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Developments in schizophrenia genetics: From linkage to microchips, deletions and duplications

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Background: There is strong evidence for significant contributions of genetic factors to the risk of schizophrenia. In the past 10 years, studies employing linkage and association approaches have identified multiple putative schizophrenia risk genes. For most of these, the evidence for association with schizophrenia remains weak and attempts of replication not always successful nor easy to interpret. *Aim:* To give an overview of new developments in genetic research of schizophrenia. *Methods:* The present literature on schizophrenia genetics was reviewed with special emphasis on new developments such as genome-wide association studies (GWAS), associations of copy number variations (CNVs) with schizophrenia and the role of endophenotypes in genetic research. *Results:* The first GWAS of schizophrenia have identified new putative candidate risk genes and opened avenues for investigating how multiple genes may act in functional biological pathways forming the genetic basis of schizophrenia and other complex diseases. There is growing evidence that rare *de novo* CNVs as well as some inherited CNVs contribute to the susceptibility to several neuropsychiatric disorders including schizophrenia. Schizophrenia endophenotypes, which possibly better represent biological phenomena than the complex clinical phenotype, are turning out to be helpful for investigating neurobiological pathways of putative risk genes. *Conclusions:* Recent studies suggest that individual common gene variants make relatively small contributions to risk of schizophrenia but some rare CNVs may be associated with much higher risk when present. Future studies employing new technologies for identifying common and rare risk markers are likely to deepen our understanding of the genetic architecture of schizophrenia.

• *Copy number variations, Endophenotypes, Genetics, Genome-wide association studies, Schizophrenia.*

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Schizophrenia is a serious psychiatric illness with a lifetime prevalence of approximately 0.7% (1). The etiology of the disorder is not well understood. Despite evidence for genetic factors playing a significant role, the mode of genetic transmission has not been defined. In recent years, it has been postulated that schizophrenia may be associated with combined effects of multiple genes each having a relatively small risk effect (2). Schizophrenia may also be associated with interactions between multiple risk genes (epistasis) as well as between genes and various environmental factors (3). Furthermore, there is growing evidence that *de novo* chromosomal mutations may be involved in the etiology of the disorder (4). In this paper, genetic research of schizophrenia will be reviewed with special focus on new developments in genome-wide association studies (GWAS) and investigations of the role of copy number variations (CNVs) in schizophrenia.

Behavioral genetics

Multiple family studies have consistently found higher risk of schizophrenia in patients' relatives than in the general population. Studies using operational diagnostic criteria and meticulously collected control samples have found that first-degree relatives have 3–15% risk of developing schizophrenia, while relatives of healthy controls have 0.5–1% risk (5).

The relative contributions of genetic and environmental factors can be investigated in twin and adoption studies. The concordance rate for schizophrenia is 45–75% among monozygotic twin pairs but only 4–15% among

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dizygotic pairs (6). This shows that genetic factors play an important role in the development of schizophrenia, while also allowing for non-genetic influences. From twin studies, heritability, which is the proportion of phenotypic variation that is attributed to genetic variation, can be assessed. A meta-analysis of 12 schizophrenia twin studies found the estimate of heritability in liability to schizophrenia to be 81% (7), which is higher than for most complex diseases with established genetic risk such as type II diabetes and breast cancer (8, 9).

Adoption studies provide a method for evaluating the role of genetic factors in schizophrenia independent of influences from the family environment. Studies show that the lifetime prevalence is about 10 times higher among individuals who are adopted away from a schizophrenic parent than among individuals who are adopted from healthy parents (10).

Molecular genetics

Modern molecular genetic research started in the early 1980s with the introduction of technologies such as polymerase chain reaction, which allowed researchers to investigate pieces of deoxyribonucleic acid (DNA) in more detail than before. The two main approaches that have been used for identifying schizophrenia genes are linkage analysis and association studies.

Linkage studies

In linkage analysis, families with two or more affected individuals are studied to identify the co-transmission of genomic regions with the disease. Statistical analysis is employed to determine whether two segments of DNA are transmitted together to an offspring more often than would be expected by chance. This approach can be applied genome-wide by using several hundred equally spaced genetic markers to screen the whole genome for possible disease genes. The linkage approach can be a powerful tool for locating DNA markers or genes of major effect as was demonstrated in disorders such as neurofibromatosis and hereditary non-polyposis colon cancer (11,12). Linkage analysis is, however, a weak strategy for identifying few or multiple genes of small effect. A significant or suggestive linkage signal does not identify a specific liability gene but a particular region of the genome, which can be quite large and may include a large number of genes.

Early genome-wide linkage studies of schizophrenia implicated multiple chromosomal areas but very few of those fulfilled criteria for statistical significance and subsequent studies were usually unable to replicate positive findings (13). The inability to find replicable positive linkage in schizophrenia was explained by inadequate sample sizes and small effects of individual genes. Alternatively, the inconsistent findings may be associated with different phenotypic models and use of different markers between studies (14). However, at the end of the 20th century, when over 20 genome-wide linkage studies had been completed, several chromosomal areas had shown linkage in two or more samples. In three meta-analyses of schizophrenia linkage studies evidence for linkage was found on chromosomes 1q, 2q, 3p, 4q, 5q, 6p, 8p, 11q, 13q, 14p, 20q and 22q (15–17). Only 8p was supported by all three meta-analyses. Overall, the message from extensive linkage studies is therefore consistent with the notion that the genetic risk in schizophrenia is probably largely explained by multiple genes, each of which account for only a small increase in risk. However, they do not exclude the existence of rare variants conferring high risk.

Association studies

In association studies, the frequencies of alleles in previously identified candidate susceptibility genes are compared between unrelated samples of affected individuals and healthy controls drawn from the same population. An allele is one member of a pair or series of genes that occupy a specific position on a chromosome. Unlike the linkage approach, association studies are able to identify specific genes of small effect provided sample size is adequate. Until recently, it was not possible to apply the association approach genome-wide because of technological limitations.

Early association studies focused on genes which were selected on the basis of their functionality (e.g. coding for a protein involved in dopamine neurotransmission) or on positional findings from previous linkage studies, thereby constituting functional and positional candidate genes, respectively. The limited knowledge of how functional candidate genes may be involved in the pathophysiology of schizophrenia and the lack of replicated linkage findings proved to be major obstacles in association studies for years. Stratification and multiple testing also posed significant problems in these studies and unequivocal evidence of replicated associations remained lacking. A stratification effect may appear when a certain marker and a specific disorder are common in a part of the population, but there is in fact no true causal relationship. A multiple testing effect refers to the risk of false positive findings because of chance when many markers are investigated in the same study.

Many association studies have looked at functional candidate genes involved in dopamine and serotonin transmission such as the genes coding for catechol-*O*-methyltransferase (*COMT*), the dopamine transporter (*SLC6A3*), dopamine receptors 1–4 (*DRD1–4*) and tryptophan hydroxylase 1 (*TPH1*). *TPH1* is the rate-limiting enzyme in the synthesis of serotonin. Meta-analyses of these studies have demonstrated significant associations of polymorphisms in the *DRD2* and *TPH1* gene with schizophrenia (18).

Linkage disequilibrium mapping

Advances in genome analysis technology and the application of linkage disequilibrium mapping have made it possible for researchers to identify candidate genes within linkage regions. Linkage disequilibrium refers to the non-random association of alleles at two or more loci either on the same or different chromosomes. This approach allows testing of specific allele variants such as single nucleotide polymorphisms (SNPs). SNPs are transformations of one DNA nucleotide to another, for example C (cytosine) to T (thymine) that is inherited across generations. Allele variants are said to be in linkage disequilibrium when they do not travel randomly but together across generations. Finding a suspected disease variant more frequently in patients than healthy controls constitutes evidence of genetic association. If such an association is not an artifact caused, for example, by multiple testing, genotyping errors or population stratification, the variant either is a causative marker or is in linkage disequilibrium with a nearby causative sequence variant.

When several SNPs are in linkage disequilibrium with each other, association analyses of individual SNPs may lead to a biased estimate of the genetic effect. This problem can be circumvented with haplotype analyses in which sets of several SNPs (haplotypes) are investigated together. Haplotype analysis can help increase the power of association analysis by differentiating the true effects of a SNP from what is related to its linkage disequilibrium with another SNP. Haplotypes also increase the power of association analyses because fewer SNPs need to be typed. This is because some of the SNPs are so-called tag SNPs, which can represent the whole set of polymorphisms belonging to the haplotype. Therefore, it is possible to identify genetic traits involving multiple SNPs by detecting only one or a few SNPs from a haplotype.

Since 2002, a series of studies employing various methods of fine mapping of linkage regions have identified several putative risk genes for schizophrenia. There is an enormous and constantly growing schizophrenia candidate gene literature including both positive and negative findings. For many of the positive studies evidence for association with schizophrenia is weak (odds ratio 1.1–1.2) and consistent replications are lacking. Odds ratio is the ratio of odds of an event occurring in one group to the odds in another group. An odds ratio of 1 indicates that there is no difference in odds between the two groups. The strongest reported evidence has been observed for the genes dystrobrevin-binding protein 1 (*DTNBP1*) and neuregulin 1 (*NRG1*). Data for several other genes such as D-amino acid oxidase activator (*DAOA*) and regulator of G protein signaling 4 (*RGS4*) have also been considered promising but less compelling (19).

Genome-wide association studies (GWAS)

Until recently, the use of association studies to search for and detect common genetic risk variants was hampered because only relatively few markers could be tested in each study. This approach was therefore limited to investigations of functional candidate genes rather than the screening for unknown candidate genes over vast areas of the whole genome. Technical advances in the past few years have made it possible to conduct GWAS on thousands of subjects to detect variations of small effect based on positional design and without requirements of functional knowledge. These studies employ so called microarrays or chips, which allow rapid scanning of each individual for 300,000–1,000,000 SNPs across complete sets of DNA to find markers associated with a particular disease. In order to obtain reliable genome-wide significance for individual genotypes, it is necessary to correct for effects of multiple testing. This methodology has been successfully used to identify genetic risk markers for a number of common complex diseases such as diabetes and breast cancer (20, 21).

In recently published GWAS of schizophrenia, no associations with any of the previously identified candidate risk genes were detected (22–24). However, some of these studies have identified a number of other interesting candidate genes and several large studies are currently ongoing, which may have power to detect additional markers. In a GWAS of 479 cases and 2937 controls with follow-up of loci reaching a significance threshold in 6829 cases and 9897 controls, O'Donovan et al. (22) found support for a locus in the vicinity of a putative transcription regulator called zinc finger protein 804A or *ZNF804A*. The association of *ZNF804A* with schizophrenia was replicated in two subsequent studies (25, 26). *ZNF804A* is therefore a promising susceptibility gene for schizophrenia. A GWAS by Shifman et al. (27) found evidence in two samples of a female-specific association between reelin (*RELN*) and schizophrenia. Reelin is involved in corticogenesis and this finding therefore supports the notion that schizophrenia is a neurodevelopmental disorder. Recently, Stefansson et al. (24) combined SNP data from several large GWAS and followed up the most significant association signals. They found significant association with five markers spanning the major histocompatibility complex (MHC) region on chromosome *6p21.3–22.1,* one SNP located upstream from the neurogranin gene (*NRGN*) on chromosome *11q24.2* and one SNP in the transcription factor 4 gene (*TCF4*) on chromosome *18q21.2*. *NRGN* encodes a postsynaptic protein kinase and is widely expressed in brain regions important for cognitive function and *TCF4* is involved in brain development. Two other research groups also found associations of SNPs within the MHC region with schizophrenia (23, 25). These findings suggest that the immune system may be involved in the pathophysiology

of schizophrenia through the MHC. Previously, a large Danish registry study had observed association of several autoimmune disorders with increased risk of schizophrenia (28). One drawback of the GWAS search strategy is the fact that it does not provide information on how the putative risk genes may influence risk in relation to the disorder. However, if replicated and found to be consistent, such findings provide previously unknown and exciting avenues for further research.

Chromosomal abnormalities

There are multiple reports of schizophrenia being associated with chromosomal abnormalities (29). Two chromosomal abnormalities have been extensively investigated in recent years and there is evidence for location of schizophrenia susceptibility genes within both of them. First, individuals with a hemideletion on chromosome 22q11 are affected with the so-called velocardiofacial syndrome (VCFS). This syndrome is associated with a large number of physical and behavioral abnormalities. Of particular relevance in this context, is a high (approximately 30%) incidence of psychotic symptoms among individuals with VCFS, which are often indistinguishable from symptoms of schizophrenia (30). Several genes mapping to this region have been studied in relation to schizophrenia such as *COMT* (31) and proline dehydrogenase (*PRODH*) (32). More research is needed to disentangle how genes deleted in the 22q11 area contribute to psychotic features in VCFS.

The other significant chromosomal abnormality associated with schizophrenia is a balanced 1:11 translocation disrupting a gene on chromosome 1 called disrupted in schizophrenia 1 (*DISC1*) (33). There is evidence for association of schizophrenia with several haplotypes and SNPs within the *DISC1* gene but the significant markers tend to differ between studies, which may indicate that there is allelic heterogeneity at this locus (34).

Copy number variations (CNVs)

Recent studies provide compelling evidence that so called CNVs contribute to the etiology of many neuropsychiatric disorders (35). A CNV is a DNA segment in which deletions or duplications have occurred. CNV segments may vary in size and they can be either inherited from parent to offspring or caused by *de novo* mutations (4). These mutations may therefore be unique to a family or unique to an individual (so-called "private mutations"). Following the completion of the Human Genome Project in 2003, it was discovered that CNVs are common and widespread among humans.

CNVs can be detected by various methods including FISH (fluorescent *in situ* hybridization), CGH (comparative genomic hybridization) and by analyzing dosage data from SNP arrays identical to those used in GWAS. The vast amount of data already generated through genotyping samples using the SNP arrays has uncovered thousands of rare CNVs throughout the genome. Genes whose number or functions are affected by CNVs are good candidates for research of disease susceptibility. However, proving causality can be difficult as many of the CNVs are rare and strong association may not be detected unless the CNV variants are recurrent.

There is growing evidence that multiple rare *de novo* CNVs as well as some inherited CNVs contribute to the genetic susceptibility to several neuropsychiatric disorders including autism spectrum disorders and schizophrenia (36, 37). Most CNVs are inherited but *de novo* CNVs have more often been implicated in disease (4). CNVs may also provide a partial explanation for the discordance rate of schizophrenia (approximately 50%) in monozygotic twins. This is supported by studies showing that monozygotic twins attain genetic and epigenetic differences during their lifetime (38) and that both phenotypically concordant and discordant monozygotic twin pairs have different CNV profiles (39). Studies have found more individually rare CNVs in schizophrenia patients than controls. In a case–control study, novel and rare CNVs were found in 15% of patients with adult onset schizophrenia, 20% of patients with childhood onset schizophrenia and 5% of healthy controls (40). Another study found an association of *de novo* CNVs with sporadic cases of schizophrenia but not with familial cases (41). Two independent research groups found rare recurrent deletions on chromosomes *1q21.1* and *15q13.3* to have strong effects on risk of schizophrenia, with odds ratios of 6.6 and 14.8 for *1q21.1* and 17.9 and 11.5 for *15q13.3* (37, 42). Recent studies have also found deletions on chromosomes *2p16* (43) and *15q11.2* (44) and duplications on chromosomes *16p11.2* (45) and *16p13.1* (46) to be associated with increased risk of schizophrenia. Based on these recent findings, it has been suggested that multiple rare and individually different CNVs may contribute to the development of schizophrenia (4). Only relatively large (>100 kb) CNVs have been associated with schizophrenia and the role of more common smaller CNVs is still unknown.

Endophenotypes and schizophrenia genetics

Over the past decade, endophenotypes have attracted increasing attention in psychiatric genetics. Endophenotypes are often defined as objectively quantifiable biological or behavioral features that are thought to be more direct expressions of disease related genes than a clinical phenotype (47). Endophenotypes are trait markers that reflect the actions of genes predisposing an individual to a disease, even in the absence of any noticeable pathology. Therefore, they can be measured not only in patients but also in groups of individuals with high risk of developing the disease such as close relatives of patients.

Endophenotypes are sometimes argued to represent the action of fewer genes than the clinical phenotype and may therefore simplify and increase the power of genetic studies of complex disorders.

Researchers have identified several criteria that a behavioral or biological deficit should fulfill in order to qualify as a promising endophenotype (47). An endophenotype should be associated with the illness. Therefore, it should be frequently found in patients and have a low base rate in the general population. It should have high heritability and be present at a higher rate in unaffected relatives of patients and other high-risk individuals than in the general population. The deficit should be a trait (i.e. have high test–retest reliability) and be independent of variations in clinical symptoms and influences of environmental factors. Unfortunately, none of the proposed psychiatric endophenotypes unambiguously fulfills all these criteria. In studies of psychiatric disorders, endophenotypes have mainly been used to facilitate discovery of disease causing genes and to investigate neurobiological or functional pathways of putative risk genes.

Several candidate endophenotypes have been proposed for schizophrenia. These include electrophysiological markers, neuroimaging phenotypes and cognitive and oculomotor deficits (48). Heritability estimates for candidate endophenotypes such as sensory-motor gating, verbal fluency, spatial working memory and oculomotor deficits have shown heritability estimates ranging from 32% to 70% (49, 50). Studies have provided evidence of association between proposed schizophrenia endophenotypes and specific genotypes. Arolt et al. (51) reported an association of deficits on the smooth pursuit eye movement task with markers on chromosome *6p21–23*. Leonard et al. (52) found deficits in inhibition of the P50 waveform of the auditory evoked response to be linked with markers on the alpha-7 nicotinic acid receptor gene. A recent genome-wide linkage scan of neurocognitive performance in schizophrenia families found a locus on chromosome 12q to be linked with measures of sustained and selective attention (53).

Originally, there were hopes that the endophenotype approach would allow schizophrenia researchers to identify a few genes of major effect. This has not come to fruition and most investigators agree that it is an unlikely outcome (54). Although the proposed schizophrenia endophenotypes may be more genetically complex than originally assumed, most experts still believe that their genetic architecture is likely to be simpler than that of the clinical phenotype. However, this notion has been contested based on meta-analysis of association studies employing a cognitive endophenotype and schizophrenia in relation to a SNP in the *COMT* gene (55).

Apart from gene discovery, the use of endophenotypes for investigating neurobiological effects of putative risk genes of psychiatric disorders has become more common in recent years following the identification of multiple new candidate risk genes. Often, little is known about the mechanisms by which these genes may confer risk of schizophrenia. By investigating relationships between risk alleles and intermediate phenotypes such as neurocognitive tasks and activity in functional brain imaging, researchers try to characterize the neural mechanisms that are affected by risk gene variants in schizophrenia (56–61). For example, Schmechtig et al. (60) observed a significant association of a *NRG1* risk genotype with spatial accuracy on the antisaccade eye movement task in healthy subjects, but Haraldsson et al. (57) found only trend-level associations of two *NRG1* risk genotypes with performance on antisaccade and smooth pursuit eye movement tasks in schizophrenia patients and controls. Two recent studies found the GWAS confirmed risk variant in the *ZNF804A* gene in healthy subjects to be associated with reduced functional connectivity of the dorsolateral prefrontal cortex and hippocampus during the n-back working memory task (56) and with decreased frontal and temporo-parietal activation during a theory of mind task (61). Theory of mind tasks probe the ability to understand the thoughts, emotions and intentions of others, which is frequently impaired in schizophrenia. These findings have shed some light on previously unknown gene pathways and support the validity of the endophenotype approach for studying neurobiological mechanisms of schizophrenia risk genes.

Conclusions

Schizophrenia is a complex brain disorder with substantial heritability. Recent technical advances in molecular genetics are helping researchers developing new strategies for investigating and identifying the genetic components of the disorder. There is growing evidence that both common and rare risk variants are involved in the pathogenesis of schizophrenia. Recent studies indicate that individual common variants make relatively small contributions to the overall risk but some very rare CNVs may have much higher effect sizes when present. GWAS have identified new putative candidate risk genes and have opened new avenues for investigating how multiple genes may act in functional biological pathways forming the genetic basis of common diseases. In the near future, new developments in whole-genomic sequencing technology will add to our knowledge of how common and rare SNPs, CNVs and other genetic variations modulate the risk of developing schizophrenia and how the genes interact with environmental factors. Endophenotypes may be useful for identifying homogeneous subgroups of patients stratified by the presence or absence of certain neural deficits in future GWAS and are already turning out to be helpful for investigating the neurobiological pathways of putative risk genes. Identification of schizophrenia risk

genes and an increased understanding of which neural deficits are associated with these genes may provide important targets for developing novel treatments for this debilitating disorder.

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