betweenness centrality network analysis, the most important central pathway in this network: signalling by NGF.

Conclusion We have performed the first ever GWAS of pharmacoresistant partial epilepsy and identified the most central pathway underlying this phenotype.

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WHICH GENETIC PATHWAYS UNDERLIE PHARMACORESISTANT EPILEPSY?

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Purpose A third of people with epilepsy are pharmacoresistant. As pharmacoresistance is a complex trait, a genome-wide pathway-level approach is likely to prove especially fruitful in its study.

Methods We performed a genome-wide association study (GWAS) of pharmacoresistant partial epilepsy, with discovery and replication cohorts including, in total, 421 cases and 2624 normal population controls, and 5,519,310 genotyped and imputed SNPs.

Results At the single variant level, there was no overlap in the top results of the two cohorts. However, at the gene-set and pathway level, there was clear replication of results between the two cohorts. For the combined 'mega-analysis', there were 71 distinct enriched pathways. We showed using network analysis that these enriched pathways form a highly interconnected network in which each pathway is directly connected, on average, to 8.4 other pathways. The enriched pathways, therefore, form a coherent whole, and changes in one pathway in this network will have a cascading effect on the rest of the network. Finally, we identified, using