

SCN1A Epilepsy Gene Test

Diagnostic advances for managing patients with seizures



genetic technologies



A rapid diagnosis of the underlying cause of childhood seizures can eliminate uncertainty and stress for the family, unnecessary procedures and investigations, inappropriate treatments, costs and the potential litigation risk for the clinician.

“It is extremely important that patients receive proper treatment, because patients with epilepsy are twice or thrice as likely to die as people without the condition.”

**Dr Sam Lhatoo commenting on
The UK General Practice Study of
Epilepsy³**

BBC News Online Oct. 2001

Genetic Diagnosis of Epilepsy

The manifestations of the different types of seizures encountered in the various epilepsy syndromes can be extremely diverse, and thus it may prove extremely difficult to achieve a precise diagnosis. Seizures during infancy are particularly challenging to diagnose and are associated with a wide range of prognoses. These may extend from entirely benign conditions to serious epileptic syndromes with outcomes that may include severe intellectual disability and early death.

Currently over 60% of people diagnosed with epilepsy are told that the cause of their seizures is idiopathic or cryptogenic.¹

A genetic aetiology for epilepsy is estimated to account for approximately 40% of affected individuals.² Recent advances have identified certain genes as the underlying cause of particular epilepsy syndromes. This has enabled the development of molecular-based diagnostic tests to assist with making an accurate and definite diagnosis.

Genetic Technologies now offers genetic testing to assist in identifying the underlying cause of epilepsy. Accurate diagnosis is essential, given the diversity of prognoses and the range of therapeutic choices available for the various forms of epilepsy.



SCN1A Gene Associations in Epilepsy

Voltage-gated sodium channels are responsible for the rapid membrane depolarization that characterizes the initial “upstroke” of neural action potentials.⁴ A mutation in the **SCN1A** gene impairs this function, and can lead to the epilepsy syndromes belonging within the Generalised Epilepsy with Febrile seizures plus (GEFS+) spectrum.

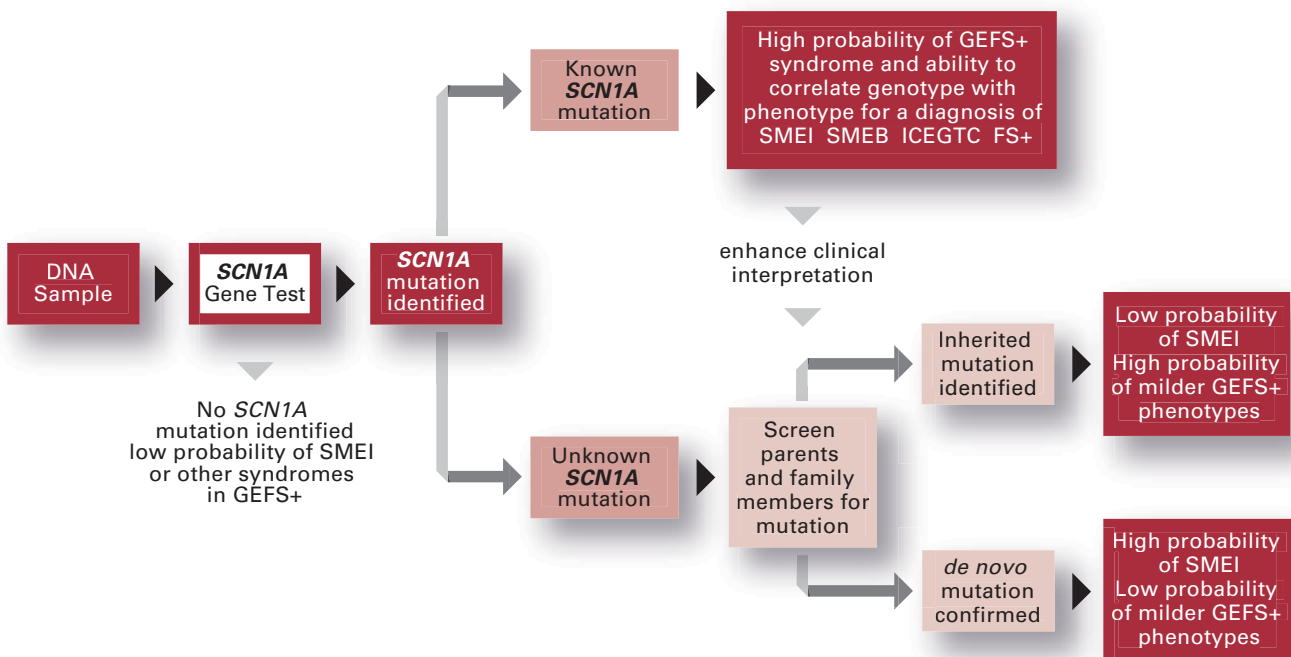
Most mutations have so far been identified in patients diagnosed with Severe Myoclonic Epilepsy of Infancy (SMEI) or Dravet Syndrome. SMEI is classified as a catastrophic epilepsy syndrome, and it exhibits symptoms of febrile seizures, generalised tonic-clonic, hemi-clonic, partial, myoclonic, and/or absence seizure types. Additionally, ataxia and severe intellectual disability is observed and sudden death occurs in up to 18% of cases.⁵

SCN1A mutations have also been identified in patients with milder phenotypes of the GEFS+ spectrum including:

- Borderline Severe Myoclonic Epilepsy of Infancy (SMEB)
- Intractable Childhood Epilepsy with Generalised Tonic Clonic Seizures (ICEGTC)
- Febrile Seizures plus (FS+)

Identification of certain mutations in the **SCN1A** gene can demonstrate a genotype/phenotype correlation, enabling the clinician to provide information to patients and their families on the potential severity of the epilepsy.⁶

In most cases, **SCN1A** mutations arise as a *de novo* phenomenon, meaning that they are not present in parental DNA. However, inherited mutations are reported in 5-10% of cases and as such, testing may be sought by a patient’s biological parents and extended family members.⁵ This in turn may enhance clinical interpretation and aid in the provision of prognostic information.





Patient Management Implications

The discovery of a *SCN1A* mutation as the basis of an epileptic syndrome may avoid further potentially invasive investigations and may prevent unnecessary use of diagnostic tests in search of alternative causes. In many cases, the result of a *SCN1A* test may be delivered within a shorter timeframe than the average waiting period for an MRI scan.

The ability to provide an early and accurate diagnosis of SMEI and other epilepsies in the GEFS+ spectrum is also of benefit when considering therapy regimes for the patient.

Anti-epileptic drugs that exacerbate myoclonic epilepsies - such as vigabatrin or tiagabine, or those that increase seizure frequency - such as lamotrigine, may be avoided.⁷

Equally, early diagnosis may enable carers of patients to implement strategies to best avoid seizure aggravation triggers such as hyperthermia and vaccinations, which may cause fever, as well as allowing appropriate management to start at an earlier point in time.

In addition promising research suggests that the understanding of pharmacogenomics is rapidly advancing and the choice of anti-epileptic drug and dosing regime may be indicated by the type of gene variation present in the patient. Using genotype data may make it possible to safely reduce the time required to reach an effective dose to control seizures.⁸

For further information on the *SCN1A* Epilepsy Gene Test call Genetic Technologies today on +61 3 9415 7688 or visit www.genetictechnologies.com.au

Genetic Technologies

Genetic Technologies Limited is a leading Australian biotechnology company with services specialising in the fields of genetics and genomics. The company's multifaceted capabilities include the molecular diagnosis of inherited and acquired genetic alterations in a range of disease types. Genetic Technologies is a member of the select worldwide GENDIA diagnostic network – and can offer access to more than 700 genetic tests.

All information and data is based on evidence and documents available July 2005.

¹ Winawer, M. et al. Evidence for Distinct Genetic Influences on Generalized and Localization-related Epilepsy. *Epilepsia* 44(9):1176-1182 (2003)

² Robinson, R., Gardiner, M. Genetics of childhood epilepsy. *Arch Dis Child* 82:121-125 (2000)

³ Lhatoo, S. et al. The Dynamics of Drug Treatment in Epilepsy: an Observational Study in an Unselected Population Based Cohort with Newly Diagnosed Epilepsy Followed up Prospectively over 11-14 years. *J Neurol Neurosurg Psychiatry* 71:632-637 (2001)

⁴ George, A. Inherited Channelopathies Associated with Epilepsy. *Epilepsy Currents* 4(2): 65-70 (2004)

⁵ Dravet, C. et al. Severe Myoclonic Epilepsy in Infancy (Dravet Syndrome). In : Roger et al. (Eds). *Epileptic Syndromes in Infancy, Childhood and Adolescence.*, 3rd ed., John Libbey, 2002, 81-102

⁶ Mulley, J et al. *SCN1A* Mutations and Epilepsy. *Human Mutation* 25: 535-542 (2005)

⁷ Chiron, C. Management of Epilepsy in Infants. In: Shorvon, S. et al. (Eds). *The Treatment of Epilepsy*. 2nd ed., Blackwell Science, 2004, p180-189

⁸ Tate, S. et al. Genetic Predictors of the Maximum Doses Patients Receive During Clinical use of the Anti-Epileptic Drugs Carbamazepine and Phenytoin. *PNAS* 102(15): 5507-5512 (2005)

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