GUEST EDITORIAL

The Future of Psychiatric Genetics

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The core aim of psychiatric genetics is the dissection of the genetic etiology of specific psychiatric disorders, with a view to understanding pathogenesis. Identification of individuals at risk and rationalization of treatment are secondary goals. Pioneering family, twin and adoption studies in the last century paved the way for these lofty goals by establishing a heritable etiology for several severe psychiatric disorders (McGuffin et al. 1994).

Recent advances in genomics have provided the tools needed to tackle these goals. The draft human genome sequence is complete, and international collaborations have assured rapid annotation of the genomic sequences (Sachidanandam et al., 2001). We are well on our way to identification of most of the variations that occur in the human genome. High-throughput genotyping technologies are evolving rapidly and will enable accurate, economic methods for analysis of genomic variations in large samples (Kwok, 2001). These resources complement the classical gene mapping approaches that have been used successfully to identify genes for several thousand hereditary diseases (Collins, 1992). The typical mapping process initially involves identification of large chromosomal segments shared among affected members of pedigrees (linkage analysis), followed by 'fine mapping', of localization of the disease gene in the linked region by comparison of cases and appropriate controls 'association analysis'.

Based on these evolving genomic resources, success in mapping genes for psychiatric disorders was predicted two decades ago (Gurling, 1985). Indeed, there have been significant strides in gene mapping efforts. For example, genetic variants that may confer risk for common (in disorders such as schizophrenia and bipolar disorder have been identified and the results replicated (Harrison & Owen, 2003). However, the typical risk conferred by such variants is relatively small (odds ratios of 2 or less). The clinical relevance of such results can therefore be questioned. The promise of linkage analysis has not been fulfilled completely (Moldin, 1997; Grottesman & Moldin, 1997). Though some consistent linkage results are available, the linked regions are typically extensive (several centiMorgans or millions of bases) (Levinson et al., 2000; Lewis et al., 2003; Segurado et al., 2003). Here, we identify the possible reasons for the inconsistencies and unfulfilled promises. We also suggest plausible routes to future success in mapping efforts.

Along with other common multi-factorial diseases such as diabetes and hypertension, the etiological dissection of psychiatric disorders poses a difficult problem: though a significant heritability is well established, the number of loci contributing to the heritable risk is unknown a Priori. If, as seems likely from current efforts, the risk conferred by individual loci is relatively small, thousands of participants may be required for consistent identification (Moldin, 1997). This problem is compounded by our relative ignorance about environmental (non-genetic) risk factors (Moldin & Grottesman, 1997). Hence it is difficult to test interactions between risk factors. In addition the available mapping tools, which rely heavily on recombination, are more suitable for heritable diseases for which variation in only one gene provides most of the risk (Risch, 2000). Compounded by our relative ignorance about the pathogenesis of most of these disorders, it is easy to understand why has been difficult to identify genes that confer only a small proportion of the overall risk (Risch, 2000).

Is there a solution for these seemingly intractable problems? We suggest that linkage studies should not be abandoned, because such approaches continue to bear fruit. For example, a susceptibility gene for Crohn’s disease was recently identified thus (Riouxt et al., 2001). Given the aforementioned difficulties, it would be preferable to confine the linkage approach to subgroups or traits that clearly provide evidence for Mendelian inheritance (Terwilliger & Goring, 2000; Weiss & Terwilliger, 2000). Such scenarios may be present in rare families or genetically isolated pedigrees. Nevertheless, they merit investigation. Linkage analysis of quantitative traits using variance component based approaches have proved successful for common (non-pathological) traits; such approaches also deserve evaluation for common human diseases, provided adequately powered samples are available (Almasy & Blangero, 1998).

At the same time, alternatives to the classical linkage based mapping approaches should also be invested in. Recent controversies regarding candidate gene association studies should be revisited (Nimgaonkar, 1997). Such approaches have been criticized in the past because of the low prior probability of detecting associations said because of inadequate attention to complexities in the genetics of outbred populations typically used for association analyses (Weiss & Terwilliger, 2000). Notwithstanding such difficulties, we believe that there continues to be a place for association studies in the geneticist’s toolbox. We suggest that this approach be reserved for positional candidates: genes localized to linked regions and which encode proteins with a persuasive role in pathogenesis. Due recognition of the prior probability for association is also merited. Arguably, the well replicated association between apoE4 and late onset Alzheimer's disease is the best example of this approach. We have recently identified association between schizophrenia and polymorphisms of the Regulator of G Protein Signaling (RG54) using this approach (Chowdari et al 2002). RG54 is localized to chromosome 1q22, a region with prior reports of linkage (Braztowicz, et al 2000). RG54 is also an interesting candidate gene as it was identified following expression analysis of post-mortem brain tissue (Mimics, et al 2001). With further refinement, agnostic methods such as expression analyses are...
likely to be particularly useful for identifying candidate genes are likely to be particularly useful for disorders of unknown pathogenesis.

Co-morbidity of the disorder of interest with chromosomal abnormalities, such as deletions and unbalanced translocations also need to be pursued aggressively. Such ‘accidents of nature’ may prove valuable reagents for mapping efforts, if it is possible to conclusively identify the gene/s disrupted in the proband. This approach recently enabled the identification of DISC1 as a susceptibility gene for schizophrenia (Devon et al., 2001).

How can researchers in India contribute to gene mapping efforts? India is a highly desirable venue for such efforts, because of the availability of large, cooperative, intact and stable families. Genetically isolated populations with particularly desirable characteristics for mapping efforts may also be present, but have not been investigated. An equally important asset is the availability of highly skilled clinical and genetic expertise. The clinical expertise is especially valued, because errors in diagnosis can contribute inordinately to major inconsistencies in mapping efforts. On the other hand, an observant clinician who identifies a patient with a cytogenetic abnormality may well provide the key to solving the puzzling etiology of heritable psychiatric disorders. With adequate support from research funding agencies, Indian efforts may open up new vistas in psychiatric genetic research.

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REFERENCES

Almasy, L., & Blangero, J. (1998). Multimarker quantitative-trait linkage analysis general pedigrees. Am Hum Genet 62(5), 1198-211.

Brezunczick, L. M., Hodgkinson, K. A., et al. (2000). Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21-q22 Science 288 (5466), 678-82.

Chowdari, K. V., Mirnics, K., Semwal, P., Wood, et al. (2002). Association and linkage analyses of RGS4 polymorphisms in schizophrenia. Hum Mol Genet. 11 (12), 1373-80.

Collins, F. S. (1992). Positional cloning: Let’s not call it reverse anymore [news]. Nature Genetics. 1 (1), 3-6.

Devon, R. S., Anderson, S., Tesque, P. W., et al. (2001). Identification of polymorphisms within Disrupted in Schizophrenia 1 and Disrupted in Schizophrenia 2, and an investigation of their association with schizophrenia and bipolar affective disorder. Psychiatr Genet. 11 (2), 71-8.

Gottesman, II, & Moldin, S. O. (1997). Schizophrenia genetics at the millennium: cautious optimism. Clio Genet. 52 (5), 404-7.

Gurling, H. M. D. (85). Candidate genes and favored loci strategies for molecular genetic research into schizophrenia, manic depression, autism, alcoholism and Alzheimer’s disease. Psychiatric Psychiatric Development. 4, 289-309.

Harrison, P. J., & Owen, M. J. (2003). Genes for schizophrenia? Recent findings and their pathophysiological implications. Lancet 361 (9355). 417-9.

Kwok, P. Y. (2001). Methods for genotyping single nucleotide polymorphisms. Ann Rev Genomics Hum Genet. 2 (235-58). Miller RD et al. The birth and death of human ... [PMID: 1167340] [Related Articles, Links.

Levinson, D. F., Holmans, P., Straub, R. E., et al. (2000). Multicenter linkage study of schizophrenia candidate regions on chromosomes 5q, 6p, 10p, and 1q: schizophrenia linkage collaborative group III Am J Hum Genet. 67 (3), 652-63.

Lewis, C. M., Levinson, D. F., Wise, L. H., et al. (2003). Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. Am J Hum Genet 73(4), 34-48. 3: segurado R, et al. Genome scan meta-analysis of ... [PMID: 12802785] Related Articles, Links.

McGuffin, P., Owen, M. J., O Donovan, M. C., Thapar, A., & Gottesman, I. I. (1994). Semi-hans in Psychiatric Genetics London, UK: Gaskell.

Mirnics, K., Middleton, F. A., Stanwood, G. D., Lewis, D. A., & Levitin, P. (2001). Disease-specific changes in regulator of G-protein signaling 4 (RGS4) expression in schizophrenia Mol Psychiatry. 6(3), 293-301.

Moldin, S. O. (1997). The maddening hunt for madness genes. Nature Genetics. 17, 127-129.

Moldin, S. O., & Gottesman, I. I. (1997). At issue: genes, experience, and chance in schizophrenia—positioning for the 21st century. Schizophrenia. 23(4), 547-61.

Nimiaonkar, V. (1997). In defense of genetic association studies, Molecular Psychiatry. 2, 275-277.

Nioux, J. D., Daly, M. J., Silverberg, M. S., et al. (2001). Genetic variation in the 5q31 cytokine gene cluster confers susceptibility to Crohn disease. Nat Genet. 29 (2). 233-8.

Risch, N. J. (2000). Searching for genetic determinants in the new millennium. Nature 405(6788). 847-56.

Sachidanandam, R., Weissman, D., Schmidt, S. C., et al. (2001). A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. Nature 409(6822). 928-33.

Segurado, R., Deters-Wadleigh, S. D., Levinson, D. F., et al. (2003). Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Bipolar disorder Am J Hum Genet. 73(1), 49-62.

Songmo N et al. Evidence for linkage by ... [PMID: 11121192] Related Articles, Links.

Tervo, V. D. J., & Gorini, M. H. (2000). Gene mapping in the 20th and 21st centuries: statistical methods, data analysis, and experimental design. Hum Biol. 72(1). 63-132.

Weiss, K. M., & Tervo, V. D. J. (2000). How many diseases does it take to map a gene with SNPs? Nature Genetics, 26(2). 151-7.