Genome-wide association study for age-related hearing loss in CFW mice.

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Age-related hearing loss (**ARHL**) is one of the most prevalent conditions affecting the elderly globally. ARHL is influenced by a combination of environmental and genetic factors. The mouse and human inner ears are functionally and genetically homologous. We used Carworth Farms White (**CFW**) mice because they are genetically diverse and exhibit variability in the age of onset and severity of ARHL. The goal of this study was to identify genetic loci involved in regulating ARHL.

Hearing at a range of frequencies was measured using Auditory Brainstem Response (**ABR**) thresholds in 946 male and female CFW mice at the age of 1, 6, and 10 months. We genotyped mice using low-coverage (mean coverage 0.27x) whole-genome sequencing followed by imputation using STITCH. To determine the accuracy of the genotypes we sequenced 8 samples at >30x coverage and used called from those samples to estimate the discordance rate which was 0.45%. We performed genome-wide association study (**GWAS**) for the ABR thresholds for each frequency at each age, and for the time of onset of deafness.

We obtained genotypes at 4.18 million single nucleotide polymorphisms (**SNP**). The SNP heritability for tested traits ranged from 0 to 42%. GWAS identified 10 significant associations with ARHL that contained potential candidate genes, including *Dnah11*, *Rapgef5*, *Cpne4*, *Prkag2*, and *Nek11*. Genetic ablation of Prkag2 caused ARHL at high frequency, strongly suggesting that *Prkag2* is the causal gene for one of the associations.

The GWAS for ARHL in CFW outbred mice helps to identify genetic risk factors for ARHL and to define novel therapeutic targets for the treatment and prevention of this common disorder. We confirmed that Prkag2 plays a role in ARHL.