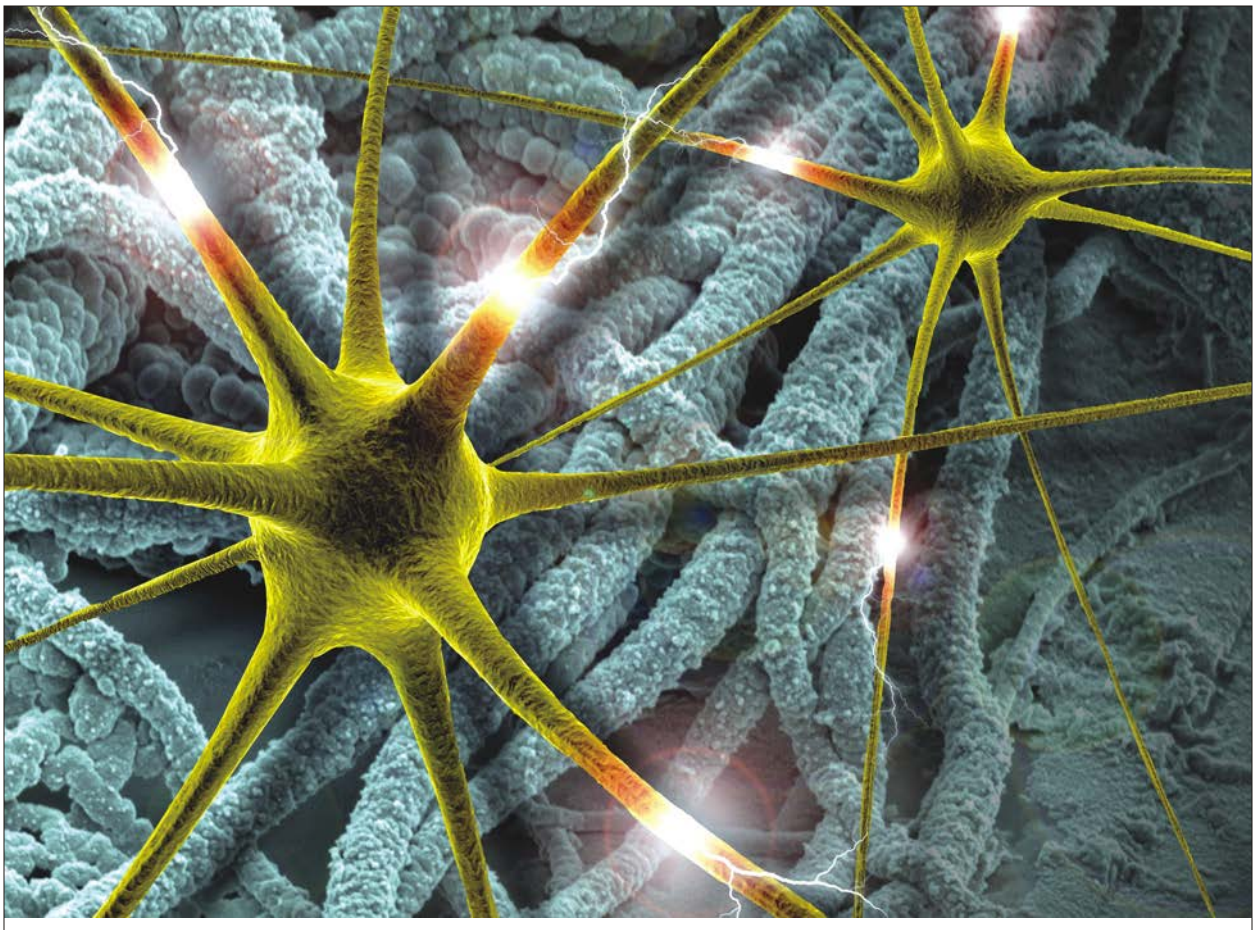

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Genetic Basis of Brain Diseases: Set of Proteins Account for Over 130 Brain Diseases

Scientists have isolated a set of proteins that accounts for over 130 brain diseases, including diseases such as Alzheimer's disease, Parkinson's disease, epilepsies and forms of autism and learning disability. The team showed that the protein machinery has changed relatively little during evolution, suggesting that the behaviors governed by and the diseases associated with these proteins have not changed significantly over many millions of years. The findings open several new paths toward tackling these diseases.

In research published Dec. 19, the researchers studied human brain samples to isolate a set of proteins that accounts for over 130 brain diseases. The paper also shows an intriguing link between diseases and the evolution of the human brain.

Brain diseases are the leading cause of medical disability in the developed world according to the World Health Organisation and the economic costs in the USA exceeds $300 billion.

The brain is the most complex organ in the body with millions of nerve cells connected by billions of synapses. Within each synapse is a set of proteins, which, like the components of an engine, bind together to build a molecular machine called the postsynaptic density -- also known as the PSD. Although studies of animal synapses have indicated that the PSD could be important in human diseases and behaviour, surprisingly little was known about it in humans.

A team of scientists, led by Professor Seth Grant at the Wellcome Trust Sanger Institute and Edinburgh University, have extracted the PSDs from synapses of patients undergoing brain surgery and discovered their molecular components using a method known as proteomics. This revealed that 1461 proteins, each one encoded by a different gene, are found in human synapses. This has made it possible, for the first time, to systematically identify the diseases that affect human synapses and provides a new way to study the evolution of the brain and behaviour.

"We found that over 130 brain diseases involve the PSD -- far more than expected," says Professor Grant. "These diseases include common debilitating diseases, such as Alzheimer's disease, Parkinson's disease and other neurodegenerative disorders as well as epilepsies and childhood developmental diseases including forms of autism and learning disability."

"Our findings have shown that the human PSD is at centre stage of a large range of human diseases affecting many millions of people," says Professor Grant.

"Rather than 'rounding up the usual suspects', we now have a comprehensive molecular playlist of 1000 suspects," says Professor Jeffrey L Noebels, Professor of Neurology, Neuroscience and Human Genetics at Baylor College of Medicine. "Every seventh protein in this line-up is involved in a known clinical disorder, and over half of them are repeat offenders. Mining the postsynaptic proteome now gives researchers a strategic entry point, and the rest of us a front row seat to witness neuroscience unravel the complexity of human brain disorders."

The findings open several new paths toward tackling these diseases.

"Since many different diseases involve the same set of proteins we might be able to develop new treatments that could be used on many diseases," says Professor Grant. To aid in this objective the group has created the first molecular network, a roadmap of the molecular organisation of human synapses, which shows how the many proteins

and diseases are interconnected. "We also can see ways to develop new genetic diagnostic tests and ways to help doctors classify the brain diseases."

To accelerate discovery and application of their data, the scientists have released all their data into the public domain on their website -- G2Cdb. The team suggests that the data on the proteome of the PSD will be extremely useful for understanding the brain in the same way the genome was useful for understanding DNA.

The scientists were able to use their study of diseases to identify the biological roots of human behaviour. They found that proteins in the PSD are especially important for cognitive behaviours such as learning and memory, emotion and mood, as well as social behaviours and addiction or drug abuse. The findings provide deep insights into how a DNA mutation can impact on fundamental aspects of our behaviour.

The team examined the rate of evolution of the PSD proteins over millions of years of mammalian evolution, expecting the proteins to evolve at the same rate as other proteins. In a fascinating and unexpected twist to the story, the team found that the PSD proteins changed much more slowly than expected, revealing that the PSD has been highly conserved or constrained from changing during evolution.

"The conservation of the structure of these proteins suggests that the behaviours governed by the PSD and the diseases associated with them have not changed much over many millions of years," said Professor Grant. "It also shows that synapses in rodents are much more similar to humans than we expected showing that mice and rats are suitable models for studying human brain disease."

Professor Jonathan R Seckl, Moncrieff-Arnott, Professor of Molecular Medicine and Executive Dean, College of Medicine and Veterinary Medicine, The Queen's Medical Research Institute, Edinburgh, says: "This splendid collaborative study is a major step forward which will surely illuminate the causes of many of the major mental health and neurological disorders that are so common in Britain as well as indicating new ways to develop treatments for these most disabling diseases."

This project was conducted as part of the Genes to Cognition Program, which is a research program aimed at understanding the molecular basis of behaviour and brain disease.

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Àlex Bayés, Louie N van de Lagemaat, Mark O Collins, Mike D R Croning, Ian R Whittle, Jyoti S Choudhary, Seth G N Grant. Characterisation of the proteome, diseases and evolution of the human postsynaptic density. Nature Neuroscience, December 19, 2010 DOI: 10.1038/nn.2719