Population Genomics of Hearing Loss in the Palestinian Population: A Model for Adapting Technology to Relevant Problem

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In communities with high rates of consanguinity and consequently high prevalence of recessive phenotypes, homozygosity mapping with SNP arrays is an effective approach for gene discovery. In 22 Palestinian kindreds with prelingual nonsyndromic hearing loss, we generated homozygosity profiles reflecting linkage to the phenotype. Family sizes ranged from small nuclear families with two affected children, one unaffected sibling, and parents to multigenerational kindreds with 12 affected relatives. By including unaffected parents and siblings and screening 250 K SNP arrays, even small nuclear families yielded informative profiles. In 14 families, we identified the allele responsible for hearing loss by screening a single candidate gene in the longest homozygous region. Novel alleles included missense, nonsense, and splice site mutations of CDH23, MYO7A, MYO15A, OTOF, PJVK, Pendrin/SLC26A4, TECTA, TMHS, and TMPRSS3, and a large genomic deletion of Otoancorin (OTOA). We have indentified the region12q14.3–q21.2 as DFNB84 (two families) This homozygous region harbors the protein tyrosine phosphatase receptor Q gene PTPRQ, which is known to be essential to hearing in mouse. Sequence of PTPRQ in affected individuals in the extended kindred revealed c.1285C>T, leading to p.Gln429Stop. All point mutations were rare in the Palestinian population (zero carriers in 288 unrelated controls); the carrier frequency of the OTOA genomic deletion was 1%. In four families, we identified five genomic regions likely to harbor novel genes for human hearing loss on chromosomes 1p13.3 (DFNB82), 9p23–p21.2/p13.3–q21.13 (DFNB83), 14q23.1–q31.1, and 17p12–q11.2 (DFNB85). Next generation sequencing of the captured exons in DFNB82 revealed a chr1:109,440,214 C>T resulting in a R128X in yet newly un characterized G protein stimulator regulator (GPSM2) protein. Functional biology is underway to reveal GPSM2 role on hearing loss.