Two major forms of genetic temporal lobe epilepsy are currently recognized: autosomal dominant lateral temporal epilepsy (ADLTE), and familial mesial temporal lobe epilepsy (FMTLE). Both syndromes are genetically heterogeneous. ADLTE is clinically characterized by auditory or aphasic auras, absence of brain structural abnormalities, and onset during the first two decades of life. We recently identified two genes whose mutations cause ADLTE: RELN, and MICAL-1, altogether accounting for the disease in about 30% of affected families (1, 2). RELN encodes Reelin, an extracellular proteins which exert multiple functions during brain development, maturation, and in adult life. We recently found that RELN pathogenic mutations strongly reduce Reelin secretion (3), and provided evidence that Reelin mutant proteins are degraded within the cell by autophagy, likely due to altered protein folding. One objective of this project is to identify small molecules that are able to restore secretion of mutant Reelin and see whether secreted mutant proteins retain their function. This would provide a proof of principle for a novel therapy based on the knowledge of the mechanism underlying Reelin-related epilepsy.

FMTLE is clinically characterized by psychic or autonomic auras and onset in adolescence or early adulthood. Brain imaging is usually normal (benign form), though in some cases hippocampal sclerosis and febrile seizures are present. The genetic basis of FMTLE is still unknown, likely owing to its genetic heterogeneity, and a proportion of families have an autosomal dominant inheritance pattern. We have recently analyzed five Italian FMTLE families with five or more affected persons by whole exome sequencing. Following several filtering and variant prioritization steps, we ended up with 18 very rare, deleterious variants, each in a single family, located in genes whose function and/or expression patterns are compatible with involvement in epilepsy. Because putative causal gene must be mutated in at least two unrelated families, we are starting a collaboration with the Epi25 Collaborative consortium (4), to screen additional families with FMTLE or epileptic phenotypes involving the temporal lobe from various countries, to identify additional potentially pathogenic variants in our candidate genes. This further step will hopefully lead us to identifying FMTLE causal gene(s).

References:

Keywords: ADLTE, FMTLE, whole exome sequencing, causal genes, mechanisms of mutations

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