Study identifies druggable brain gene network implicated in epilepsy

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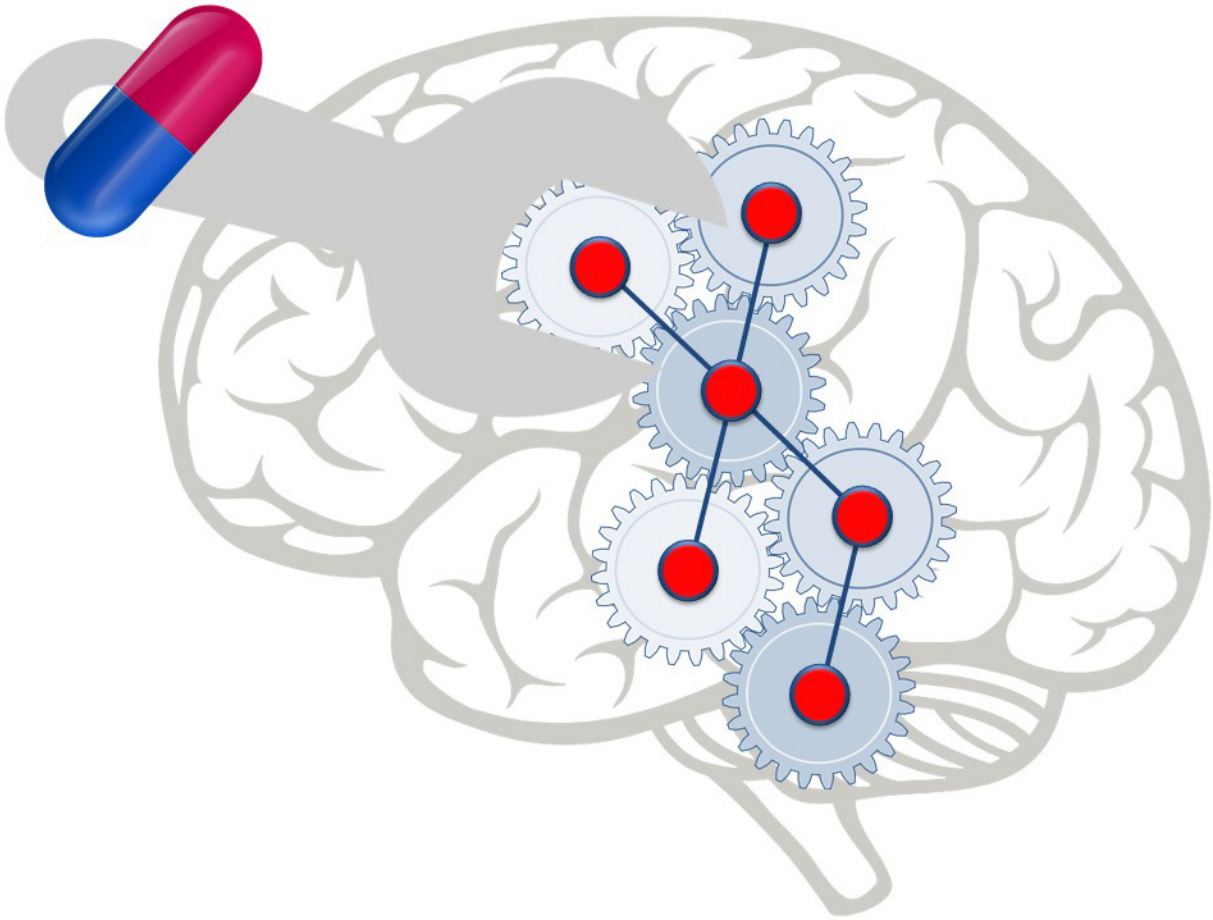

'Network-biology' reveals how multiple interconnected genes in the brain can be simultaneously targeted for antiepileptic treatment. Credit: Duke-NUS Medical School

A new study has identified a network of genes in the brain that, when disrupted, causes epilepsy; the results also predicted that a known anti-epileptic drug works to restore the network's function. This discovery has not only offered a new target for developing anti-epileptic drugs, but the original 'network biology' approach developed by the team may provide a quicker and cheaper way to accelerate the discovery of novel drug candidates that are effective treatments for disease.

The study was published on 13 December 2016 in the journal *Genome Biology* and was led by Associate Professor Enrico Petretto from the Centre for Computational Biology at Duke-NUS Medical School (Duke-NUS) in Singapore and in collaboration with Imperial College London.

Epilepsy is a common and serious neurological disorder which afflicts many people, and is characterised with a tendency to have recurring, unprovoked seizures. While many anti-epileptic treatments have been discovered, a third of epileptic patients still suffer from seizures. As a result, the search for effective treatments and cures is still ongoing. Research to identify new anti-epileptic drugs has been largely unsuccessful because the current widely-employed process of targeting one-gene-at-the-time, to find suitable targets and develop new drugs, is very slow and expensive.

Assoc Prof Petretto's lab has developed a 'network-biology' approach to identify a network of genes in the brain that underlie risk of developing both common and rare epilepsies. The approach identifies entire pathways, networks of genes and processes of disease that can be studied. Most importantly the approach can be used to predict how to manipulate the disease-networks with drugs to return them to a healthy state.

Using brain samples of healthy subjects, Assoc Prof Petretto's team built gene networks that were expressed across the human brain. Then, a using

large database of mutations and genes associated with epilepsy, they discovered a gene network associated with rare and common forms of epilepsy. This 'epileptic-network' contained 320 genes and is called M30. This network represents a previously unknown convergent mechanism regulating susceptibility to epilepsy broadly.

The analyses the team did in mouse models of epilepsy suggested that the down-regulation or disruption of M30 contributed to the manifestation of epilepsy. To confirm this, the team employed computational approaches, based on 'network-biology', and leveraged public data resources to predict the effect of drugs and small molecules on the network to restore the 'epileptic-network' to its healthy state. The effect of valproic acid, a commonly-used anti-epileptic drug, to restore M30 to health was confirmed during this process. Other new drugs were also identified, which may have been acting in combination with valproic acid.

The results of the study suggest that targeting the M30 'epileptic-network' with combination of drugs may be a viable strategy to treat epilepsy.

"Like a mechanic who can predict how to fix or rewire a broken or malfunctioning set of highly interconnected gears in a car, my group uses a 'network-biology' approach to identify interconnected genes in the brain and other organs that may be dysregulated in diseases. We then predict how these genes can be targeted for restoration of function to a normal healthy state," explained Assoc Prof Petretto.

"Our approach allowed us to identify a network associated with epilepsy and provide a compelling proof-of-principle by predicting a known anti-epileptic drug to target the network. We were able to do this in a matter of few months only using publicly available data, while a typical effort to identify anti-epileptic drugs would usually take years."

The next step for Assoc Prof Petretto is to exploit his novel 'network-biology' approach for the discovery of new drugs for specific forms of epilepsy and other untreatable neuropsychiatric disorders. This will allow his team to leverage their approach on a larger scale and identify new potentially effective drugs that can be tested in a clinical setting.

More information: Andree Delahaye-Duriez et al, Rare and common epilepsies converge on a shared gene regulatory network providing opportunities for novel antiepileptic drug discovery, *Genome Biology* (2016). DOI: 10.1186/s13059-016-1097-7

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