Identification of novel mutations in patients with Leber congenital amaurosis and juvenile RP by genome-wide homozygosity mapping with SNP microarrays.

Purpose: Leber congenital amaurosis (LCA) and juvenile retinitis pigmentosa (RP) cause severe visual impairment early in life. Thus far, mutations in 13 genes have been associated with autosomal recessive LCA and juvenile RP. The purpose of this study was to use homozygosity mapping to identify mutations in known LCA and juvenile RP genes.

Methods: The genomes of 93 consanguineous and nonconsanguineous patients with LCA and juvenile RP were analyzed for homozygous chromosomal regions by using SNP microarrays. This patient cohort was highly selected, as mutations in the known genes had been excluded with the LCA mutation chip, or a significant number of LCA genes had been excluded by comprehensive mutation analysis. Known LCA and juvenile RP genes residing in the identified homozygous regions were analyzed by sequencing. Detailed ophthalmic examinations were performed on the genotyped patients. Results: Ten homozygous mutations, including seven novel mutations, were identified in the CRB1, LRAT, RPE65, and TULP1 genes in 12 patients. Ten patients were from consanguineous marriages, but in two patients no consanguinity...
was reported. In 10 of the 12 patients, the causative mutation was present in the largest or second largest homozygous segment of the patient's genome. CONCLUSIONS: Homozygosity mapping using SNP microarrays identified mutations in a significant proportion (30%) of consanguineous patients with LCA and juvenile RP and in a small number (3%) of nonconsanguineous patients. Significant homozygous regions which did not map to known LCA or juvenile RP genes and may be instrumental in identifying novel disease genes were detected in 33 patients.