

Searching for the true genetic vulnerability for schizophrenia

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Abstract

The search for a genetic basis for schizophrenia has taken a new turn recently with the publication of three reports of various rare copy-number variations that are associated with schizophrenia. While some of the findings may simply disappear as spurious reports, others remain interesting: that is, deletions in the Velocardiofacial syndrome region of chromosome 22, and regions of chromosome 1q21.1 and 15q13.3. These results will gain greater significance if future validation in family studies shows their segregation with illness within families, and when it is understood how the genes containing these variants affect the underlying neurochemistry and neuropathology characteristic of schizophrenia.

Introduction

Development into adulthood has, at its origins, strands of DNA inherited from two parents combined with endogenous or external environmental influences. Which aspect of this input is most crucial for development is not well understood. Yet it is well known now that siblings or twins adopted away at birth share very similar physical, personality and mental traits with their close biological relatives [1]. On the other hand, it is also known that changing the prenatal and perinatal environment of a fetus and infant can have a long-lasting effect on the developed adult and even their offspring [2].

It is in this context that we try to unravel the genetic mechanism that leads to high risk for schizophrenia, particularly given the last decade of progress that has led us into a new era of human genome research. Early genetic studies ([3]; reviewed in [4]) led to several false starts and inconsistent chance findings of gene variants associated with schizophrenia and linkages to specific chromosomal regions. These studies culminated in the presence of over 2,000 reports in the current literature examining allelic associations to schizophrenia and well over 50 genes that are claimed to have positive associations. In fact, almost every chromosome arm has a reported linkage to schizophrenia (reviewed in [4-6]).

The inheritance and genetic mechanism of schizophrenia

Schizophrenia is a lifetime brain disorder detectable in late adolescence to early adulthood that particularly affects the higher cortical centers for complex learning, memory and communication with others. People with this illness frequently hear disturbing voices that are not there and have multiple delusionary perceptions that prevent them from functioning in society on a daily basis. It has long been established through epidemiological studies of families, twins and adoptees to be highly heritable. However, its inheritance does not follow any Mendelian pattern. Once schizophrenia had been accepted as one of the so-called 'complex' genetic disorders and it had become clear that simple methods that were useful for studying the inheritance of Mendelian disorders were not leading to clear candidate genes, other study designs came into fashion. These included examination of differential patterns of inheritance for imprinting and anticipation effects [7-10], examining linkage in genetically isolated cohorts [11-14], and searching for 'intermediate phenotypes' or 'endophenotypes' [15,16] to use as alternative variables in linkage analyses. None of these have yet been successful in definitively finding a gene defect linked to schizophrenia. General conclusions from the literature are

Table 1**Comparison of three recent genome-wide searches for CNV differences between large cohorts of people with schizophrenia and control populations**

Study	Number of subjects	Geographical locations	Laboratory methods	Results
Stefansson <i>et al.</i> [21]	1,433 patients with schizophrenia; 33,250 controls. Follow-up with 3,285 cases and 7,951 controls	England, Finland, Germany, Iceland, Italy and Scotland	High-density SNP microarrays	Deletions at chromosomes 1q21.1, 15q11.2 and 15q13.3 associated with schizophrenia (findings in bold are those that are present in more than 1 study)
The International Schizophrenia Consortium [22]*	3,391 patients with schizophrenia (according to the DSM-IV or ICD-10 definitions [†]); 3,181 ancestrally matched controls	Several sites: Bulgaria, England, Ireland, Portugal (Azores), Scotland and Sweden	High-density SNP microarrays	1.15x increase in schizophrenia for CNVs greater than 100 kb and in less than 5% of the sample. Deletions found in the VCFS region on chromosome 22, ad in chromosomes 15q13.3 and 1q21.1
Walsh <i>et al.</i> [20]	150 patients with schizophrenia; 268 ancestrally matched controls	USA (various locations)	CGH screen (85,000 probe arrays initially, and an Illumina 550 array for validation to identify microdeletions greater than 100 kb)	Novel deletions and duplications present in 15% of adult and 20% of COS patients versus 5% of controls. No one of these specifically associated with schizophrenia. In COS deletions in 2q31.2, 2p16.3 (<i>NRXN1</i> gene), 16p11.2 were associated
Sutrala <i>et al.</i> [23]*	85 unrelated Caucasians with schizophrenia (DSM-IV definition); control DNA was from the CEPH [†] collection	England and Ireland	CGH screen with oligonucleotide probes of 891 candidate genes, then allele quantification by DNA pooling for 15 genes	CGH screen yielded CNVs in six genes, but no excess in schizophrenia. No CNV was found by either method to be in excess in schizophrenia

*There is an overlap in authorship and perhaps a minor overlap in samples between these papers and [21]. [†]Abbreviations: CEPH, Centre d'Etude du Polymorphisme Humain genotype database; CGH, comparative genomic hybridization; COS, childhood onset; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ICD-10, WHO International Classification of Diseases; SNP, single nucleotide polymorphism; VCFS, velo-cardio facial syndrome.

that (i) neither imprinting nor anticipation have major roles in schizophrenia genetics; (ii) the genetic isolate studies thus far have not yielded any findings that are clearly different from the studies on heterogeneous outbred populations; and (iii) no endophenotype has currently been found that seems to be more heritable than the clinical diagnosis of schizophrenia itself. Nevertheless, there can be optimism for future progress towards uncovering a genetic mechanism for schizophrenia because of the parallel and rapid progress in the field of molecular genetics and the recent discoveries of novel genetic processes.

It remains clear from consistent and accepted observations among clinicians that schizophrenia clusters heavily in some families, whereas in others it seems to be a sporadic occurrence; sometimes it appears in two successive generations, frequently without having occurred in previous generations, and thus it seems more horizontal in inheritance than vertical in these cases. There are a few speculative hypotheses that emerge from these observations: (i) that environmental effects on gene expression could be a key [17]; (ii) that other epigenetic effects on expression of genes, perhaps endogenous effects (effects within ones own body), may be taking place [18]; or (iii) that there are many rare variants that occur by deletions or insertions in active

regions of crucial genes, and that these may lead to schizophrenia, having a major effect in specific families or simply occurring sporadically [19].

Copy number variations

The hypothesis that rare variants of crucial genes have a role in schizophrenia has received much attention recently in three major publications of genome-wide copy-number variations (CNVs; Table 1) [20-22] and at least one specifically examining copy number in several candidate genes [23]. These papers were preceded by success in locating some pathological CNVs consistently associated with autism (for example, [24]). If CNVs are relevant to autism, it is a reasonable assumption that they could be important in other major serious mental illnesses. Following this logic, Walsh and colleagues [20] published an initial finding on a relatively small set of two US cohorts, one a clinic population from the Northwestern USA and the other a tertiary referral population of unusual childhood onset cases. Tertiary referral in this case means another doctor has referred the case, usually because it is a difficult case that does not respond to the usual treatments. In both cohorts the number of large deletions was significantly greater in the patient groups than in controls, but no one deletion or mutation stood out.

This study [20] was only a very preliminary attempt to confirm the same group's past speculation that the genetic basis for schizophrenia is multiple rare mutational events, perhaps in genes of relevant neuronal pathways [19]. Most recently, the work of Walsh and colleagues [20] was followed by two highly publicized multicenter large international combinations of cohorts that both examined whether CNVs were more prevalent in schizophrenia than would be expected by chance [21,22]. Although increases in CNVs were suggested, overall the amount of excess was minimal (1.14 in one report [22]) and only mentioned as 'nominal' in the other [21] but clearly less than the over three-fold increase observed by Walsh and colleagues [20] studying a much smaller cohort. Sutrala and colleagues [23] in the UK studied CNVs using a similar comparative genomic hybridization method to that used in the other studies [20], but with oligonucleotide probes rather than the bacterial artificial chromosome (BAC) clones, and they were thus able to detect smaller deletions than those found in the previous studies. They did not do a whole genome-wide screen, however, but rather focused on sequences in 891 different candidate genes, and they failed to find any associations with schizophrenia. Thus, if rare mutational events account for the genetics of schizophrenia, this is likely to be only a minor contributing mechanism and will not explain the majority of the inheritance of schizophrenia.

Although in some instances consistent CNV findings have emerged that seem to be interesting (such as chromosomes 1q21.1 and 15q13.3, which have associated deletions in two studies [21,22] or the uncovering of a CNV in the region associated with velo-cardio facial syndrome (VCFS) [22], which is frequently implicated in schizophrenia), other findings might not be replicated, or their locations might not be consistent with any gene that is known to be relevant to brain functioning or associated with schizophrenia. These findings should therefore be taken with considerable caution at present, as it is too early to determine whether any of the observed candidate CNVs will be confirmed as an important schizophrenia risk factor. It is still possible that CNV detection might just be a 'fad'. Alternatively, the presence of CNVs might eventually become important as a new-found mechanism for complex genetic and psychiatric disorders.

Certainly, any CNV apparently associated with illness will first need to be verified in large family-based studies to determine whether it segregates with illness within families. There has long been a debate as to whether all of schizophrenia is inherited or whether a proportion of cases with no apparent family history of illness could be sporadic [25]. Although environmental factors have been assumed to cause sporadic cases, the alternative could certainly be *de novo* germline mutations, such as CNVs.

When considering schizophrenia, we need to question whether the CNV hypothesis is consistent with what we

know about the nature of the illness. Can multiple rare variants be an explanation for a disease with worldwide and unchanging incidence and prevalence rates, with sex differences in clinical presentation, with the characteristic delayed age of onset, outcome and familial patterns, with the response to neuroleptic drugs, with the consistent brain structural anomalies across groups of patients worldwide and with the many reported environmental risk factors? Finally, is there any other disease model for this mechanism that would be relevant to schizophrenia? We continue to hope that the genetic basis for schizophrenia will be clarified in the near future by novel technology and ultimately by complete gene sequencing. Once the mechanism is established there is optimism that new medications will be developed to target the relevant pathways uncovered.

Abbreviations

CNV, copy number variation; VCFS, Velocardiofacial syndrome.

Competing interests

The author declares that she has no competing interests.

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