Psychiatric genetics in South Africa: cutting a rough diamond

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Abstract
Psychiatric disorders place a considerable healthcare burden on South African society. Incorporating genetic technologies into future treatment plans offers a potential mechanism to reduce this burden. This review focuses on psychiatric genetic research that has been performed in South African populations with regards to obsessive-compulsive disorder, schizophrenia and bipolar disorder. Preliminary findings from these studies suggest that data obtained in developed countries cannot necessarily be extrapolated to South African population groups. Psychiatric genetic studies in South Africa seem to involve relatively low-cost methodologies and only a limited number of large national collaborative studies. Future research in South Africa should therefore aim to incorporate high-throughput technologies into large scale psychiatric studies through the development of collaborations. On a global level, the vast majority of psychiatric genetic studies have been performed in non-African populations. South Africa, as the leading contributor to scientific research in Africa, may provide a foundation for addressing this disparity and strengthening psychiatric genetic research on the continent. Although the elucidation of the genetic architecture of psychiatric disorders has proved challenging, examining the unique genetic profiles found in South African populations could provide valuable insight into the genetics of psychiatric disorders.

Keywords: Bipolar disorder; Obsessive-compulsive disorder; Pharmacogenetics; Psychiatric genetics; Schizophrenia; South African populations

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pharmacogenetic studies). The Afrikaners are an example of a homogenous population as they arose from a small founder population of 1000-2000 Dutch immigrants that arrived in South Africa in the 17th century.\(^6,13\) The ancient southern African Khoisan population possesses the highest level of genetic diversity reported to date, while the Mixed Ancestry population shows the greatest global admixture of any of the world’s populations analysed thus far.\(^8\) Additionally, the Nguni-speaking Xhosa population shows a significant genetic contribution from the Khoisan in their genomes, reflecting admixture between these ancient individuals and ancestral Bantu populations; artefacts of this exchange are also linguistically evident through the click consonants present in the isiXhosa language.\(^6,8\)

The prevalence of psychiatric disorders in the different ethnic groups of South Africa is not known, although evidence from the South African Stress and Health Study\(^16\) suggests very little difference from non-African populations. However, alarmingly, it appears that the majority of individuals suffering from psychiatric disorders in South Africa do not receive treatment.\(^11\) Revised burden of disease estimates place neuropsychiatric disorders as the third highest cause of disability-adjusted life years in the country, mainly due to the extended morbidity of such conditions.\(^11\) Unipolar depression, alcohol use, bipolar affective disorder, schizophrenia, drug use, obsessive-compulsive disorder (OCD) and panic disorder are neuropsychiatric disorders that fall into the top 20 causes of years lived with disability in South Africa.\(^12\) This is exacerbated by the fact that the pharmacological treatment of these disorders is often inadequate and limited South African data exists for adverse drug reactions (ADRs) and drug inefficacy during the treatment of such conditions. Mehta et al.\(^13\) found that ADRs were detected in 14% of patients treated in a South African hospital in Cape Town. It was found that 46% of these ADRs were regarded as preventable and that 1.5% of community-acquired ADRs resulted in fatality. When compared to an extensive meta-analysis of the incidence of ADRs in United States (US) hospitals, the ADR rate as well as the rate of fatal ADRs was much higher in South Africa (6.7% versus 14.0% and 0.3% versus 1.5%, respectively).\(^14\)

Elucidating the genetic architecture of psychiatric disorders and designing tailor-made pharmaceutical treatment plans would therefore improve the quality of life for affected individuals and their caregivers in South Africa.

The heritability of the majority of the psychiatric disorders is believed to be high, but similar to many complex diseases, the actual genetic mechanisms that underlie them remain to be established and susceptibility is believed to occur as a result of an intricate interaction between a number of genes and the environment. Traditional candidate gene studies have often produced contradictory findings, while genome-wide association studies (GWAS) have only explained a fraction of the heritability of such disorders.\(^15\) This review will focus on psychiatric genetic research into schizophrenia, OCD and bipolar disorder in South African populations with reference to global research, as the vast majority of South African research to date has been performed on these disorders. A glossary of relevant genetic terminology discussed in this review can be found in Table 1.

**Schizophrenia**

Schizophrenia is a chronic psychiatric disorder characterised by positive (i.e. hallucinations and delusions) and negative (e.g. amhedonia, avolition, alogia and blunted affect) symptoms, a lifetime prevalence rate of roughly 1% and a high heritability (reviewed by Van Os & Kapur\(^16\)). Studies investigating the genetic susceptibility to this disorder in South African populations have predominantly been performed by foreign researchers. Riley and collaborators were the first to investigate schizophrenia in a South African population and published a series of manuscripts on linkage analyses in a cohort of Bantu-speaking black South Africans.\(^17-22\) Areas of implied linkage to schizophrenia identified by these studies are displayed in Table II and include genomic regions surrounding the coding regions for subunits of N-methyl-D-aspartate (NMDA) receptors\(^19\) and the alpha7 acetylcholine receptor gene (CHRNA7).\(^22\) NMDA receptors form part of the glutamate system, which is believed to be of relevance as NMDA antagonists (i.e. phencyclidine) cause effects similar to the positive and negative symptoms of schizophrenia.\(^23\) Genetic variants of the CHRNA7 gene have been found to be linked to impaired response to auditory stimuli, frequently observed in schizophrenia patients.\(^24\)

The small sample sizes of these studies involving a cohort of black South African individuals that were broadly classified as Bantu-speaking, however, indicate that these findings should be interpreted with caution, as highlighted by a recent meta-analysis of genome-wide linkage studies of schizophrenia.\(^25\)

To date, some of the most significant research into the genetic component of psychiatric disorders in South African populations has been performed in the Afrikaner schizophrenia population. This group of individuals is largely homogenous (environmentally and genetically) and are therefore less likely to present with confounding factors in genetic epidemiology studies (e.g. population stratification).\(^2\) Since the Afrikaners are a founder population established in the 17th to 18th centuries, linkage disequilibrium (LD) in their genomes extends over further distances than in other populations, including genetically isolated populations such as the Finns and the Sardinians.\(^28\) This therefore aids in the identification of regions of the genome that contribute towards complex traits such as schizophrenia.

Chromosomal locations that have been identified to be putatively linked to the disorder in the Afrikaner schizophrenia group can also be found in Table II.\(^17-28\) The region on chromosome 22q11 is of particular significance for schizophrenia research, as hemizygous microdeletions of this region cause 22q11 deletion syndrome (22q11DS),\(^29\) a syndrome with an elevated prevalence of psychiatric disorders such as schizophrenia (i.e. ~25-30%, compared with a prevalence of 1% in the general population).\(^31,32\) Over 35 genes are deleted in the majority of 22qDS patients, which has lead to the hypothesis that haploinsufficiency of one or more of these genes may contribute to the increased risk for schizophrenia in these individuals.\(^30\) Approximately 1% of schizophrenia patients are believed to harbour 22q11 deletions\(^30\) and in the Afrikaner population, Wiehahn et al.\(^33\) noted, in a small cohort of schizophrenia patients (n=85), that 2.4% of cases possessed 22q11 deletions.

The importance of rare copy number variation (CNV) in Afrikaner schizophrenia patients was recently confirmed by two studies.\(^32,34\) De novo CNV mutations were found to be approximately eight times more frequent in sporadic schizophrenia cases when compared to healthy controls. Deletions of the 22q11 locus were detected in three sporadic cases, confirming this region as the most reproducible, highly penetrant CNV mutation contributing towards schizophrenia-
susceptibility identified to date. Conversely, familial cases of schizophrenia were subsequently shown to have a higher frequency of inherited rare CNV mutations when compared to unaffected individuals. These findings emphasize the heterogeneous nature of the disorder, as susceptibility to familial and sporadic schizophrenia may be caused by different genomic regions or mechanisms.29

Studies have shown that Afrikaner schizophrenia patients are clinically comparable to Caucasian patients diagnosed in the US.7,35 It is, however, also important to investigate indigenous black African populations if the benefits of molecular medicine are to be realised in all of South Africa’s population groups. Our research group has therefore focussed predominantly on schizophrenia subjects from the South African Xhosa population. Although the core symptomatology of Xhosa schizophrenia patients appears to be similar to Caucasian schizophrenia patients36, there are clinical differences between Xhosa schizophrenia patients and those of European descent (e.g. Afrikanders). Considerably less Xhosa patients present with comorbid OCD when compared to Afrikaner cases (0.5% versus 10.7% respectively)36,37 Additionally, to date, no Xhosa schizophrenia patients have been found to carry 22q11 microdeletions, indicating that CNV at this locus may not contribute to schizophrenia-susceptibility in this population.38 It should also be noted that one of the studies of a Bantu-speaking schizophrenia cohort

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**Table I. Glossary of genetic terminology**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Allele</strong></td>
<td>An alternative form of a gene caused by change in the DNA sequence at a particular chromosomal position. CYP gene alleles are designated with an asterisk (i.e. &quot;*) and should contain polymorphisms that &quot;affect transcription, splicing, translation, posttranscriptional or posttranslational modifications or result in at least one amino acid change (<a href="http://www.cypalleles.ki.se).%E2%80%9D">www.cypalleles.ki.se).”</a></td>
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<tr>
<td><strong>Candidate gene study</strong></td>
<td>A genetic study involving a gene thought to be implicated in a particular phenotype (e.g. disease of interest). This is usually based on prior evidence suggesting that the protein may be involved with that phenotype, or linkage data showing an association with the chromosomal region where the candidate gene is located.</td>
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<tr>
<td><strong>Copy number variation (CNV)</strong></td>
<td>Deletion or duplication of chromosomal segments greater than 1 kb in size, which may contain genes, and are caused by non-homologous recombination.</td>
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<tr>
<td><strong>Genome-wide association study (GWAS)</strong></td>
<td>Genomic studies where several hundred thousand variants, spanning the genome, are assayed on “SNP chips”. Unlike candidate gene studies, GWAS has the power to detect associations with genes/pathways that are not previously thought to be associated with the phenotype of interest. Such studies usually follow a case-control design, where allele frequency differences between the two cohorts are tested for significance.</td>
</tr>
<tr>
<td><strong>Genotype</strong></td>
<td>The genetic composition of an organism or the allelic makeup of an individual. A homozygous genotype refers to a sample with two identical alleles, while a heterozygous one describes a sample with two different alleles.</td>
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<tr>
<td><strong>Haploinsufficiency</strong></td>
<td>The situation where an individual possess only one functional copy of a gene, where two functional copies are required to express enough of the respective protein for normal functioning.</td>
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</tr>
<tr>
<td><strong>Haplotypes</strong></td>
<td>Combinations of variants that are inherited together.</td>
</tr>
<tr>
<td><strong>Linkage study</strong></td>
<td>A family-based genetic study that examines the co-segregation of the phenotype of interest with genetic markers to identify relevant chromosomal regions. These data are subsequently used to identify positional candidate genes.</td>
</tr>
<tr>
<td><strong>Linkage disequilibrium (LD)</strong></td>
<td>The process where variants on the same chromosome tend to occur together in a non-random manner (i.e. segregate with one another). LD is caused when a new mutation occurs on a stretch of DNA on a chromosome that is in close proximity to another variant and tends to decay over time due to recombination.</td>
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<tr>
<td><strong>Microsatellite markers</strong></td>
<td>A highly variable type of genetic marker that consists of nucleotide repeats, usually di-, tri-, or tetranucleotide in nature. Microsatellites have been frequently used in linkage studies.</td>
</tr>
<tr>
<td><strong>Next generation sequencing</strong></td>
<td>A recent type of sequencing technology that allows for high-throughput sequencing of millions of DNA sequences in a short amount of time. Advances in this area have applications in personalised medicine, allowing for whole genomes as well as exomes (i.e. coding region of the genome) to be generated in less than a week, at a dramatically reduced cost when compared to traditional methods.</td>
</tr>
<tr>
<td><strong>Pharmacogenetics and pharmacogenomics</strong></td>
<td>Pharmacogenetics and pharmacogenomics involve the study of the genetic determinants of drug response. Pharmacogenetic research focuses on individual genes/alleles, while pharmacogenomics involves the analysis of the entire genome.</td>
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<tr>
<td><strong>Phenotype</strong></td>
<td>The observable characteristics (physical or biochemical) of an organism.</td>
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<tr>
<td><strong>Population stratification</strong></td>
<td>A confounding factor in genetic studies, where there are ancestry differences between cases and controls. Differences in allele frequencies may therefore be caused by differences in ancestry and not the phenotype of interest, resulting in spurious associations.</td>
</tr>
<tr>
<td><strong>Single nucleotide polymorphism (SNP)</strong></td>
<td>A point mutation (i.e. DNA base change affecting a single nucleotide) in the genome. SNPs are catalogued on the dbSNP database (<a href="http://www.ncbi.nlm.nih.gov/snp/">http://www.ncbi.nlm.nih.gov/snp/</a>) using unique reference SNP (rs) identification numbers.</td>
</tr>
</tbody>
</table>
mentioned earlier, found no evidence for 22q linkage. These data indicate that genetic, as well as cultural, differences exist between the black African Xhosa schizophrenia patients and those of Caucasian ethnicity. Therefore, results obtained from one population cannot necessarily be extrapolated to another.

Studies of genetic susceptibility to schizophrenia in the Xhosa population have investigated polymorphisms in the central nervous system related genes, KCNN3 and PPP2R2B, as well as a gene encoding a mitochondrial protein involved in the antioxidant defence system, MnSOD (also known as SOD2).39,40 Neither of these studies, utilising cohorts of over 500 samples, however, found significant associations with schizophrenia. Alternative approaches, such as classifying patients by means of measurable heritable internal biomarkers known as endophenotypes, may produce more successful results.41 The endophenotype concept has gained popularity in psychiatric genetic research as patients suffering from polygenic disorders such as schizophrenia can be classified into more homogenous groups than with conventional diagnoses (e.g. DSM and ICD), thus increasing the chances of identifying causative genes. A putative endophenotype that has been studied in the Xhosa schizophrenia population is the impairment of facial affect recognition when compared to healthy control individuals. Xhosa schizophrenia patients and their unaffected siblings have difficulties recognizing faces displaying negative emotions (i.e. anger), yet show normal recognition to positive emotions (i.e. happiness).42,43 This deficit could serve as a neurocognitive endophenotype that could be investigated in future schizophrenia genetic studies in the Xhosa population.

Obsessive-compulsive disorder (OCD)

OCD is an anxiety disorder that is characterised by obsessions (unwanted, recurrent thoughts or images) and/or compulsions (repetitive behaviours or mental activities), causing marked stress and anxiety for patients (reviewed by Stein44). The disorder displays heterogeneous symptoms and genetic factors are believed to contribute towards OCD susceptibility (from OCD twin study data: heritability reported to be between 45-60% in children and 27-45% in adults).45 Despite the fact that a number of OCD candidate gene studies have been conducted, inconsistent results have been obtained (reviewed by Nicolini et al.46). In South Africa, the majority of research into the genetic susceptibility of the disorder has been performed in the South African Caucasian population, including the Afrikaner population. In line with international research, these studies have predominantly focussed on genes involved in serotoninergic and dopaminergic function.47-58 A summary of genes that have been significantly associated on occasion with OCD and related traits in South African populations can be found in Table III.

The serotoninergic genes are believed to be involved in OCD pathogenesis as selective serotonin reuptake inhibitors

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Effect</th>
<th>Association</th>
<th>References</th>
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<tbody>
<tr>
<td>5-HT1Db</td>
<td>G861C (rs6296)</td>
<td>Synonymous</td>
<td>OCD-susceptibility (Afrikaner male subgroup)</td>
<td>[51]</td>
</tr>
<tr>
<td>5-HT2A</td>
<td>T102C (rs6313)</td>
<td>Synonymous</td>
<td>Trichotillomania</td>
<td>[56]</td>
</tr>
<tr>
<td>BDNF</td>
<td>Val66Met (rs6265)</td>
<td>Amino acid change</td>
<td>OCD-susceptibility, Age of OCD onset</td>
<td>[70]</td>
</tr>
<tr>
<td>COMT</td>
<td>Val158Met (rs44680)</td>
<td>Amino acid change – methionine allele causes a reduction in enzyme activity</td>
<td>OCD-susceptibility, Hoarding in OCD, OCD- symptomatology</td>
<td>[48] [55] [58]</td>
</tr>
<tr>
<td>DRD4</td>
<td>48 bp VNTR</td>
<td>Causes proteins that differ in length (located in exon 3)</td>
<td>Age of OCD onset</td>
<td>[53]</td>
</tr>
<tr>
<td>MAO-A</td>
<td>C1460T (rs137070)</td>
<td>Synonymous</td>
<td>OCD-susceptibility (female subgroup), Sexual dimorphism</td>
<td>[51]</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>5-HTTLPR</td>
<td>S-allele causes decreased expression</td>
<td>Dissociative experiences in OCD</td>
<td>[57]</td>
</tr>
</tbody>
</table>
(SSRIs) effectively treat OCD and form the first-line of pharmacotherapy for the disorder. Genes that have been investigated with regards to OCD in South African populations due to their functional relevance in the serotonergic system include the serotonin transporter (5-HTT) gene (SLC6A4), two serotonin receptor genes, 5-HT_{1A} (also known as HTR1B) and 5-HT_{2A} (also known as HTR2A), and the monoamine oxidase A gene (MAO-A). The SLC6A4 gene is involved in serotonin reuptake at the synapses and variation of this gene has been linked to various psychiatric disorders, including OCD. A functional promoter polymorphism, 5-HTTLPR, has been extensively studied. The resulting alleles differ in transcriptional activity, with the short (S-) allele linked to lower expression of the gene than the long (L-) allele. In South African OCD studies, this polymorphism has not been associated with susceptibility to the disorder, yet homozygosity for the S-allele, in conjunction with neglect, was found to be predictive of dissociative experiences in OCD patients. Results from a meta-analysis of this polymorphism with regards to OCD-susceptibility, emphasize that the 5-HTTLPR polymorphism may be only associated with certain OCD subtypes (e.g. paediatric-onset cases). This may explain the inconsistent results obtained from case-control association studies of this polymorphism.

With regards to the serotonin receptor genes: (i) the genotype distribution of the 5-HT_{1A} G861C polymorphism differed significantly between Afrikaner OCD patients and healthy controls, with more C-homozygotes observed in this patient subgroup, and (ii) interestingly, although variants in the 5-HT_{1A} gene were not found to be associated with OCD in the abovementioned studies, the T-allele of the T102C variant of the MAO-A gene (MAO-A) was associated with dissociative experiences in OCD. Bipolar disorder is an affective mood disorder, which displays heterogeneous symptomatology and is broadly classified into two main types – bipolar I disorder and bipolar II disorder. Patients with bipolar I disorder have at least one major manic episode, while bipolar II disorder is characterized by a milder form of mania. Major depressive episodes are found in both forms of the disorder. An overlap in clinical features exists between bipolar disorder and schizophrenia, and it is believed that the two disorders share a large proportion of genetic risk factors. Research into the genetic component of bipolar disorder in South African populations has been predominantly performed by Savitz and colleagues, using a cohort of Caucasian families, mostly of Afrikaner and British descent (approximately 47 pedigrees of 350 samples). Many of these studies have focussed on gene-environment interactions with potential endophenotypes or intermediate traits. As mentioned previously, the use of endophenotypes in this manner reduces reliance on heterogeneous DSM diagnoses and therefore potentially simplifies the identification of genetic susceptibility factors. However, when interpreting the results of these studies, the effects of multiple testing which may cause false positive associations.
should be considered, as a number of variables have been analysed in a single study cohort.

Linkage studies in this South African cohort employed a targeted approach, focussing on putative bipolar-susceptibility loci. Linkage to the disorder was detected on three chromosomal regions using a broad diagnosis model (Table II), which included, in addition to bipolar disorder, individuals with other psychiatric disorders. The same set of markers was used to examine linkage to a potential endophenotype, neurocognitive function, yet none of these markers reached statistical significance in the entire cohort. However, in one of the Afrikaner pedigrees, a region on chromosome 22q appeared to be associated with this endophenotype. This chromosomal region harbours the COMT gene, discussed in the preceding section, although the Val158Met polymorphism itself was not found to be associated with this endophenotype. This indicates that another polymorphism in this gene, or another gene in the region, could account for linkage to the chromosome 22q region. In other studies of this South African bipolar disorder cohort, the Val158Met polymorphism of COMT was found to: (i) influence dissociation when previous childhood abuse was taken into account; (ii) indirectly impact schizotypal personality traits as a result of childhood trauma and (iii) possibly be implicated in right handedness and by proxy, brain lateralisation, although this final finding is debatable.

Further associations with gene-environment interactions and traits of interest have been detected within this South African bipolar disorder cohort. The extensively-researched psychiatric candidate gene, BDNF, was found to influence neurocognitive performance when combined with childhood sexual trauma. Contrastingly, in another study of this cohort, the 66Met allele was found to interact with childhood abuse and decreased levels of dissociation. These inconsistent findings and those mentioned earlier in this review may be explained if the BDNF Val66Met polymorphism is in partial LD with an unobserved causal variant in certain populations. A recent population genetics study of the BDNF locus reinforced this hypothesis by detecting substantial inter-population haplotype diversity as well as observing positive selection at the cornerstone of the pharmaceutical treatment of bipolar disorder, affects neurotransmitter systems and has been found to influence the glutamate receptors (for a review, see McCarthy et al. None of the SNPs genotyped by Dalvie et al. were associated with susceptibility to the disorder, but the G-allele of the GRIM3 variant appeared to be associated with a tendency for carriers to develop psychotic symptoms (i.e. four times greater risk). Furthermore, a gene-gene interaction was detected between the GRIN2B and DAOA SNPs, which significantly influenced the risk of hospitalisations due to mania. The functionality of the glutamatergic SNPs analysed in the study, however, remains to be elucidated in future studies as they fall within non-coding regions and were selected on the basis of previous associations with psychotic disorders.

Psychiatric pharmacogenetics in South Africa

Pharmacogenetics is a field of research that has grown tremendously over the last two decades and involves the investigation of the genetic determinants of drug response. Pharmacogenomic research has arisen more recently as a term coined to mark the transition from the research of individual pharmacogenetic genes/alleles towards holistic studies that focus on the entire genome and are aided by the use of high throughput technologies (e.g. DNA microarrays). We have previously reviewed the status of pharmacogenetic and pharmacogenomic research in South Africa. This section of the paper will therefore focus on the applications of such technologies in psychiatric settings in South Africa.

A recent review highlighted that the overwhelming majority of psychiatric pharmacogenetic studies have been performed in Caucasian and Asian populations, indicating the need for research that includes the genetically and ethnically diverse African populations. Due to the complex genetic nature of African populations, the majority of pharmacogenetics-related studies have focussed on determining the baseline allele frequencies of relevant pharmacogenetic genes in local South African populations. As can be seen in Figure 1, many of these functional pharmacogenetic alleles differ substantially between populations. For example, the *1B allele of the CYP3A4 gene, which metabolises the majority of clinically available drugs, occurs at a much higher frequency in African individuals. This may have profound implications for African individuals, as they remain underrepresented in pharmacogenetic and genomic research and a great deal of functional variation remains undocumented. The CYP3A4 gene forms part of the cytochrome P450 (CYP) gene family, which encode a group of polymorphic Phase I drug metabolising enzymes that have formed the basis of a large number of pharmacogenetic candidate gene studies. Antipsychotic treatment forms the basis of the...
psychiatric pharmacogenetic research as it is involved in the antipsychotic treatment. Interlinked to those responsible for the therapeutic effects of involved in the pathophysiology of the disorder may be DRD genes), as the neurotransmitter systems potentially pharmacogenetics (e.g. COMT, SLC6A4 and the 5-HT and genes for schizophrenia and antipsychotic products. CMA, Cape Mixed Ancestry.

Figure 1: Frequency distribution amongst South African and worldwide populations of alleles from genes with putative relevance for the pharmacogenetic applications in psychiatric disorders.86-96 The majority of these alleles differ substantially between populations, which could have clinical significance when administering medications that are metabolised or transported by the relevant gene functional CYP2D6 allele frequency in the Xhosa schizophrenia population appears to be approximately 25%, which contributes to the fact that around 12.5% of schizophrenia patients of this ethnicity fall on the extreme ends of the phenotypic spectrum (i.e. individuals who possess no functional copies of the gene or carry more than two functional copies of the gene and are thus likely to experience ADRs or treatment inefficacy, respectively).95 Other pharmacogenetic research in the Xhosa schizophrenia population has revealed a potential association between the MnSOD Ala9Val genotype and the development of abnormal involuntary movements and/or tardive dyskinesia in these individuals.96 These results, however, remain to be replicated in other African schizophrenia populations.

With regards to the treatment of OCD with SSRIs, studies in South African populations have also revealed differences in the frequencies of functional variation in genes that may be relevant for this drug class. The L-allele of the 5-HTTLPR polymorphism of the SLC6A4 gene was observed at an extremely high frequency in the South African Mixed Ancestry and African populations (i.e. 84% and 86% respectively, while other worldwide populations range in frequency 19%-72%).103 This has implications for SSRI therapy, as this allele has been associated with an increase in response to this class of medication.104 The CYP2C19 gene is also involved in the metabolism of SSRIs (e.g. citalopram and sertraline).105 A study of variation of CYP2C19 in healthy individuals from the South African Xhosa and the Cape Mixed Ancestry populations identified novel alleles which should be included in genotype panels for pharmacogenetic association studies of CYP2C19 substrates in these individuals.106 The ATP-binding cassette (ABC) B1 gene encodes a membrane-associated protein, which transports a wide variety of xenobiotic compounds. The 3435C>T polymorphism of this gene has been studied with regard to the SSRI, paroxetine.106 In this study, the C allele of the polymorphism, which is more frequent in African populations (Figure 1), formed part of a haplotype associated with poor response to the SSRI. Future studies could therefore investigate the role that this polymorphism plays with regards to SSRI response in South African OCD patients.

Finally, no research into the pharmacogenetics of lithium response in bipolar disorder has been performed in South African populations to date, although the review of this topic by McCarthy et al.83 could serve as a primer for the direction of future research.

Future directions
This review has highlighted the initial progress that has been made in the field of psychiatric genetic research in South African populations. These findings, however, only scratch the surface of the genomic architecture of psychiatric disorders. This is a global phenomenon, reflecting the complex nature of such disorders. To date, GWAS data from studies of schizophrenia and bipolar disorder have only identified a handful of genetic variants which contribute towards the susceptibility of these two disorders. For example, a meta-analysis of three large schizophrenia GWAS identified one region of genome-wide significance –
chromosome 6p22.1\textsuperscript{106}, while a meta-analysis of bipolar GWAS data identified individual SNPs in the CACNA1C and ANK3 genes that passed the significance threshold.\textsuperscript{107} Strong LD was detected in the region on chromosome 6p22.1, however the exact genes in this region that confer risk to schizophrenia remain to be elucidated. CACNA1C is known to influence neuronal sodium channel activity, while ANK3 encodes an integral adaptor protein for cell membranes, which may provide insight into the association with bipolar disorder. Currently, no comparable GWAS data are available for OCD, but considering the findings for the GWAS studies of the other two psychiatric disorders mentioned here, these studies are unlikely to explain a large proportion of the genetic liability for OCD.

It is important to follow up psychiatric GWAS signals in South African patients to determine whether these findings can be extrapolated to these individuals. A significant challenge in replicating GWAS findings is that the frequencies of many significantly associated GWAS variants vary by 20–40 fold between populations and that ~90% of these types of studies have been performed in European cohorts.\textsuperscript{108} This has implications in all areas of genomic medicine, since the disparity in the number of studies in diverse African populations questions the sensitivity and specificity of genetic tests, which have been designed from European reference assays. It is therefore important to include African individuals in genomic studies to analyse the transferability of risk markers to predict disease or other traits (e.g. drug response) in these populations.\textsuperscript{109}

On a global scale, future research into the psychiatric disorders will see the generation of larger GWAS datasets and a consequent increase in our understanding of the biological pathways contributing towards these disorders.\textsuperscript{110} Additionally, whole genomes of psychiatric patients will become available due to advances in sequencing technologies. Applying next generation sequencing technologies in South African populations should be especially beneficial as the full extent of genetic variation in African populations remains to be catalogued. Current GWAS SNP arrays therefore do not necessarily capture the full extent of haplotypic diversity in these individuals and, additionally, the accuracy of imputation algorithms is lowest in African populations, due to the complex LD patterns observed in their genomes.\textsuperscript{111} Consequently, it is important to build local infrastructure to enable the resequencing and analysis of South African genomes within the country. The benefits of analysing genetic diversity in these individuals using high throughput technologies were clearly illustrated when two genomes and three exomes were generated from five southern African individuals and analysed by Schuster et al.\textsuperscript{112} This study identified over one million novel DNA variants – the highest number of such variants per an individual genome identified to date – yet, currently, these individuals remain the only southern African genome/exome sequences publically available. It will also be important to sequence South African psychiatric patients’ exomes and/or genomes in the future as they may possess unique, rare variation not present in healthy individuals. This is relevant, as rare variants may help explain some of the ‘missing heritability’ which remains undocumented with psychiatric disorders.\textsuperscript{113}

Deep resequencing of psychiatric candidate genes or exomes in South African patients using capture-based methodologies in conjunction with next generation sequencing offers an alternative approach to analysing genetic variation in these individuals. If this cannot be achieved due to certain constraints (e.g. financial), future studies should, at least, include more comprehensive genotyping assays than those used in the past and should simultaneously look at additional genes involved in neurotransmitter pathways. Significant associations should be replicated in independent cohorts; alternatively, in vitro functional analyses can be performed if no such cohorts are available. Another area of genomics that requires further investigation is CNV. These types of polymorphisms take up a similar amount of ‘genomic real-estate’ as SNPs\textsuperscript{113} and rare highly penetrant CNVs are believed to be important in certain psychiatric patients (e.g. chromosome 22q microdeletions and schizophrenia, discussed in preceding sections). Furthermore, another exciting area of research which is believed to be relevant for psychiatric disorders is epigenetics.\textsuperscript{114} This field of research forms the bridge between the genotype and phenotype, investigating changes independent from the underlying DNA sequence. For example, the epigenetic mechanism, DNA methylation, is influenced by exposure to environmental stimuli and can subsequently change the expression patterns of relevant genes in a reversible, yet heritable manner.\textsuperscript{115} Epigenetic variation may therefore explain an additional portion of the ‘missing heritability’ of complex disorders and warrants further attention.\textsuperscript{115}

Future research into the genetic component of psychiatric disorders in South Africa should also strive towards the recruitment of large cohorts of psychiatric patients representing the country’s diverse population groups. For example, research into OCD and bipolar disorder in South African cohorts should be performed in populations other than the South African Caucasian population and the Afrikaner subgroup. It is especially important to include the genetically diverse, indigenous African populations in these studies, as this will help elucidate whether genetic susceptibility loci for psychiatric disorders found in one ethnicity are relevant for another. In terms of schizophrenia research, it would be beneficial if patients from additional indigenous African populations other than the Xhosa could be collected. These samples could be utilised to replicate significant results in the Xhosa population, ensuring robust findings that are suitable for translation research.

Samples gathered for these purposes should be stored in biorepositories and electronically linked to detailed clinical data, therefore enabling potential endophenotypes to be investigated in future research. For example, neurophysiological, neuroimaging, and cognitive traits could be studied and thereby replace dichotomous classification of disease status. Comprehensive data regarding pharmacological treatment as well as the occurrence of ADRs would permit large-scale pharmacogenetic studies to be performed. Future psychiatric genetic studies could also investigate the genomic architecture of psychosis and the overlap between schizophrenia and bipolar disorder. Furthermore, genetic studies of psychiatric disorders that show an elevated prevalence in the country compared to other areas in the world are required. For example,
methamphetamine (known by its local street name, “Tik”) addiction occurs at an alarmingly high frequency in the Western Cape, South Africa. Additionally, psychiatric disorders that place a considerable burden on South African society which have not been studied, such as unipolar depression, require attention.12

Before new pharmacogenetic studies are conducted in South Africa, the phenotypes of drug efficacy or ADRs need to be defined. Future pharmacogenetic studies in the psychiatric setting should aim to limit phenotypic heterogeneity and thus reduce the influence of confounding factors. For example, drug-drug interactions encountered with concomitant treatments (frequently employed in psychiatric patient management) can influence drug response and/or ADRs.13 A high level of antipsychotic polypharmacy (28.6%) has been documented in South African Xhosa schizophrenia patients treated in the Western Cape, South Africa, which was more than double that observed in sites in the US.14

Additionally, prescription patterns varied widely between the different hospitals in this study, emphasising the importance of the standardisation of treatment protocols, especially for research involving patients recruited from more than one study site. Compliance can also adversely affect the outcome of pharmacogenetic studies, specifically in studies involving psychiatric outpatients. Pharmacogenomic phenotypes can be improved by homogenizing treatment protocols, clarifying ADR definitions and setting up procedures that ensure compliance (e.g. prescription monitoring and/or measurement of plasma drug concentration). Study design is therefore imperative to generate clinically relevant findings. More longitudinal studies of patients recruited at their first clinical intervention who are placed on a standardised treatment regime, preferably incorporating depot injections to ensure compliance, are therefore required. Further information on the steps necessary to establish efficient pharmacogenetic studies in large cohorts of patients in South Africa can be found in an article by Warnich et al.84

Conclusion

The field of psychiatric genetics remains under-utilised in South Africa, as highlighted in preceding sections of this review. In comparison, South Africa boasts one of the largest diamond industries in the world, yet traditionally large numbers of rough diamonds have been sent overseas for cutting, reflecting a loss of potential capital and job creation in the country. This mirrors the field of genomics in the country – South Africa has access to some of the most genetically diverse populations and patient cohorts in the world, however limited research has been performed within the country and DNA samples have frequently been sent abroad to be analysed by foreign researchers. It is therefore imperative to create infrastructure to perform large scale psychiatric genetic studies on local soil. Various other aspects, such as the ethical, legal and social implications for performing research in local communities need to be addressed. Although beyond the scope of this review, relevant aspects to be considered include genomic sovereignty (reviewed by Slabbert & Pepper115) and cultural sensitivity towards involvement in genetic/genomic studies. Additionally, it will be important to educate the South African public, psychiatrists and medical students with regards to psychiatric genetics and pharmacogenetics. Performing such studies in South African populations will hopefully allow the communities that have provided valuable samples for research to benefit from pharmacogenetic treatment regimes as well as potential royalties in the future, so that the research remains mutually beneficial. Developing the culture of psychiatric genetic research in South Africa will allow the country to contribute towards the global arena of this form of research and potentially help alleviate the country’s burden of disease as a result of psychiatric disorders.

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