

Genetic Association in Aminoglycoside-Induced Ototoxicity

PI: Peter Steyger

Patients with cystic fibrosis (CF) experience frequent respiratory infections that are controlled by obligatory aminoglycoside treatment that induces sensorineural hearing loss in a sub-group of patients, while the remainder with equally extensive aminoglycoside exposure retains normal auditory function. This bimodal distribution is highly suggestive of genetic susceptibility to aminoglycoside ototoxicity.

Aminoglycosides are trafficked into the cochlea and sensory hair cells via drug-permeant cation channels that also mediate pain sensitivity and systemic water balance functions. We hypothesize that single nucleotide polymorphisms (SNPs) in three aminoglycoside-permeant channels enhance cochlear and sensory cell uptake of aminoglycosides and predispose individuals to aminoglycoside ototoxicity. We have a cohort of CF patients with chronic exposure to aminoglycosides and monitor their hearing status. We will genotype 34 SNPs with a minor allele frequency >10% in 3 genes for aminoglycoside-permeant channels expressed in the cochlea. Prospective identification of individuals with genetic susceptibility to aminoglycoside ototoxicity will permit individually-tailored antibiotic therapy to prevent or ameliorate ototoxicity, and permit optimal (and early) allocation of otoprotective or rehabilitation resources when aminoglycoside exposure is obligatory and there is a greater risk of ototoxicity. Preventing hearing loss is especially crucial for children developing listening skills essential for speech and language acquisition that leads to optimal educational attainment. The significance of this research-driven cohort development study is that it will allow, for the first time, the ability to screen individuals for genetic susceptibility (in genomic DNA) to aminoglycoside-induced ototoxicity prior to treatment.