Meta-analysis of hundreds of seizure-related traits reveals putative modifiers of epilepsy resilience and susceptibility

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The epilepsies are a genetically complex family of neurological disorders characterized by unprovoked seizures. Despite decades of concerted development of anti-seizure medications, 30% of individuals diagnosed with epilepsy are refractory to all treatments and none of these therapies are disease modifying. Experimentally, seizures can be induced in mice by multiple modalities, including chemoconvulsants and prolonged loud sounds (audiogenic seizures), or as comorbidities of other insults, including handling induced seizures after cocaine or ethanol intoxication. Seizures have been extensively studied in genetically diverse mice allowing us to perform a genetic mapping meta-analysis of seizure phenotypes to identify putative universal genetic modifiers of seizure phenotypes. In this study, we used hundreds of publicly available seizure-related phenotypes from Gene Network 2 as input to the GWAS meta-analysis tool in the Mouse Phenome Database, which performs a Bayesian meta-analysis of the input traits. Using a $-\log_{10}(p)$ cutoff of 15, we identified 118 non-overlapping loci containing putative modifiers of seizure phenotype. To prioritize candidate genes within these loci, we performed a functional network analysis to score genes based on gene interactions with known epilepsy genes, resulting in a candidate list of 169 protein genes. For high-ranking genes, we performed a variant prioritization using GERP scores to identify SNPs in evolutionarily conserved positions that were linked to the lead SNP in each locus, resulting 141 SNPs of interest. Among these 141 SNPs, five SNPs were in transcription factor binding site motifs and were predicted to decrease binding affinity. The corresponding genes— *Igsf21, Tenm4, Dtna, Itpk1, and Cadps2*—are strongly connected to epilepsy-related neurological functions are potentially novel candidate modifiers of epilepsy.