New 'systems genetics' study identifies possible target for epilepsy treatment

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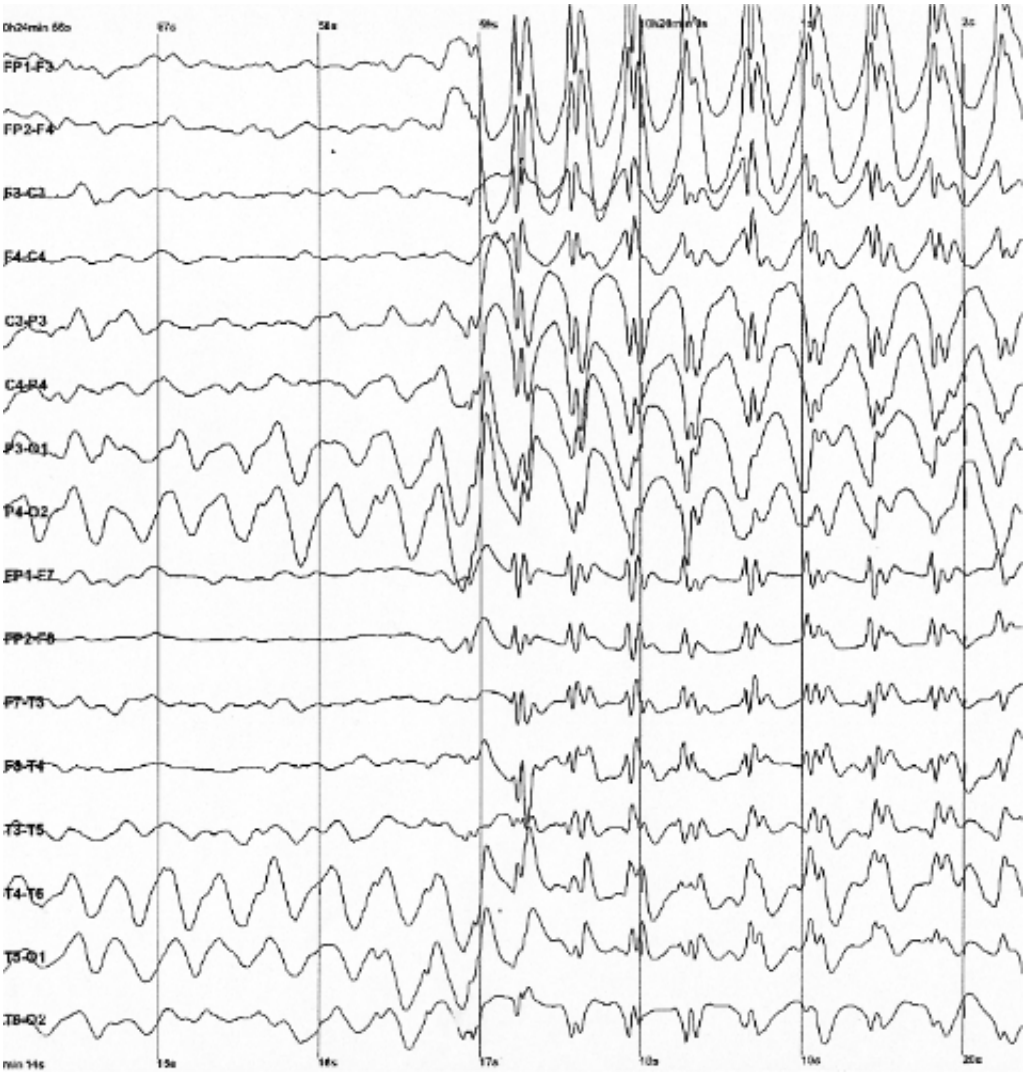

Generalized 3 Hz spike and wave discharges in a child with childhood absence epilepsy. Credit: Wikipedia.

A single gene that coordinates a network of about 400 genes involved in epilepsy could be a target for new treatments, according to research.

Epilepsy is a common and serious disease that affects around 50 million people worldwide. The mortality rate among people with epilepsy is two to three times higher than the general population. It is known that epilepsy has a strong genetic component, but the risk is related to multiple factors that are 'spread' over hundreds of genes. Identifying how these genes are co-ordinated in the brain is important in the search for new anti-epilepsy medications. This requires approaches that can analyse how multiple genes work in concert to cause disease.

Instead of studying individual genes, which has been the usual approach in epilepsy to date, researchers from Imperial College London developed novel computational and genetics techniques to systematically analyse the activity of genes in epilepsy. Published in *Nature Communications*, the study is the first to apply this 'systems genetics' approach to epilepsy.

The researchers studied samples of brain tissue removed from patients during neurosurgery for their epilepsy. Starting from these samples, they identified a gene network that was highly active in the brain of these patients, and then discovered that an unconnected gene, Sestrin 3 (SESN3), acts as a major regulator of this epileptic gene network. This is the first time SESN3 has been implicated in epilepsy and its co-ordinating role was confirmed in studies with mice and zebrafish.

Dr Enrico Petretto, from the Medical Research Council (MRC) Clinical Sciences Centre at Imperial College London and co-senior author of the study, said: "Systems genetics allows us to understand how multiple genes work together, which is far more effective than looking at the effect of a gene in isolation. It's a bit like trying to tackle a rival football team. If you want to stop the team from playing well, you can't just target an individual player; you first need to understand how the team

plays together and their strategy. Likewise in systems genetics we don't look at just one gene at a time, but a network or team of genes and the functional relationships between them in disease.

"After understanding how the team plays together, a possible approach to beating a strong side is then to identify a major control point- say the captain or the coach - who co-ordinates the players. This is like our 'master regulator gene', which in this case is SESN3. If we can develop medication to target this gene in the brain, then the hope is that we could influence the whole epileptic gene network rather than individual parts and in turn achieve more effective treatments."

Using surgical samples of brain tissue provides a unique opportunity to study how genes are coordinated in the brains of people with epilepsy. Patients with severe temporal lobe epilepsy who do not respond to medication can undergo surgery to remove part of the brain to relieve their seizures. Our research was able to use brain tissue samples donated by 129 patients to analyse the genetic and functional activity underlying their epilepsy.

Co-senior author of the paper, Dr Michael Johnson from Imperial's Department of Medicine, said: "This study is proof-of-concept for a new scientific approach in epilepsy. Existing epilepsy medications are symptomatic treatments only; that is they act to supress the seizures but they don't treat the underlying disease.

Consequently, we find that existing medications don't work in about one-third of people with epilepsy. Here we have taken a new approach, and identified a network of genes underlying the epilepsy itself in these patients and mapped its control to a single gene, SESN3. This offers hope that new disease-modifying therapies can be developed for the treatment of epilepsy itself.

"Imperial has pioneered the systems genetics approach to common human disease and by applying its specialism in epilepsy and working in collaboration with pharmaceutical companies and other institutes worldwide, we have identified SESN3 as a new 'master regulatory' gene of key inflammatory processes in the brain that could be a potential target for new and more effective treatments."

The Imperial researchers collaborated with the global pharmaceutical company UCB, as well as researchers at the University of Sheffield and the University of Bonn.

"We are currently undertaking further research to better understand how SESN3 controls the epileptic gene network and, more importantly, how we can modify it to treat epilepsy," said Dr Petretto. "We are also planning to broaden the applications of our systems genetics approach to other disorders of the human brain, such as Alzheimer's disease and neurodevelopmental disorders."

The research was funded by the Medical Research Council (MRC), the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre (BRC), the Wellcome Trust and the EU's 7th Framework Programme through its EPITARGET project.

More information: Johnson, M. et al. 'Systems-Genetics identifies Sestrin 3 as a regulator of a proconvulsant gene network in human epileptic hippocampus' *Nature Communications* (2015). DOI: 10.1038/ncomms7031

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