Identification of novel genetic defects in cone-rod dystrophy patients from an outbred population by using homozygosity mapping

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Aim

The purpose of this study was to unravel the causative gene defects in patients with autosomal recessive cone-rod dystrophy.

Background

Cone-rod dystrophy (CRD) is a group of retinal dystrophies in which cones are equally or more severely affected than rods. Main symptoms are reduced visual acuity, photophobia, loss of color vision and visual field defects. ~30% of autosomal recessive cases are caused by mutations in ABCA4.

Method

In the outbred Dutch population we previously found homozygous mutations in ~35% of patients with retinal dystrophy. We therefore hypothesize that the parents of these patients share a common ancestor that carries the disease-causing mutation, and that new disease genes can be identified by homozygosity mapping.

In patients with an unknown cause for CRD we searched for sizeable homozygous regions using whole genome SNP arrays. In these regions we analyzed candidate genes for causative mutations.

Size of region: 20 generations → ~5 Mb
10 generations → ~10 Mb

(size region = 100 Mb/number of generations from patient to common ancestor)

Conclusions

By unraveling the molecular cause in 4 of 11 multiplex families we show that homozygosity mapping is a powerful tool in identifying novel mutations in patients from an outbred population. The most important result was the identification of a novel retinal dystrophy gene; EYS. Furthermore, we show that molecular knowledge of the disease may lead to a better phenotypic understanding.

Results

In 4 multiplex CRD families we found the causative mutation; three in known retinal disease genes (ABCA4, PROM1, CABP4) and one in a novel gene (EYS). In two families the mutation was located in the largest homozygous region, in two families it was located in the second large region. (table 1)

Clinical re-evaluation led to another diagnosis than cone-rod dystrophy in 3 out of 6 patients. (table 2)

References

1. Woods et al. AJHG 2006 May;78(5):889-96
2. Littink et al. IOVS 2009 May;50(5):344-50
3. Collin et al. AJHG 2008 Nov;83(5):594-603

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FIG. 1 Principle of homozygosity mapping in outbred population in which parents of a patient have a common ancestor. The original region (in orange) surrounding the mutation (red bar) becomes smaller every generation due to meiotic recombination.