two main specific aims: (1) to conduct within-disorder meta-analyses (i.e., separately on all available GWAS data for ADHD, autism, bipolar disorder, major depressive disorder, and SCZ) to attempt to identify convincing genotype-phenotype associations, and (2) to conduct cross-disorder analyses to identify genetic associations that cut across the clinically-derived DSM/ICD disease boundaries. The analytic plans conform to current best practices for GWAS quality control and meta-analysis, particularly in attention to sources of heterogeneity. Statistical power will be superior to any prior study in psychiatric genetics. Results will be made available as soon as possible, probably in late 2008 or early 2009 (http://pgc.unc.edu).

Second, Crow uses his impression of the "failure" of SCZ GWAS efforts as supporting a theory of an epigenetic basis for SCZ. This conclusion is doubly premature as there are multiple genetic models that might be operative should a polygenic model be rigorously shown not to apply to SCZ. Ironically, an epigenetic hypothesis for SCZ may be difficult to falsify due to technical limitations in assessing epigenetic marks on a genomic scale and because of the plausible requirement for inaccessible tissue (i.e., discrete portions of the brain) sampled at critical developmental periods well before a psychotic prodrome becomes evident clinically.

As articulated more fully elsewhere (Psychiatric GWAS Consortium, Submitted), debates about the "success" or "failure" of GWAS for SCZ miss the point. Indeed, the PGC is an exceptional opportunity in the history of psychiatry. No matter what the findings, we should uncover some certainties about the genetic architecture of SCZ. Formulated differently, the massive efforts that comprise the PGC are a large-scale test of an over-arching "meta-hypothesis" about the etiology of the most important psychiatric disorders. This latter point is exceptional – both positive and negative results will enable us to learn hard facts about ADHD, autism, bipolar disorder, major depressive disorder, and SCZ.

The potential outcomes of PGC meta-analyses for SCZ can logically be viewed as a set of sequential hypotheses. (1) It is possible that GWAS meta-analysis for SCZ identifies a genomic region that is strongly significant after careful consideration of technical artifacts and correction for multiple comparisons. This would constitute an historical advance, and it is difficult to over-emphasize how important such a landmark would be to patients, families, clinicians, and researchers. As GWAS power is optimal under a polygenic model, it is most

likely that any such identified variant would be relatively common and confer modest risk. (2) It is possible that rarer copy number variants of strong effect could be identified; indeed, there are some early data that these may be the first fruits of the GWAS era for psychiatric genetics (Walsh et al., 2008, Weiss et al., 2008). These first two options are not mutually exclusive. (3) If no replicated associations are found, the available sample sizes may be too small – a true genetic effect may be present but statistical power is insufficient. Efforts efficiently to obtain considerably larger samples for SCZ are underway as there currently are too few SCZ samples in the world. (4) Assumptions that SCZ is a distinct disease and that clinical heterogeneity is ignorable may be incorrect, and careful cross-disorder analyses could prove informative (as are planned in the PGC). (5) A polygenic model may be correct for SCZ, but the salient regions of the genome may not be adequately covered in a GWAS. For example, after quality control, one GWAS had no genetic markers in several key genes important in dopaminergic neurotransmission (*DRD1*, *DRD4*, and *TH*) (Sullivan et al., In press). More complete coverage requires the next generation of GWAS platforms. (6) Genetic variation might function solely via a more complex genetic model – higher order interactions (e.g., gene-gene or gene-environment interactions) instead of main effects. Explicitly modeling interactions might prove informative. (7) As Crow believes, a polygenic model might be incorrect for SCZ and there might be a large number of different but individually rare risk variants each with strong effect. The next generation of genomic technology (individual genome sequencing) might be needed to resolve this model. (8) Finally, GWAS tests the simplest conceivable model of how a genetic variant might cause a phenotype like SCZ. Alternative models are certainly possible – these include the epigenetic model favored by Crowe and perhaps even mechanisms not yet described.

It is possible that Crow's assessment of the dire state of SCZ genetics is correct. However, elements of his argument have not been rigorously evaluated. It is sensible thoroughly to test and reject simple models before moving to more complex possibilities. Within the year, a massive bolus of data should be available for GWAS meta-analysis. Evidence from these meta-analyses could transform the field or add more modestly to our knowledge base about SCZ. Either way, we will learn.

References

Allen N, Bagade S, McQueen M, Ioannidis J, Kavvoura F, Khoury M, Tanzi R, Bertram L. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: The szgene database. Nature Genetics. (In press).

Chanock SJ, Manolio T, Boehnke M, Boerwinkle E, Hunter DJ, Thomas G, Hirschhorn JN, Abecasis G, Altshuler D, Bailey-Wilson JE, Brooks LD, Cardon LR, Daly M, Donnelly P, Fraumeni JF Jr. Freimer NB, Gerhard DS, Gunter C, Guttmacher AE, Guyer MS, Harris EL, Hoh J, Hoover R, Kong CA, Merikangas KR, Morton CC, Palmer LJ, Phimister EG, Rice JP, Roberts J, Rotimi C, Tucker MA, Vogan KJ, Wacholder S, Wijsman EM, Winn DM, Collins FS. Replicating genotype-phenotype associations. Nature. 2007; 447:655–660. [PubMed: 17554299]

Crow TJ. Schizophrenia: The polygene emperors have no clothes. Psychological Medicine. (In press).

Frayling TM. Genome-wide association studies provide new insights into type 2 diabetes aetiology. Nature Reviews Genetics. 2007; 8:657–662.

Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett

AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Davey-Smith G, Hattersley AT, McCarthy MI. A common variant in the *fto* gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 2007; 316(5826):889–894. [PubMed: 17434869]

Konneker T, Barnes T, Furberg H, Losh M, Bulik CM, Sullivan PF. A searchable database of genetic evidence for psychiatric disorders. (Submitted).

Lencz T, Morgan TV, Athanasiou M, Dain B, Reed CR, Kane JM, Kucherlapati R, Malhotra AK. Converging evidence for a pseudoautosomal cytokine receptor gene locus in schizophrenia. Molecular Psychiatry. 2007; 12:572–580. [PubMed: 17522711]

Psychiatric GWAS Consortium. A framework for interpreting genomewide association studies of psychiatric disorders. (Submitted).

Sanders A, Duan J, Levinson DF, Shi J, He D, Hou C, Burrell GJ, RIce JP, Nertney DA, Olincy A, Rozic P, Buccola NG, Mowry BJ, Freedman R, Amin F, Black DW, Silverman JM, Byerley WF, Crowe RR, Cloninger CR, Martinez M, Gejman P. No significant association of fourteen candidate genes to schizophrenia in a large european-ancestry sample: Implications for the field. American Journal of Psychiatry. (In press).

Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Rastam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjogren M, Sterner M, Surti A, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purcell S. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science. 2007; 316:1331–1336. [PubMed: 17463246]

Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, Erdos MR, Stringham HM, Chines PS, Jackson AU, Prokunina-Olsson L, Ding CJ, Swift AJ, Narisu N, Hu T, Pruim R, Xiao R, Li XY, Conneely KN, Riebow NL, Sprau AG, Tong M, White PP, Hetrick KN, Barnhart MW, Bark CW, Goldstein JL, Watkins L, Xiang F, Saramies J, Buchanan TA, Watanabe RM, Valle TT, Kinnunen L, Abecasis GR, Pugh EW, Doheny KF, Bergman RN, Tuomilehto J, Collins FS, Boehnke M. A genome-wide association study of type 2 diabetes in finns detects multiple susceptibility variants. Science. 2007; 316:1341–1345. [PubMed: 17463248]

Shifman S, Johannesson M, Bronstein M, Chen SX, Collier DA, Craddock NJ, Kendler KS, Li T, O'Donovan M, O'Neill FA, Owen MJ, Walsh D, Weinberger DR, Sun C, Flint J, Darvasi A. Genome-wide association identifies a common variant in the reelin gene that increases the risk of schizophrenia only in women. PLoS Genetics. 2008; 4:e28. [PubMed: 18282107]

Stefansson H, Sigurdsson E, Steinthorsdottir V, Bjornsdottir S, Sigmundsson T, Ghosh S, Brynjolfsson J, Gunnarsdottir S, Ivarsson O, Chou TT, Hjaltason O, Birgisdottir B, Jonsson H, Gudnadottir VG, Gudmundsdottir E, Bjornsson A, Ingvarsson B, Ingason A, Sigfusson S, Hardardottir H, Harvey RP, Lai D, Zhou M, Brunner D, Mutel V, Gonzalo A, Lemke G, Sainz J, Johannesson G, Andresson T, Gudbjartsson D, Manolescu A, Frigge ML, Gurney ME, Kong A, Gulcher JR, Petursson H, Stefansson K. Neuregulin 1 and susceptibility to schizophrenia. American Journal of Human Genetics. 2002; 71:877–892. [PubMed: 12145742]

Straub RE, Jiang Y, MacLean CJ, Ma Y, Webb BT, Myakishev MV, Harris-Kerr C, Wormley B, Sadek H, Kadambi B, Cesare AJ, Gibberman A, Wang X, O'Neill FA, Walsh D, Kendler KS. Genetic variation in the 6p22.3 gene *dtnbp1* the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. American Journal of Human Genetics. 2002; 71:337–348. Erratum in American Journal of Human Genetics 2002 Oct;72(4):1007. [PubMed: 12098102]

Sullivan PF. Spurious genetic associations. Biological Psychiatry. 2007; 61:1121–1126. [PubMed: 17346679]

Sullivan PF, Lin D, Tzeng JY, van den Oord EJCG, Perkins D, Stroup TS, Wagner M, Lee S, Wright FA, Zou F, Liu W, Downing AM, Lieberman JA, Close SL. Genomewide association for schizophrenia in the catie study: Results of stage 1. Molecular Psychiatry. (In press).

Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, Nord AS, Kusenda M, Malhotra D, Bhandari A, Stray SM, Rippey CF, Roccanova P, Makarov V, Lakshmi B, Findling RL, Sikich L, Stromberg T, Merriman B, Gogtay N, Butler P, Eckstrand K, Noory L, Gochman P, Long R, Chen Z, Davis S, Baker C, Eichler EE, Meltzer PS, Nelson SF, Singleton AB, Lee MK, Rapoport JL, King MC, Sebat J. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science. 2008; 320:539–543. [PubMed: 18369103]

Weiss LA, Shen Y, Korn JM, Arking DE, Miller DT, Fossdal R, Saemundsen E, Stefansson H, Ferreira MA, Green T, Platt OS, Ruderfer DM, Walsh CA, Altshuler D, Chakravarti A, Tanzi RE, Stefansson K, Santangelo SL, Gusella JF, Sklar P, Wu BL, Daly MJ. Association between microdeletion and microduplication at 16p11.2 and autism. New England Journal of Medicine. 2008; 358:667–675. [PubMed: 18184952]