Epilepsy Genetics and Precision Therapies – Trials and Tribulations:

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Whilst epilepsy may be a consequence of an acquired insult including trauma, stroke, and brain tumours, the genetic component to epilepsies has been greatly under-estimated. Considerable progress has recently occurred in the understanding of epilepsy genetics, both at a clinical genetic level and in the basic science of epilepsies. The evidence for genetic components will be first briefly discussed including data from population studies, twin analyses and multiplex family studies. Recent hypothesis-free whole exome studies searching for rare variants and genome-wide association studies detecting common variants will be reviewed. Research in simple systems, and utilizing animal models with mutant epilepsy genes observed in humans, is revealing mechanistic insights at cellular, network and whole animal levels. Examples will be given as to how discoveries beginning with clinical research in patient populations leads to molecular genetic discoveries with subsequent unravelling of pathophysiology that informs clinical care and provides a realistic pathway to new treatments tailored to the individual. Proof of principle that this is feasible is provided by examples of dietary therapy for GLUT1 deficiency, pyridoxine treatment in encephalopathy due to ALDH7A1 or PNPO mutations, preliminary data that quinidine may be effective in some subjects with KCNT1 mutation, and the use of rapamycin analogues in the expanding family of mTORopathies. Major challenges include establishing how widely applicable this strategy may be, and how it might be applied to epilepsies with complex inheritance.