GENETICS OF CHRONIC TINNITUS

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Tinnitus is a highly prevalent condition marked by the perception of sound in the absence of external stimuli. However, the etiology of chronic tinnitus remains poorly understood. Involvement of genetic factors into tinnitus susceptibility is assumed due to clinical experiences such as frequent familial aggregation or an association between tinnitus and certain personality traits, which in turn are partly genetically linked. Here we report first results from investigations of gene variants of the serotonin and BDNF transmitter system:

**Serotonin**
Serotonin plays a key role in the processing of acoustic information in the auditory pathway, and is known to affect tone-evoked responses in a frequency-dependent fashion. We addressed serotonin reuptake, as determined by a common length polymorphism in the serotonin transporter gene (5-HTT), with regard to tinnitus susceptibility. 186 subjects who complained of primary tinnitus lasting for a minimum of 6 months, were recruited from a tinnitus clinic and were included in an association study of the 5-HTT promoter length polymorphic region (5-HTTLPR). Genotype and allele distributions were compared to data obtained from a control group of 256 healthy individuals. When contingency tables were calculated, carriers of the short, low-expressing 5-HTTLPR allele did not differ between the two populations under investigation (p > 0.86, OR = 0.97, 95% CI = 0.64-1.46). Contrary to our conjecture, the 5-HTT variant thus does not per se appear to confer an increased risk of tinnitus.

**Brain derived neurotropic factor**
Neurotrophic factors play key roles in the developing auditory pathway including the sensory epithelium of the inner ear, and structures involved in the central nervous processing of auditory stimuli. In the present investigation, we explored a possible implication of variant BDNF in the susceptibility to chronic tinnitus. 222 subjects complaining of chronic tinnitus were recruited from a tinnitus clinic and underwent detailed neuro-otological examinations including otoscopy, stapedius reflexes, middle ear pressure measurements, pure tone audiometry, tinnitus pitch and loudness matches. Subjects were genotyped for a biallelic BDNF missense variant (Val66Met). Prevalence of the substitution was compared to the prevalence in an ethnically homogenous group of healthy controls (N=317). Carriers of the Met variant were significantly less likely to develop chronic tinnitus with comorbid hearing impairment (p = .02, OR = 1.62, 95% CI = 1.1-2.5). When no assumptions of dominance were made for the minor allele, the Met allele still conferred protection against tinnitus with hearing impairment (p = .05, OR = 1.42, 95% CI = 1.0-2.0). The present study suggests a role of variant BDNF in modulating the genetic susceptibility to chronic tinnitus with hearing impairment. Possible implications of this finding include a differential response to the pharmacological treatment of tinnitus, and specifically, to the neurotrophic effects of antidepressants.