Genetics of Schizophrenia: Clinical and Neurobiological Implications

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INTRODUCTION:
• Schizophrenia (SZ) occurs throughout the world with a prevalence of 1%. As much as 80% of SZ can be attributed to genetic factors. Individuals with SZ reproduce at a lower rate: females produce 50% as many children as normal; males 25%. Genetic factors accounting for SZ should therefore behave like highly lethal genes. Principles of Hardy-Weinberg equilibrium predict that SZ should disappear from the human gene pool. How can we explain the persistence of SZ at a constant frequency of 1%?
• Clinicians appreciate that the natural course of SZ varies widely from patient to patient and cannot be predicted. The Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) concluded that the response of any individual with SZ to treatment with second generation antipsychotic agents cannot be predicted: either the effectiveness of the treatment or the myriad of side effects. Each pharmacological intervention is a virtual clinical trial.
• More than 50 candidate genes have been identified within kindreds with high frequencies of SZ. There is no identified candidate gene common to all afflicted patients.

METHODS:
• We have reviewed the literature establishing the genetic inheritance of schizophrenia. We have considered these data in light of recent studies analyzing individual genomes of patients with SZ via DNA hybridization methodology. Finally, as co-investigators in the CATIE trial, we observed the highly individualized and unpredictable responses of patients to structured treatment protocols.
• This study is not a review article. Nor is it a meta-analysis. It makes use of genetic data derived from a century of study of Drosophila as well as contemporary studies on the genetic control of development of highly complex neural networks in the brain, which, when perturbed, lead to mental retardation, the autism spectrum disorders, and probably SZ. We propose a hypothesis to reconcile these apparently disparate lines of evidence.

RESULTS:
• The development of nucleic acid hybridization technology has revised our understanding of the structure and function of the human genome. Several recent publications have identified chromosomal rearrangements of large coding and non-coding regions including certain candidate or neurodevelopmental genes.

DISCUSSION:
• These structural variations include microdeletions and/or duplications ranging from 100KB to 15 MB. These structural mutations are called copy number variants (CNV’s). In vivo mutations are a normal aspect of brain development; found in control DNA at a frequency of 5%, in SZ DNA at a frequency of 15%, and among children with the most severe childhood-onset SZ (COS) a frequency of 22%.
• Balanced polymorphism is the genetic mechanism explaining how non-adaptive genetic factors are maintained in natural populations in combination with other genes to confer increased fitness to the entire population, thus insuring their preservation in the gene pool. Sickle Cell Anemia is a classic example of balanced polymorphism.
• Diverse evidence suggests a neurodevelopmental model of SZ, the autism spectrum, Asperger’s Syndrome, and others. A family of genes has been identified that are activated by diverse extracellular mechanisms. They are the interface between the organism and its environment, at the cellular and organismic level. Neurodevelopmental genes account for the organization of complex neuronal networks that are analogous to organogenesis. An example of such a regulatory gene is Disrupted in Schizophrenia (DISC-1).

Genetic elements which are adaptive must exist to account for the persistence of SZ as well as its familial pattern of inheritance. In vivo mutations, occurring in somatic tissue, not germinal tissue, cannot explain the genetic transmission of SZ. An unidentified class of genes that increases the frequency of in vivo mutations must exist. We propose that these unidentified genetic elements might, in other neurodevelopmental conditions, produce increased lateralization, language skills, and/or creativity thereby providing an adaptive advantage and guaranteeing their preservation in the human gene pool.
• These hypotheses, in conjunction with the findings of CATIE, raise the possibility that each patient with SZ may be genetically unique, a phenocopy.