



Genetic Biomarkers of Drug Response: Carbamazepine and Valproate Treatment for Epilepsy

Overview

Epilepsy is one of the most prevalent, serious and incurable disorders of the central nervous system. Carbamazepine and valproate are the two most commonly used first-line treatments for epilepsy, considered the gold standard due to well-established safety and efficacy profiles. However, the use of these drugs is limited due to inadequate response, poor tolerance, or an adverse drug reaction.

The present technology, invented by researchers at the Royal Melbourne Hospital and the University of Melbourne, includes single nucleotide polymorphisms (SNPs) useful as a genetic test to predict patient response to carbamazepine, valproate, and their analogues for the treatment of epilepsy. With the advent of personalised medicine, these genetic biomarkers offer improved outcomes for doctors and patients, reduced costs for payers, and consequently, a valuable product development opportunity for pharmacogenetic companies.

Medical and Economic Significance

Epilepsy is a chronic neurological condition that involves seizure recurrence. A seizure occurs when abnormal electrical activity in the brain causes an involuntary change in body movement or function, sensation, awareness, or behavior. Seizures can vary from a momentary disruption of the senses, to short periods of unconsciousness or staring spells, to convulsions.

The disease is characterised by neuronal hyper-excitability, and is associated with mutations in several genes involved in nerve communication or energy production. Epilepsy can occur as a result of many different conditions that affect a person's brain. Examples of these conditions include stroke, complications during childbirth, infections (such as meningitis, encephalitis, cysticercosis, or brain abscess), head trauma, and certain genetic disorders. Often, no definite cause can be found.

Approximately 9% of the population have a seizure at some stage in their lifetime and 3% develop epilepsy. The World Health Organization estimates that epilepsy affects approximately 50 million people worldwide, with approximately 2.5 million cases in the US. The combined market for epilepsy drugs in the US and Europe is greater than US\$3b, with annual growth of approximately 15%.

Current epilepsy treatment has limited efficacy, with 40% of patients having a significant adverse drug reaction (ADR) and 20-40% experiencing seizure recurrence. Because patient response to anti-epileptic drugs (AEDs) varies widely and no pharmacogenetic tests are presently available, physicians must rely on “trial and error” to select the best medication for each patient.

The identification and development of genetic biomarkers for individual AED response promises to significantly improve current medical practice for the treatment of epilepsy. The ability to predict individual responses to a medication before prescribing the drug would not only provide better treatment outcomes for patients, but would also create substantial economic benefit by reducing the cost of ineffective and potentially harmful treatments. Uncontrolled epilepsy is conservatively estimated to cost several thousand dollars annually per patient, including loss of productivity and opportunity. In addition, ADR in general (including ADR to all medications) is the cause of over 1.5 million hospitalizations in the US each year. The overall market for molecular diagnostics, including pharmacogenetic testing, is expected to more than quadruple from approximately US\$1 billion today to over \$5 billion by 2010.

Technology and Advantages

Individual genetic variations governing the metabolism and disposition of drugs, and genetic polymorphisms in drug targets or modulatory factors, can greatly influence the efficacy and toxicity of medications. Researchers from the Royal Melbourne Hospital and Melbourne University have discovered genetic biomarkers based upon single nucleotide polymorphisms (SNPs) that may predict drug response, including pharmacoresistance and adverse drug reactions to common AEDs such as carbamazepine, valproate, phenytoin, lamotrigine and Keppra®. The advantages of the technology are highlighted below:

- Identification of several SNPs with high correlation to carbamazepine response and with high statistical significance
- Predictive odds ratios in the range of 4 to 8; p-values under .0005
- Markers validated with 100% sensitivity and 78.6% positive predictive value
- Large cohort of previously untreated patients (n>300)
- Further studies are ongoing with an additional 600 patient samples
- Extensive clinical data included
- Non-invasive, genetic test that requires only a blood sample
- Samples have ethics approval for commercial use

Applications

The genetic biomarkers of the present technology are potentially useful for both clinical practice and industrial drug development. The following applications are envisioned:

- Genetic test to assist physicians in determining the most efficacious and safe anti-epileptic therapies for their patients
- Estimation of optimal drug dosage for individual patients
- Identification of individuals likely to experience adverse drug reactions
- Genetic biomarkers for more efficient drug development. A better understanding of genetic variations could facilitate the identification of new disease subgroups or their associated molecular pathways leading to improved drug design.
- Early elimination of potentially toxic drug candidates
- Repositioning of established drugs for new indications or the revival of drugs that failed clinical trials for reasons other than efficacy
- Identification of likely responders or non-responders to a treatment
- Stratification of patients to improve the design and outcome of clinical trials

Intellectual Property

An Australian provisional patent specification entitled "A Diagnostic Assay" was filed in October 2007. The patent application covers methods for genetic testing based upon proprietary genetic biomarkers, diagnostic kits, and improved therapeutic protocols for the treatment of epilepsy.

Research Team and Capabilities

The genetic biomarkers were discovered by a team of researchers in Melbourne, Australia, including: Associate Professor Terence J. O'Brien; Dr. Cassandra Szoeko; and Mr. Slave Petrovski of the Epilepsy and Neuropharmacology group of the Royal Melbourne Hospital and Melbourne University; and Associate Professor Leslie Sheffield of the Murdoch Children's Research Institute. The group has published 104 peer-reviewed scientific papers published in high quality neurology, neuroscience and pharmacology journals, with 51 of them having been published since 2003.

The Epilepsy and Neuropharmacology offers exceptional capabilities in a wide range of basic science and clinical disciplines, including:

- Neurophysiology of seizures/epilepsy and mechanisms by which AEDs act to control seizures and cause adverse events, with particular interest in factors that determine individual variability in drug response
- Functional neuroimaging in epilepsy and epileptogenesis

- Clinical outcomes and quality-of-life studies utilizing psychosocial instruments; outcomes of medical and surgical treatment for epilepsy; and outcomes following new-onset seizures and epilepsy
- Neuropharmacology utilising basic studies with animal models of epilepsy, as well as human clinical trials of new and established AEDs
- Medical Genetics encompassing pharmacogenetics, linkage analysis, analysis of gene polymorphisms, and discovery of genes for susceptibility to epilepsy

Selected Publications

Petty SJ, Paton LM, O'Brien TJ, Makovey J, Erbas B, Sambrook P, Berkovic SF, Wark JD. Effect of antiepileptic medication on bone mineral measures. *Neurology* 2005;65:1358-1363.

Szoeke CIE, Newton M, Wood JM, Goldstein D, Berkovic SF, OBrien TJ, Sheffield LJ. Pharmacogenetics in Epilepsy – A Review. *Lancet Neurology* 2006;5:189-196.

Liu L, Zheng T, Morris MJ, Wallengren C, Clarke A, Reid C, Petrou S, O'Brien TJ. The mechanism of carbamazepine aggravation of absence seizures. *J Pharmacol Exp Ther* 2006 319: 790-798.

Vajda, F, O'Brien, TJ, Cook, M, Hitchcock, A, Graham, J, Lander, C & Eadie, M (2004). Critical dose-effect relationship for sodium valproate and teratogenicity in pregnancy. *Journal of Clinical Neurosciences*, 11(8):854–8.

Licensing Opportunity

Bio-Link presents a unique opportunity for pharmacogenetic companies or anti-epileptic drug developers to license a genetic test for response to carbamazepine, valproate, and potentially other anti-epileptic drugs. The technology is available for exclusive or non-exclusive licensing to industry partners with capability to fully exploit the intellectual property rights in the fields of medical diagnostics and industrial drug development. Interested parties are invited to contact Christopher Boyer, Bio-Link Business Development Manager, at the contact details listed below.