What have the genomics ever done for the psychoses?

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Background. Despite the substantial heritability of the psychoses and their genuine public health burden, the applicability of the genomic approach in psychiatry has been strongly questioned or prematurely dismissed.

Method. A selective review of the recent literature on molecular genetic and genomic approaches to the psychoses including the early output from genome-wide association studies and the genomic analysis of DNA structural variation.

Results. Susceptibility variants at strong candidate genes have been identified including neuregulin, dysbindin, DISC1 and neurexin 1. Rare but highly penetrant copy number variants and new mutations affecting genes involved in neurodevelopment, cell signalling and synaptic function have been described showing some overlapping genetic architecture with other developmental disorders including autism. The *de-novo* mutations described offer an explanation for the familial sporadic divide and the persistence of schizophrenia in the population. The functional effects of risk variants at the level of cognition and connectivity has been described and recently, ZNF804A has been identified, and the MHC re-identified as risk loci, and it has been shown that at least a third of the variation in liability is due to multiple common risk variants of small effect with a substantial shared genetic liability between schizophrenia and bipolar affective disorder.

Conclusions. The genomics have done much for the psychoses to date and more is anticipated.

Introduction

From classical family, twin and adoption studies, the major psychoses are strongly familial and have a substantial genetic component. As with other complex genetic disorders, the underlying genetic models involved are far from certain, but are likely to involve interaction between multiple genetic and possibly environmental risk factors. Given that these disorders have a significant public health impact, are only partially amenable to current treatments, and are not readily preventable by environmental change, identifying genes and underlying pathophysiology is of more than academic interest (Merikangas & Risch, 2003). The emergence of molecular genetics offered the hope that such genetic variants could be identified, potentially illuminating the pathophysiology involved. However, because of the nature of the problem – identifying multiple small effects *contributing* risk, rather than large genetic effects *causing* Mendelian

disorders – and the investigative tools available, we remain (largely) in the dark as to the nature of the genetic mechanisms involved.

With the early developments in molecular genetic methodology, family-based studies identified regions of the genome genetically linked to a number of Mendelian disorders. Due to limitations of the molecular resources available at the time, for conditions such as Huntington's disease, it took many years following the initial identification of genetic linkage to the disorder before causative mutations were identified. However, technologies improved, the Human Genome Project began and successes with Mendelian disorders began to pile up. Similar work began for neuropsychiatric disorders despite well recognized problems including the delineation of the diagnostic boundaries of the particular disorder, and the lack of obvious models of transmission. Penrose (1971) began his editorial in this journal with 'Genetics and psychiatry make strange bedfellows'. This can still be said today, with molecular genetics having little or no impact as yet on clinical psychiatry.

There has been scepticism from the early days about the use of molecular genetic methods for any

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common complex disorder, but particularly relating to psychiatric or behavioural disorders (Rose, 1998). This scepticism was given apparent substance by the lack of reliable findings emerging from what was becoming an extensive literature of linkage and association studies (van den Oord, 2002). The field was not encouraged by initial results with some high-profile reports of genetic linkage for both bipolar affective disorder (Egeland *et al.* 1987) and schizophrenia (Sherrington *et al.* 1988), emerging as false-positive findings (Kelsoe *et al.* 1989). The early association studies also brought criticism for the small samples used and for the statistical handling of multiple testing. It was observed that success would depend on the underlying genetic model and that if, for example, there was very significant phenotypic and genetic heterogeneity – the multiple rare variant model – then linkage might be successful in some large multiply affected families, but with the absence of common risk variants, that association studies would fail. That psychiatric genetics might become the graveyard of molecular genetics (Owen, 1992) was a serious consideration.

Genomics, in particular the recently demonstrated ability of genome-wide association studies (GWAS) to identify common risk variants for other disorders of public-health significance, is transforming medicine. The list of genetic variants reliably associated with common human disease has expanded from single-digits to hundreds in less than 2 years (http://www.genome.gov/GWAstudies/). More than simply confirming suspected genes these data have lead to novel genetic findings and new avenues for investigating the biology of, *inter alia*, type 2 diabetes, inflammatory bowel disease and breast cancer (Zeggini *et al.* 2008). Clinically this is identifying relationships between disorders (Dubois & van Heel, 2008) and suggesting potential applications such as improving screening programmes for breast cancer (Pharoah *et al.* 2008) or predicting therapeutic response to warfarin therapy (Schwartz *et al.* 2008). Unsurprisingly, testing a million genetic markers for small genetic effects in one experiment poses a multiple-testing problem: a study of 1500 cases and 1500 controls has only 13% power to detect an allele conferring modest risk [odds ratio (OR)=1.3] for a variant with 20% frequency in the population. Success in the three medical disorders described has required pooled GWAS data from 5000 to 20 000 subjects. In each case only a small proportion, typically less than 5%, of genetic variance has been explained: in illuminating genetic architecture of complex disease this is candles in the darkness rather than the flicking of a switch.

Despite the substantial heritability of the psychoses and other neuropsychiatric disorders and their genu-ine public health burden, the applicability of this approach in psychiatry has been strongly questioned or prematurely dismissed (Rose, 1998; Crow, 2008). Data from the large Psychiatric GWAS Consortium (of five disorders including the major psychoses and autism) should be available during 2009, but contrary to the 'candle-snuffing' view, promising findings have already been reported in bipolar affective disorder, schizophrenia and autism (Ferreira *et al.* 2008; O'Donovan *et al.* 2008; Wang *et al.* 2009). GWAS are only one type of experiment, addressing the contribution of common genetic variants of modest effect to susceptibility: the experience of other human diseases tells us that these studies are likely to explain a small, albeit potentially biologically important, component of genetic variance, and additional approaches such as high throughput sequencing are likely to be required to identify rare variants. The 1000 Genomes Project (http://www.1000genomes.org/page.php), is already underway to support this approach.

With the completion of the human genome project and the HapMap project; with exponentially increasing knowledge of individual gene structure, regulation and function; with new Chip-based technologies able to examine most of the common genetic variations and some of the structure of the genome in a single experiment; with gene expression Chip arrays and high throughput sequencing, has there been any important advances in our knowledge of the aetiology of neuropsychiatric disorders? To paraphrase the line from the Monty Python film (for readers not familiar with this film, a clip of the relevant scene is available at http://www.youtube.com/watch?v=ExWfh6sGyso&feature=related):

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Asking this question some years ago, the reply after a pause to stretch the definition of the psychoses would have been:

The identification of APP and Presenilin mutations and ApoEε4 as a general risk factor in Alzheimer's disease?

Autosomal dominant Alzheimer's disease accounts for only 5–10% of all clinically presented cases and includes mutations around the processing sites of the APP molecule resulting in increased production of the β-amyloid peptide; multiple different mutations in the *PSEN1* gene increasing production of Aβ42, and mutations within *PSEN2* resulting in increased β-amyloid production. ApoEε4 is the only molecule that has been associated with all of the biochemical disturbances of the disease including β-amyloid production, fibrillary tangle formation, oxidative stress,

lipid metabolism, synaptic plasticity and cholinergic dysfunction (Cedazo-Minguez, 2007). The insights into the pathophysiology of Alzheimer's disease as a result of genetic findings have suggested novel therapeutic strategies, some of which are in the early stages of clinical trials.

So, apart from identifying β-amyloid production, fibrillary tangle formation, oxidative stress, lipid metabolism, synaptic plasticity and cholinergic dysfunction as key features of Alzheimer's disease, what have the genomics done for the psychoses?

The identification by linkage and association methods of *neuregulin* and *dysbindin* genes as risk genes for schizophrenia?

Neuregulin 1 (*NRG1*) is a large complex gene spanning 1.1 Mb, and belongs to a family of growth and differentiation factors that interact with the ErbB tyrosine kinase transmembrane receptors. Following suggestive evidence of linkage to chromosome 8 p in a study of 33 Icelandic families, the deCode group identified several risk haplotypes within this region in a large case-control sample (Stefansson *et al*. 2002). The core risk haplotype located at the 5′ end of *NRG1* was later replicated in a Scottish sample and, in truncated form, in an Irish sample (Corvin *et al*. 2004). The pattern of both positive and negative results since then, analysed in two follow-up meta-analyses, suggests support for involvement of the locus, but also evidence of genetic heterogeneity. Resolving the presence, or indeed, absence of complex genetic mechanisms at putative susceptibility loci is likely to be answered only by high-throughput DNA sequencing experiments.

NRG1 is also implicated in biological processes thought to be involved in schizophrenia – including glutamatergic *N*-methyl-D-aspartate (NMDA) receptor function and myelination. This positions *NRG1* as both a functional and positional candidate gene for the disorder, making the efforts to tease apart the complexity of its contribution valuable as a model for investigating other susceptibility genes. Animal and human post-mortem studies suggest that NRG1 stimulation suppresses NMDA receptor activation in the prefrontal cortex and that this suppression may be more pronounced in schizophrenia (Hahn *et al*. 2006). Neurodevelopmental roles include attracting (GABAergic) interneurons towards the cortex through its ErbB4 signalling partner, facilitating thalamocortical connectivity (López-Bendito *et al*. 2006), and synapse development (Harrison & Law, 2006). Identified risk variants at NRG1 are associated with reduced white-matter volume and/or white-matter integrity in patients and controls (McIntosh *et al*. 2008). Consistent with this role in grey- and white-matter structure and function, and with its role in NMDA receptor activity, risk variants at *NRG1* have also been associated with variance in multiple behavioural and neuroimaging indices of cognition, although further replication of this work is required (Stefanis *et al*. 2007).

Dysbindin 1. Evidence for the involvement of the dystrobrevin-binding protein 1 (*DTNBP1*; dysbindin) gene came from a dense fine-mapping study of the chromosome 6p susceptibility locus in affected Irish families. The *DTNBP1* association now has been reported in more than 10 independent samples (Williams *et al*. 2005) and studies have again differed in the alleles/haplotypes reported. As with *NRG1*, the lack of a clear risk variant precludes definitive evidence of statistical association. However, there is additional functional evidence implicating the gene in schizophrenia susceptibility, even if its cellular functions are poorly understood. DTNBP1 binds synaptic and microtubule-interacting proteins (Talbot *et al*. 2004; Camargo *et al*. 2007), some of which interact with DISC1, suggesting a link between these two pathways and the possible involvement of DTNBP1 in cell migration or other aspects of neural development. Expression studies have suggested a role for dysbindin in decreased exocytosis of glutamate-containing synaptic vesicles (Bray *et al*. 2005; Weickert *et al*. 2004). In the dysbindin mutant mouse 'Sandy', use of SiRNA to decrease availability of both dysbindin and a related gene *Muted* leads to decreased dopamine levels, and impaired internalization of D_2 receptors from the cell surface and increased intracellular trafficking (Iizuka *et al*. 2007). This suggests a novel regulatory pathway associated with dysbindin; whether this is a main effect, or some compensatory effect, of dysbindin remains to be confirmed.

Consistent with evidence that *DTNBP1* may be associated with a clinical presentation involving more enduring and disabling features of psychosis (Fanous *et al*. 2005; Corvin *et al*. 2008), a series of studies have associated dysbindin risk variants with poorer cognitive function. This association has been with poorer performance in both higher cognitive domains in controls (Burdick *et al*. 2005; Fallgatter *et al*. 2006) and with both general and domain-specific deficits in schizophrenia (Burdick *et al*. 2006; Fallgatter *et al*. 2006; Donohoe *et al*. 2007). The dysbindin risk variant is also associated with significant deficits in early visual processing, indexed by the P1 response (Donohoe *et al*. 2008). Both this 'general' impact on cognition and the association with a more 'trait-like' schizophrenia presentation reflected in an association with poorer pre-morbid functioning in early onset

schizophrenia (Burdick *et al*. 2007), has contributed to the idea of dysbindin as a 'prototypical' schizophrenia gene.

So apart from Alzheimer's disease; identifying neuregulin and dysbindin, genes involved in basic biological functions such as nerve cell growth and differentiation, myelination, cell structure and motility, NMDA receptor function and dopaminergic system modulation, what have the genomics done for the psychoses?

Chromosomal abnormalities and risk of psychosis – Velocardiofacial syndrome (VCFS), Disrupted in Schizophrenia (DISC1) and DNA copy number variation (CNV)?

Many common syndromes have been shown to be related to chromosomal abnormalities. Early examples included trisomy 21 in Down's syndrome, deletion of chromosome 5p in cri-du-chat, a fragile X chromosome site in a syndrome with a variable but characteristic set of physical abnormalities and cognitive impairment, and a reciprocal translocation involving chromosomes 9 and 22 in chronic myeloid leukaemia – the 'Philadelphia chromosome'. An expanding group of genomic disorders have been described, each caused by a structural or CNV in the genome

Chromosome examination in cases with psychosis has not been a common clinical investigation but there are multiple case and short series reports of chromosomal abnormalities in such cases, particularly when the psychosis is associated with cognitive impairment (Demirhan & Tastemir, 2003; MacIntyre *et al*. 2003). Abnormalities in single cases or in small families have been reported for almost all chromosomes but rarely have there been multiple independent cases with the same abnormality, or multiple cases in the same family with evidence of linkage between the psychosis phenotype and the abnormality. There are, however, important examples for both of these scenarios; the 22q microdeletion, reported in multiple cases, and the 1:11 translocation with significant evidence of linkage to psychoses and other psychiatric diagnoses in a large Scottish family.

VCFS

A microdeletion at 22q11.2, is responsible for VCFS, also known as DiGeorge syndrome, a syndrome that is associated with a wide range of variable clinical features including a characteristic physiognomy, cardiac defects, palate abnormalities, learning disability and a rate of psychosis some 20–30 times greater than in the general population (Gothelf *et al*. 2008). The microdeletion is typically of $\sim$3 Mb but is smaller

in some cases. Recent use of microarray technology allows for much greater resolution showing small but significant differences between deletions apparently the same using conventional cytogenetic methods (Urban *et al*. 2006). VCFS has provided a model for investigation of the biological basis of psychosis, with most individuals having 40 genes deleted, including among them *COMT* and *PRODH*, genes also reported to be associated with non-VCFS psychosis (Karayiorgou & Gogos, 2004; Arinami, 2006). The increased risk for schizophrenia is thought to be due to haploinsufficiency of one or more of the genes involved. Mouse models with an engineered deletion similar to the human deletion show deficits in sensorimotor gating and cognitive impairment (Paylor & Lindsay, 2006). Stark *et al*. (2008) have engineered a mouse model by deleting the mouse sequence relating to the smaller 1.5 Mb deletion region in humans, including the genes *COMT*, *PRODH* and *DGCR8*. These mice show dysregulation of genes outside the deletion region, including those involved in synaptic transmission. Other mutation studies in mice have implicated TBX1, a member of the T-box family of transcription factors. Altered TBX1 dosage appears to account for most of the VCFS equivalent phenotype in mice (Liao *et al*. 2004; Aggarwal & Morrow, 2008). Supporting this finding is the identification of inactivating TBX1 mutations in rare non-deleted VCFS patients (Paylor *et al*. 2006).

DISC1

Interest in the DISC1 locus spans almost 40 years since a balanced translocation at 1:11 (q42; q14.3) was initially reported in an individual with adolescent conduct disorder (Jacobs *et al*. 1970), and later identified in several additional family members who also presented with major psychiatric disorders (St Clair *et al*. 1990). Detailed clinical investigation of the family and a linkage analysis generated odds score of 3.6 when schizophrenia was taken as the phenotype, increasing to 7.1 when relatives who had bipolar disorder and recurrent major depression also were included (Blackwood *et al*. 2001). The breakpoint on chromosome 1 disrupted two overlapping and opposite sense genes, *DISC1* and *DISC2*. *DISC1* gene has at least 13 exons and spans more than 300 kb, with exon 8 comprising one third of this area. Protein expression associated with *DISC1* is disrupted within intron 8, removing exons 9–13 to chromosome 11. Association studies of DNA variants around these genes in Finnish, North American, Scottish, Japanese, and Han Chinese populations suggest that DNA variation, in addition to disruption caused by translocation, confers susceptibility to major mental illness

(Hennah *et al.* 2003; Cannon *et al.* 2005; Kilpinen *et al.* 2008; Chubb *et al.* 2008). Some of these findings require further replication, and DNA variation at the gene may yet prove to be a very rare cause of disorder, nonetheless, the emerging neurobiology associated with the translocation mutation is increasingly compelling as outlined below.

Implication of the DISC1 protein in multiple cell functions including cAMP signalling, centrosomal and microtubule-based functions, kenesin-mediated intracellular transport and neurite extension have led to its description as a 'hub protein' for both the developing and adult brain (Schurov *et al.* 2004; Sawamura & Sawa, 2006; Chubb *et al.* 2008). Intriguingly, these functions may alternate depending on the stage of development – with important implications for brain plasticity – particularly within the hippocampus. Austin *et al.* (2004) reported that embryonic brain development in DISC1 knockdown mice was associated with inhibited neuronal migration and dendritic arborization. By contrast, Duan *et al.* (2007) found that injecting retroviral vectors expressing DISC1 shRNA into in adult neurons in DISC1 knockdown mice resulted in over-extended migration of newborn neurons, aborization, and abnormal electrophysiological response. DISC1 does not appear to confer these changes in isolation; Duan *et al.* reported similar findings for Ndel1, a DISC1 signalling partner. Other reported signalling partners include LIS1, NDE1, PDE4B, 14-3-3ε, Grb2, and FEZ1, each of which are also implicated in neural cell growth and/or migration (Porteous & Millar, 2006; Chubb *et al.* 2008). In addition to DISC1 being involved in the development of post-mitotic neurons, Mao *et al.* (2009) report that DISC1 also regulates the proliferation of embryonic and adult neural progenitor cells through the GSK3β/β-catenin pathway. Furthermore, GSK3 inhibitors were shown to normalize progenitor proliferation and the behavioural defects caused by DISC1 loss-of-function mutations.

These subtle changes in neuronal growth and migration, particularly in the hippocampus, have been examined in terms of their association with changes in cognitive function, particularly in hippocampus-dependent memory function. In the original discovery of the DISC1 locus, one of the most interesting phenotypic aspects of carriers of 1:11 translocation was that all of the carriers, but none of the non-carriers showed deficits in the P300 response, which is thought to provide an index of memory and attention. Since this initial finding, association between risk variants at DISC1 and deficits in cognition have been reported in multiple studies, primarily in the area of memory function (Burdick *et al.* 2005; Cannon *et al.* 2005). At one level, the agreement between studies is surprising given the alternative SNPs and haplotypes tested. Association of the Ser allele of Ser704Cys with reduced hippocampal grey-matter volume may reflect a specific effect of DISC1's role in brain development, which is being expressed by deficits on memory tasks.

Small structural changes (DNA CNV) in the genome and risk of psychosis

Cytogenetic investigations have become increasingly sophisticated enabling the rapid characterization of identified chromosomal abnormalities but molecular techniques, initially confined to specific regions of the genome such as the telomeres, and more recently genome-wide are identifying a form of genetic variation between individuals consisting of small chromosomal abnormalities known as CNVs (Sebat *et al.* 2004). It is likely that this form of DNA variation is at least as common, if not more so, as sequence variation, accounting for a difference between random individuals of 0.12%, compared to a difference of 0.08% at the sequence level (Sebat, 2007). Small genomic structural changes can be defined as deletions, insertions, duplications and inversions of kilobase to megabase size although the term CNV may be confined to those leading to changes in gene copy number (Korbel *et al.* 2008). CNVs are likely to be important in the evolution of higher organisms with duplicated genes becoming free to develop new functions. In addition, CNVs seem to relate to proteins involved in response to the environment, a finding that may be relevant to the psychoses.

Samples of patients with schizophrenia and other psychoses have been surveyed using CNV detection technologies (Wilson *et al.* 2006; Moon, 2006). Because techniques are still developing, the frequencies reported might be inaccurate. However, if the genome-wide methods are followed with experimental validation then the figures given are likely to be conservative. Novel deletions and duplications appear to be more common in cases of schizophrenia (15%) compared to controls (5%) and especially so for very early onset cases (Walsh *et al.* 2008). Walsh *et al.* identified several gene pathways and processes that were over-represented by genes affected by duplications and deletions in the schizophrenia cases, including amongst others, glutamate receptor signalling, neuregulin signalling, synaptic long-term potentiation and nitric oxide signalling. Many of these gene families have already been implicated in psychoses. These findings suggest that schizophrenia can be caused by rare mutations that disrupt genes in pathways of neuronal development and regulation.

Two recent surveys [International Schizophrenia Consortium (ISC), 2008; Stefansson *et al.* 2008], using

different technologies to the Walsh *et al.* (2008) paper have confirmed that rare chromosomal deletions and duplication increase risk for schizophrenia and have identified specific deletions on chromosomes 15q11.2 15q13.3 and 1q21.1 in multiple cases similar in frequency to the 22q deletions seen in cases of schizophrenia with VCFS. Even though very rare, the OR are $21.6 - \propto$ for the 22q11.2 deletion, 3.9 for 15q11.2, 8.94–17.9 for 15q13.2, and 6.6–8.68 for 1q21. The 15q region is consistent with a deleted region reported in cases of mental retardation with seizures and five of the nine patients with schizophrenia had mild cognitive impairment and one had a history of seizures. The 1q region was previously reported in some cases of autism and in a patient with learning disability and epilepsy. In the second survey, *de-novo* CNVs were identified in a family-based sample and tested for association in a further sample of cases. As well as the two loci in the ISC (2008) report, an additional locus at 15q11.2 was identified. These events are a rare cause of disorder; for example, the 15q11.2 deletion occurred in 0.55% of cases compared to 0.19% of controls. This deletion, ∼470 kb in length is consistent with a region deleted in a small number of cases of Angleman and Prader–Willi syndromes and includes the gene *CYFIP1*, which interacts with the fragile X mental retardation protein as well as *RAC1*, which is involved in regulating axonal guidance and dendritic outgrowth, functions similar to the *DISC1* gene. Cases of fragile X and obligate carriers show features of autism with attentional deficits and psychotic symptoms. The 15q deletion contains the *CHRNA7* gene, previously implicated in schizophrenia. This gene is targeted to axons by neuregulin 1, described above.

The evidence that CNVs are causative of schizophrenia is both statistical and biological. There is an increased frequency of some CNVs individually, and CNVs collectively in cases compared to controls. They target gene pathways that could plausibly be involved in the disease (Walsh *et al.* 2008), and several CNVs have arisen *de novo* and affect known candidate genes. *De-novo* copy number mutations appear to be up to eight times more common in sporadic cases, but not familial cases, compared to controls (Xu *et al.* 2008). These authors argue that the marked and specific enrichment of rare *de-novo* CNVs in sporadic cases is strong evidence that they are highly likely to contribute to the disorder. Other studies of CNVs have focused on a given region of the genome or indeed a single gene. Rujescu *et al.* (2009) report a study of *neurexin* genes showing a frequency for deletions and duplications disrupting *neurexin 1* of 0.47% in cases compared to 0.15% in controls, an OR of ∼9 (compared to an OR of ∼30 for VCFS). Mutations in *neurexin 1* were previously described in a sibling

pair with schizophrenia and their unaffected mother (Kirov *et al.* 2008). They are also described in autism (Kim *et al.* 2008) and consistent with that literature, the common theme in these mutations is disruption of the gene itself rather than a sharing of size and breakpoints. Neurexin is found predominantly at the presynaptic membrane and functions as a neuroligin receptor. This creates a trans-synaptic complex involved in excitatory glutaminergic and inhibitory GABAergic synapses (Craig & Kang, 2007). In turn, neuroligin binds a set of scaffold proteins in the membrane associated with the guanylate kinase family that includes PSD-93 that have been reported as affected by CNVs in schizophrenia (Walsh *et al.* 2008). A further study (Friedman *et al.* 2008) has identified CNVs in *CNTNAP2* in some cases of schizophrenia. The *CNTNAP2* encoded protein is a member of the neurexin super-family. A further CNV was reported in a single case in the *APBA2* gene, the protein of which binds neurexins. These genes link with the *neuregulin* gene and its interacting partners ERBB4 and MAG12 through PSD-95, the protein of which recruits ERBB4 to the neurexin–neuroligin complex (see Südhof *et al.* 2008 for a review of neurexin function).

The emerging findings from analyses of CNVs are that they are more common in cases, particularly early onset cases, cluster in certain regions of the genome, account for small but significant numbers of cases, and involve neurodevelopmental, cell signalling, and synaptic function genes. They may be recurrent, such as with VCFS, chromosomes 1q21.1, 15q11.2, and 15q13.3; affect particular genes, such as *neurexin 1*, unique in cases but inherited, or occur *de novo*. The *de-novo* findings are more common in sporadic than in familial cases and provide a source of new mutation, contributing to the persistence of schizophrenia in all populations despite its association with reduced fecundity (Stefansson *et al.* 2008).

Apart from Alzheimer's disease; identifying neuregulin, dysbindin, DISC1 and neurexin 1; rare CNVs and new mutations affecting genes involved in neurodevelopment, cell signalling and synaptic function; overlapping genetic architecture with other developmental disorders including autism; and with new mutations offering an explanation for the familial sporadic divide and the persistence of schizophrenia in the population, what has the genomics done for the psychoses?

Novel genes identified through GWAS?

GWAS have the power to detect DNA variation of small risk effect and have the major advantages of being unbiased regarding genome location and requiring

no prior knowledge of disease aetiology. They have been enormously successful in a very few years since they became technically and financially practical in multiple complex genetic disorders and traits. The National Human Genome Research Institute's catalogue of published GWAS included 254 publications identifying 788 SNPs associated with a significance value of $p < 1.0 \times 10^{-8}$ (Hindorff *et al.* 2009). GWAS studies in schizophrenia and other psychiatric disorders are beginning to appear in this catalogue. The first studies reported used DNA pooling techniques for economic reasons. Kirov *et al.* (2008) studied 574 parent proband trios following up the most significant findings using individual genotyping. Their best result was within the gene *CCDC60* and their third best within RBP1, a cellular retinol-binding protein that inhibits PI3K/Akt signalling, a previously suggested pathway in schizophrenia pathogenesis. Shifman *et al.* (2008) used the same technique in an initial population of Ashkenazi Jews and identified variants of the *RELN* gene as associated in women only with replication of the sex-specific association in further samples. Reelin, the protein product of the *RELN* gene is involved in neurodevelopment, in particular corticogenesis. Mutations in this gene cause lissencephaly, a neurodevelopmental syndrome with mental retardation. The first fully individually typed GWAS using reasonably sized samples (Sullivan *et al.* 2008) identified only a set of promising SNPs for further study with no result reaching genome-wide significance. O'Donovan *et al.* (2008) in a genome-wide study with extensive follow-up of 12 loci tested at $p < 1.0 \times 10^{-5}$ in multiple samples. Three of these loci provided independent support in the follow-up samples including ZNF804A, which provided the greatest statistical evidence on meta-analysis, and especially so when the phenotype included bipolar disorder. The function of the protein is unknown, but its predicted zinc ion and DNA-binding domains suggest a role in gene expression regulation. Investigating the effect of this variant on cortical connectivity in healthy participants, Esslinger *et al.* (2009) found that risk-allele carriers showed reduced connectivity both within and between the two dorsolateral prefrontal cortex (DLPFC) areas, increased connectivity between the hippocampal formation and the DLPFC, and between the amygdala and the hippocampus, orbitofrontal cortex, and medial prefrontal cortex. Examining brain function at the level of cognition (J. T. Walters *et al.* unpublished observations) showed that the risk allele was also associated with altered neuropsychological performance in episodic and working memory, cognitive functions closely related to the areas of the brain highlighted in the Esslinger *et al.* (2009) study.

Additional large-scale GWAS are beginning to emerge or are completed and awaiting publication. The first of these relates to the sample on which the ISC (2008) published their findings on CNVs. In more than 3000 cases and a similar number of controls, the strongest association findings occurred within the *myosin XVIIIB* gene on chromosome 22, and intriguingly, given the history of linkage studies in schizophrenia, a large number of SNPs on chromosome 6p covering the major histocompatibility complex (MHC). The strongest SNP association which, with imputed data, reached genome-wide significance, is in the MHC 7 kb from *NOTCH4*, a gene previously associated with schizophrenia.

The ISC study also tested the polygenic theory of schizophrenia inheritance by using the ISC sample as a 'discovery' sample, and used SNPs showing nominal association at different levels of significance to test 'target' samples from independent GWAS samples to determine if the nominally associated alleles were enriched. The ISC sample generated SNPs that were highly enriched in three independent schizophrenia samples, estimating that up to a third of the variance in schizophrenia is accounted for by common polygenic variation lying somewhere within the ISC nominally associated SNPs. Interestingly, the same SNPs were also enriched in the WTCCC Bipolar Affective Disorder sample, but not in the other non-psychiatric disorders suggesting that a substantial proportion of risk variants are shared between the two disorders.

The results from further large-scale GWAS are awaited but the data from the ISC study suggests that even with sample sizes between 1000 and 3000 cases and similar or large numbers of controls, individually, these studies are underpowered to reliably detect genes of very minor effects. To address this problem, the Psychiatric GWAS Consortium Steering Committee has been established to conduct within and across disorder mega-analyses of as much GWAS data as can be obtained from publically available databases or through collaboration (Psychiatric GWAS Consortium Steering Committee, 2009). Final numbers for the schizophrenia part of the study are likely to be between 15 000 and 20 000 cases with a similar or larger number of controls. Additional sequencing studies are planned to attempt to identify rare variants, supported by the 1000 Genomes Internal Consortium (http://www.1000genomes.org/page.php). Many additional risk variants should emerge from these studies providing novel leads into gene pathways underlying the biology of schizophrenia.

Will the genetic findings in psychoses translate into clinical practice? It is premature to make predictions as genomic research will continue for some time to be predominantly about discovery of underlying

biological processes and these discoveries may have little immediate impact on clinical psychiatry. It is highly likely that they will have an ongoing impact on diagnostic classification. The recent large family study of schizophrenia and bipolar disorder in the Swedish population (Lichtenstein *et al.* 2009) provides convincing evidence that these two disorders share a common genetic aetiology. Taken together with emerging GWAS data showing risk variants associated with both disorders (O'Donovan *et al.* 2008) and a more general sharing of risk variants (International Schizophrenia Consortium, 2009), these findings have all but destroyed the dichotomous model of the psychoses (Craddock *et al.* 2006). However, their impact on the emerging DSM-V and ICD-11 classification systems is as yet unclear. A more complete understanding of the molecular mechanisms underlying the psychoses may indicate disease subtypes based on shared molecular mechanisms with implications for diagnosis, treatment and prognosis. Further work needs to be done with the emerging rare but more highly penetrant CNVs to determine if they index a particular phenotypic or endophenotypic form of disorder. Perhaps knowledge of particular mutations, for example, those implicating the *neurexin 1* gene might, despite having a variable clinical presentation, plausibly respond to a therapy targeted at the downstream effects of the mutations. Indeed, novel therapies are highly likely to emerge *only* from a better understanding of biological mechanisms. However, even for diseases caused by highly penetrant mutations there are many challenges that remain to be overcome in translating genetic findings and tests into clinical practice (Rogowski *et al.* 2009).

Finally, apart from Alzheimer's disease; identifying neuregulin, dysbindin, DISC1, neurexin 1 and ZNF804A; rare CNVs and new mutations affecting genes involved in neurodevelopment, cell signalling and synaptic function; overlapping genetic architecture with other developmental disorders including autism; and with new mutations offering an explanation for the familial sporadic divide and the persistence of schizophrenia in the population; the functional effects of risk variants at the level of cognition and connectivity; re-identification of the MHC as a risk locus and the demonstration that at least a third of the variation in liability is due to multiple common risk variants of small effect; and a shared genetic liability between schizophrenia and bipolar affective disorder, is it any longer necessary to ask what the genomics has and is doing for the psychoses?

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Declaration of Interest

None.

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