Whole genome sequence data implicate RBFOX1 in epilepsy risk in baboons

Mark Z Kos[1], Melanie A Carless[2], Lucy Blondell[1], M Michelle Leland[3], Koyle D Knape[3], Harald HH Göring[1], Charles Ákos Szabó[3,4]

[1]The University of Texas Rio Grande Valley School of Medicine, San Antonio, TX, USA

[2]The University of Texas at San Antonio, San Antonio, TX, USA

[3]UT Health San Antonio, San Antonio, TX, USA

[4]South Texas Comprehensive Epilepsy Center, San Antonio, TX, USA

Abstract

Background: Baboons exhibit a genetic generalized epilepsy (GGE) that resembles juvenile myoclonic epilepsy and may represent a suitable genetic model for human epilepsy. The genetic underpinnings of epilepsy were investigated in a baboon colony at the Southwest National Primate Research Center (San Antonio, TX) through the analysis of whole-genome sequence (WGS) data.

Methods: Baboon WGS data were obtained for 38 cases and 19 healthy controls from the NCBI Sequence Read Archive and, after standard QC filtering, two subsets of variants were examined: (1) 20,881 SNPs from baboon homologs of 19 candidate GGE genes; and (2) 36,169 protein-altering SNPs. Association tests were conducted in SOLAR, and gene set enrichment analyses (GSEA) and protein-protein interaction (PPI) network construction were performed on genome-wide significant association results (P<0.01; n= 441 genes).

Results: Heritability for epileptic seizure in the pedigreed baboon sample was estimated at 0.76 (SE=0.77; P=0.07). A significant association was detected for an intronic SNP in *RBFOX1* (P=5.92 × 10^{-6}; adjusted P=0.016). For protein-altering variants, GSEA revealed significant positive enrichment for genes involved in the extracellular matrix structure (ECM; FDR=0.0072) and collagen formation (FDR=0.017).

Conclusions: SNP association results implicate *RBFOX1* in baboon epilepsy, a gene that plays a key role in neuronal excitation and transcriptomic regulation, and has been previously linked to human epilepsy, both focal and generalized. Moreover, protein-damaging variants from across the baboon genome exhibit a wider pattern of association that links collagen-containing ECM to epilepsy risk. These findings suggest a shared genetic etiology between baboon and human forms of GGE.