MOLECULAR GENETICS IN CLINICAL PSYCHIATRY


Introduction

“Molecular medicine has the capacity to deliver a precise diagnosis of an individual’s complaint/disease so that therapy can be more effectively tailored. While oncologists are leading the way in this field, psychiatry needs to catch up,” Dr Kobus Roux, psychiatrist in private practice, Benoni, stated at the outset of his well-attended meeting held in February 2016, with support from the Cipla Neuroscience Academy, at the Arabella resort near Hermanus.

Advances in bioinformatics will soon allow storage of an individual’s total genomic data on a single gigabyte memory stick. Costs of DNA determination are also dropping rapidly and analysis of the whole genome can be done for less than US$1000. 23andMe and Illumina market directly to the public and advertise analysis and reporting of raw data from as little as US$390.

KEY MESSAGES

• Understanding of coding genes (exons) and their control by non-coding mechanisms, which are situated in the chromosome (introns) and around the chromosome in the epigenetic environment, is set to re-classify medical illnesses because the ICD10 codes and the DSM-V are not appropriate to the delivery of precision medicine

• All branches of medicine are behind oncology in the use of genetic information to tailor therapeutic options and individualise treatment

• Neuropsychiatry will, over time, move away from defining drugs as affecting particular neurotransmitters to defining them in terms of their capacity to ‘switch on/off’ or modify gene expression

• Pharmacogenomic insights can already be added to current pharmacokinetic and pharmacodynamic knowledge to avoid under-reaction and hypersensitivity reaction to psychiatric drugs

• The methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism is associated with increased risk of coronary artery disease (CAD) in young South African Indians

• A number of treatable genomic MTHFR polymorphisms are important in mood disorders, particularly depression, suggesting that there is a need to augment medication with nutrients such as L-methylfolate or folate

• Lithium should be considered not only as first line for bipolar disorders, but also for other neuropsychiatric disease such as Parkinson’s and mild cognitive impairment (namely the early stages of Alzheimer’s). (Dosage not yet determined)

This article was made possible by an unrestricted educational grant from Cipla, which had no control over content.

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ADVANCING HEALTHCARE FOR ALL

APRIL 2016 1
Relation between genotype and phenotype

There is a complex relationship between genotype and phenotype (Figure 1). “All our phenotypical differences are encoded by 0.1% of an individual's DNA; the larger variations in phenotype are determined by the epigenetic environment and its capacity to modify gene function,” Dr Roux pointed out. On average, 60 new mutations occur in the coding genes de novo (referring to new mutations that were not present in the maternal or paternal genomes), while point mutations (SNPs) occur on average once per 1 000 base pairs (Figure 2). SNPs can be either active or silent, and can also cluster and be inherited together (haplotypes).
For example, in breast cancer, the Human Hapmap project has determined 2600 different alleles of the BRCA1 gene. Of these, some 1100 alleles are associated with a high risk of breast cancer, colon cancer and other specific cancers, and encode for a protein that aggressively stimulates cancer cell replication.

Control of human gene expression – switching genes on and off

Complex mechanisms control the switching on and off of genes. The epigenetic environment is a relatively stable area of gene control; once set, it reacts mostly to severe challenge or in specific pathologies. The dangerous time for modification of the epigenetic area is during the period of conception to birth and during the perinatal period. This highlights the importance of being exceedingly cautious in prescribing drugs during pregnancy and breastfeeding. Figure 3 describes the process of control of gene expression and notes also the importance of small non-coding RNA in the control of micro-RNA. Errors in these microRNAs have been linked causatively with conditions such as muscular dystrophy and offer a potential target for therapy.

The promoter area (illustrated in Figure 3) acts as a switch to silence or express genes. About 32% of all human genomic promoters have a TATA box (consisting of TATA sequences). “To read the TATA box you need a PHD, which in this case stands for ‘planthomodomain’.” Examples of these PHDs are zinc fingers and leucin zippers. This explains the high association across the entire genome between zinc finger genes and many disorders, including mental disorders.

Further regulatory functions are now being ascribed to RNA, beyond its being merely a messenger between RNA and DNA.²

A ‘Google map’ of an individual’s molecular profile

The ENCODE project, undertaken as part of the 1000 Genomes Project, focuses on the control of gene expression and identified four million switches involved in gene expression, thereby placing ‘junk DNA’ in a premier regulating role.

While the data sets are large, a matrix data set built in layers could provide a functional ‘Google map’ of an individual’s total genome against the background of the big data collected from numerous projects. This would allow a prediction to be made of an individual’s health and disease over time (Figure 4). This idea was proposed in a workshop hosted in 2011 by a special task team of the national academies, namely the Committee on a Framework for Developing a New Taxonomy of Disease.

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![Diagram of gene expression](https://via.placeholder.com/150)

**Figure 2. Single nucleotide polymorphisms (SNPs) are the most common genetic variation between people**

![Diagram of gene control](https://via.placeholder.com/150)

**Figure 3. Control of gene expression**

![Diagram of gene expression](https://via.placeholder.com/150)

**Figure 4. Building a knowledge network for biomedical research and a new taxonomy of disease**
Pharmacogenomics of major depression – Dr Eugene Allers

The over-arching aim of pharmacogenomics is individualisation of drug choice for the best treatment outcome with minimum side effects. Using the science of genomics and the understanding of genes and their functioning, optimal drug choice for the individual is possible. In psychiatry, this will help to avoid the situation where patients with the same diagnosis are non-responders to a classic treatment while others experience more toxic events than the norm.

The most significant advance has been in the understanding of the role of telomeres and telomerase, which functions as a reverse transcriptase and protects the telomeres, thereby protecting an individual from the chronic diseases of ageing, including psychiatric illness. (Lectures by the Nobel Prize winner, Elizabeth Blackburn, at www.ibiology.org are insightful.)

“The environment/gene interaction is critical to our health and the development of disease,” Dr Eugene Allers said. “Overall, our resistance to disease is built on genetic modification.” In psychiatry, it is evident that major depression is polygenic, involving more than one gene with their associated SNPs. This makes drug targeting much more difficult and complex.

“Currently, pharmacogenetics is being used to anticipate adverse drug reactions; either hypersensitivity or resistance to medication beyond the well-recognised pharmacokinetic properties and drug-drug interactions,” Dr Allers pointed out.

Pharmacokinetics and pharmacogenomics overlap

The metabolism of most antidepressant drugs involves oxidation by the cytochrome P450 system. There are more than 50 forms of the CYP450 enzyme, but only six (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5) metabolise 90% of drugs. Genetic information on these enzymes can be clinically useful. For example, when patients are extremely sensitive or resistant to a drug at a normal dose, the clinician should first exclude drug-drug interactions and then maybe search for genetic variations in the CYP450 enzyme as an underlying cause1 (Figure 5).

Figure 5. CYP450 inhibitor, inducer and substrate data for drugs present in the Dutch drug top 500 and frequently used food components. (Amended from reference 3)
Similarly, hypersensitivity reactions to drugs can be caused by human leukocyte antigen class 1 (HLA-class 1) alleles and the HLA-allele test for HLA-B*1502 (not yet available in South Africa) can be used to assess the likelihood of a severe hypersensitivity/allergic reaction to carbamazepine.

The future of pharmacogenomics in psychiatry

Currently, GENESIGHTRx is available to test for psychiatric medication responses by analysing a number of relevant genes; the serotonin transporter and receptor genes (SLC6A4 and HTR2A), the P450 and the HLA system. “While this is currently beyond the average South African’s health budget, these reports provide a view of the future of choosing psychiatric therapy for a particular individual,” Dr Allers concluded (Figure 6).

Figure 6. An example of genesight psychotropic results.

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>USE AS DIRECTED</strong></td>
<td><strong>USE AS DIRECTED</strong></td>
</tr>
<tr>
<td>desvenlafaxine (Pristiq®)</td>
<td>asenapine (Saphris®)</td>
</tr>
<tr>
<td>levomilnacipran (Fetzima®)</td>
<td>lurasidone (Latudex®)</td>
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<tr>
<td>paliperidone (Invega®)</td>
<td>paliperidone (Invega®)</td>
</tr>
<tr>
<td>tiotixene (Navane®)</td>
<td>clozapine (Clozaril®)</td>
</tr>
<tr>
<td>ziprasidone (Geodon®)</td>
<td>olanzapine (Zyprexa®)</td>
</tr>
<tr>
<td><strong>USE WITH CAUTION</strong></td>
<td><strong>USE WITH CAUTION</strong></td>
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<tr>
<td>bupropion (Wellbutrin®) [1,4]</td>
<td>clozapine (Clozaril®) [1,4]</td>
</tr>
<tr>
<td>selegiline (Emsam®) [1]</td>
<td>fluphenazine (Prolixin®) [1]</td>
</tr>
<tr>
<td>sertraline (Zoloft®) [1,4]</td>
<td>haloperidol (Haldol®) [1,4]</td>
</tr>
<tr>
<td>trazadone (Desyrel®) [1]</td>
<td>olanzapine (Zyprexa®) [1,4]</td>
</tr>
<tr>
<td>vilazodone (Viibryd®) [1]</td>
<td>quetiapine (Seroquel®) [1]</td>
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**Reference:**
[1]: Serum level may be too high, lower doses may be required.  
[4]: Genotype may impact drug mechanism of action and result in reduced efficacy.  
[6]: Use of this drug may increase risk of side effects.  
[8]: FDA label identifies a potential gene-drug interaction for this medication.  
[9]: Per FDA label, this medication is contraindicated for this genotype.

All psychotropic medications require clinical monitoring. Drugs are reported in alphabetical order. This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient’s individual needs and the characteristics of the drug prescribed.

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Molecular Genetics in Clinical Psychiatry

6 APRIL 2016

Treatable Genomic Polymorphisms of 5,10-Ethylene Methylene Tetrahydrofolate Reductase (MTHFR) – Dr Elizabeth Peter-Ross, Groote Schuur Hospital, Neurogenetic Psychiatric Clinic

Introduction

“Psychiatrists are going to have to stretch their understanding – moving from clinical evaluation to a molecular and cellular understanding of the conditions they treat. The clinical construct referred to as schizophrenia, for example, is an ‘umbrella term’ and in the future there will be many different causative environmental factors and genetic abnormalities identified, each giving rise to a specific subtype,” Dr Elizabeth Peter-Ross noted at the outset of her presentation. Psychiatrists should keep up to date on the latest clinical and molecular psychiatric findings by reading Molecular Psychiatry and the free online publication, Translational Psychiatry. These informative journals are part of Nature publications and are available to better understand developments in this rapidly expanding field. www.nature.com/mp/index.html and www.nature.com/tp/index.html

Genomic Polymorphisms of MTHFR include MTHFR C677T and MTHFR A1298C

“Patients with resistant depression should be tested for MTHFR polymorphisms. These polymorphisms are the only known treatable genomic polymorphisms. A resulting additional benefit of this approach is that the patient begins to focus on better nutrition and making lifestyle changes,” noted Dr Peter-Ross.

MTHFR is a key enzyme in the folate metabolism pathway because it directs folate from the diet either to DNA synthesis or homocysteine remethylation. MTHFR is on chromosome 1p36.22. There are a number of SNPs of the MTHFR gene. MTHFR C677T and MTHFR A1298C are considered the most relevant ones for neuropsychiatric disorders as they can reduce methylation. Homozygous MTHFR A1298C is common but does not seem to pose as much of a problem as MTHFR C677T. However, if homozygous for both MTHFR polymorphisms, the residual enzymatic activity may be further diminished. These two treatable genomic polymorphisms need to be DNA tested. Genomic polymorphisms are treatable with L-methylfolate, a prescribed medical food (as yet not available in South Africa in tablets containing a large enough amount of L-methylfolate). The therapeutic dose range for depression is thought to be 7.5-15mg. Only low-dose preparations are available in South Africa at present: Metafolin 1000ug, Folapro 800ug and 5-MTHF ES as nutrient supplements to be taken along with vitamin B complex (vitamin B2, 6 and 12) supplements and dietary and lifestyle changes.

Dietary folate (vitamin B9) requires the two enzymes dihydrofolate reductase (DHFR) and MTHFR to transform folate into L-methylfolate within the brain. Folic acid is a synthetic substance taken as a nutrient or as a supplement in fortifying food. The healthiest way to obtain folate and L-methylfolate is by eating the correct foods (Figure 7).

Figure 7. L-methylfolate’s mechanism of action

Patients with resistant depression should be tested for MTHFR polymorphisms. These polymorphisms are the only known treatable genomic polymorphisms.”

“A resulting additional benefit of this approach is that the patient begins to focus on better nutrition and making lifestyle changes.” Dr Elizabeth Peter-Ross

[Diagram of folate metabolism]
L-methylfolate, along with the co-factor of tetrahydrobiopterin (BH4), produces the monoamine neurotransmitters (serotonin, dopamine and noradrenaline). L-methylfolate is essential for single carbon methylation and functions to turn genes on and off. Other functions of methylation include synthesis of nucleic acids, producing and repairing DNA and tRNA, maintenance of methyl pool, genomic stability, energy production and myelination, processing estrogen hormones and building immune T cells and natural killer (NK) cells.

**Medications and factors that lower folate levels**

It is hoped that the alphabetical list below of medications and lifestyle factors that lower folate levels will be helpful for all healthcare practitioners and their patients (Table 1).

<table>
<thead>
<tr>
<th>Medication</th>
<th>Folate plasma level with adjuvant drugs</th>
<th>Drug plasma level with adjuvant high dose folate*</th>
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<tbody>
<tr>
<td><strong>Medication</strong></td>
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<tr>
<td>Anticonvulsants (1st generation): carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone, valproic acid, valproate</td>
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<tr>
<td>Anticonvulsants/mood stabilisers, lamotrigine</td>
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<td>Cholestyramine</td>
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<td>Colchicine</td>
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<td>Colestipol</td>
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<td>Isotretinoin (Roaccutane)</td>
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<td>Methotrexate</td>
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<td>Methylprednisone</td>
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<td>NSAIDs (high dose): ibuprofen, naproxen, indomethacin, sulindac</td>
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<td>Oral contraceptives</td>
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<td>Pancreatic enzymes: pancrélipsase, pancratin</td>
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<td>Pentamidine</td>
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<td>Pyrimethamine</td>
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<td>Sulfasalazine</td>
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<td>Triameterene</td>
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<td>Trimethoprim</td>
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<tr>
<td><strong>Lifestyle</strong></td>
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<td>Smoking</td>
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<td>Alcoholism</td>
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<td>Poor nutrition</td>
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<tr>
<td>Coffee (more than four cups/day)</td>
<td>↓</td>
<td>–</td>
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<tr>
<td>Gastrointestinal and absorption disorders</td>
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<tr>
<td>Pregnancy</td>
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Lithium increases MTHFR and thus increases L-methylfolate in the brain

Lithium is still the most important and first-line treatment for bipolar disorder. “In this presentation, I want to focus on the cellular and molecular pathways involved in lithium’s mechanism of action,” Dr Peter-Ross pointed out (Figure 8). Current research is exploring the pharmacogenetics of lithium responders – but this is still in its infancy.

Lithium is known to increase the essential cellular process of autophagy and as part of the underlying etiopathology of Parkinson’s disease and neurodegenerative disorders includes impaired and/or altered autophagy, lithium is now being considered as a possible preventive and way to reduce the progression of the neurocognitive aspects of these diseases.

Figure 8. First-line treatment for bipolar disorder
Immunology, stress and brain circuits – Dr Leigh Janet

There is extensive evidence supporting the role of activation of the immune system in the serious mental illnesses, such as schizophrenia, bipolar disorder and major depressive disorder.

The models described are derived largely from rodent models and caution should be exercised when extrapolating the findings to humans. Immune activation may arise from many causes, including, but not limited to, intrauterine challenges such as maternal infections and maternal stressors. There is also growing appreciation that the gut microbiome plays a significant role in the modulation of the state of inflammatory preparedness of the body (Figure 9).

Figure 9. Microbiota-gut-brain axis in health and disease

Early postnatal psychosocial stressors also give rise to immune activation. One of the key messages is that psychosocial stressors impact the brain, and the stress may be transferred to the brain via the immune system, among others.

Other mediators of stress that impact the brain are the HPA axis, predominantly through the activity of cortisone/corticosterone (in rodents). The role of cortisone was discussed. Dr Janet focused particularly on the hippocampus, the amygdala and the prefrontal cortex, which are the best studied sites, but there are probably many other brain areas affected by these processes.

The impact of the stressors on the brain affects the genetics and epigenetics of the neurons in the regions mentioned. However, there are also effects on the structure and function of the neurons, including the length and branching of dendrites - which implicitly affect local synaptic connections and networks. Different areas of the brain react differently to the stress. In some areas the dendrites shorten and lose their spines (e.g. area CA3 of the hippocampus) whereas in parts of the amygdala, the spines may lengthen in response to stress. Other changes that occur under stress are changes in neurogenesis and receptor and mitochondrial trafficking.

The impact of excitatory amino acid activity, the kynurenic acid system and possible mechanisms for monoaminergic amino acid depletion in the immune-stress model were reviewed. Apart from the structural changes in the neurons which follow exposure to stressors, signalling molecules, such as BDNF, tissue plasminogen activator, CRF, lipocalin-2 and endocannabinoids, are secreted in response to stressors. In resilient rodents these changes reverse when the stress passes, but in other vulnerable rodents...
the changes, especially the epigenetic markers, do not reverse when the stress passes. This has the effect of ‘biologically embedding’ the vulnerable state, so that when exposed to subsequent stressors, the rodent’s response, in the form of the abovementioned changes, is exaggerated and further changes are inflicted on the stress response mechanisms of the brain.

Dr Janet discussed the epigenetic mediation of stress in the brain via, among other mechanisms, histone modifications. There is a possible ‘window of opportunity’ in respect of the time to intervene if these processes are to be modified in order to mitigate the prior negative impact of stressors on the brain.

References