Case of Stargardt Disease Caused by Uniparental Isodisomy

Stargardt disease is the most common form of juvenile macular degeneration, with an incidence of 1 in 10,000 persons. Clinically, it is characterized by pisciform flecks at the level of the retinal pigment epithelium and a bull’s-eye maculopathy. A variant of Stargardt disease, fundus flavimaculatus, demonstrates a more peripheral distribution of flecks. In 1997, mutations in the ABCA4 gene on chromosome 1 were associated with both Stargardt disease and fundus flavimaculatus. Stargardt disease is an autosomal recessive condition. Consequently, patients are expected to inherit 1 copy of a mutant ABCA4 gene from each parent. However, we recently identified a patient affected with Stargardt disease who inherited 2 mutant alleles of the ABCA4 gene from her father through a mechanism known as uniparental disomy.

A female patient aged 15 years was diagnosed with Stargardt disease with visual acuities of 20/200 OD and 20/150 OS and characteristic retinal findings (Figure 1). Goldmann visual fields confirmed bilateral central scotomas, and a standard electroretinogram was normal. The patient was tested for ABCA4 mutations using standard methods and was found to be homozygous for an ABCA4 mutation of proline to leucine at position 1380 (P1380L). Interestingly, only the patient’s father is a carrier of the P1380L mutation. Her mother does not harbor this mutation (Figure 2). Maternity and paternity were confirmed by genotyping the family members with genetic markers including X and Y chromosome markers and short tandem repeat polymorphisms located on chromosomes 4, 5, and 11. Quantitative polymerase chain reaction experiments confirmed that the patient was truly homozygous for P1380L. Therefore, it remains possible that some of the 40 subjects in this experiment are homozygous for markers near the ABCA4 gene as a consequence of uniparental heterodisomy.

Figure 1. Fundus photograph of the patient’s left eye shows macular and extramacular pisciform yellow flecks characteristic of Stargardt macular dystrophy.

Figure 2. Family pedigree and genotypes at the ABCA4 gene. The proband (filled symbol) has Stargardt disease and is homozygous for the ABCA4 P1380L mutation (mutation of proline to leucine at position 1380) in ABCA4. However, only 1 of her parents, her father, carries the mutation. Wt indicates wild type; square, male; and circle, female.

We investigated whether the patient inherited both P1380L alleles of the ABCA4 gene from her father by genotyping the patient and her family at 24 short tandem repeat polymorphism genetic markers distributed across chromosome 1 using standard techniques (Figure 3). For all of the 24 markers, the patient was homozygous for a marker allele possessed by her father, and 16 of these markers demonstrated nonmaternal inheritance of chromosome 1 alleles (neither marker allele was of maternal origin). The other 8 marker genotypes, although uninformative, were consistent with nonmaternal inheritance of chromosome 1. The patient’s sister, however, exhibited normal Mendelian inheritance of chromosome 1 alleles from both parents. These data suggest that the patient is homozygous for the P1380L ABCA4 mutation as a consequence of inheriting 2 identical copies of chromosome 1 from her father (uniparental paternal isodisomy).

The frequency of uniparental isodisomy in Stargardt disease was assessed by screening a panel of 830 unrelated patients for homozygosity at chromosome 1 markers. Forty of the 830 patients were homozygous at markers closely flanking ABCA4; however, none were homozygous across all of chromosome 1, ruling out the possibility of uniparental isodisomy (data not shown). Therefore, uniparental isodisomy occurs rarely in Stargardt disease at a frequency of less than 0.12% (1/831) of cases. Although unlikely, it remains possible that some of the 40 subjects in this experiment are homozygous for markers near the ABCA4 gene as a consequence of uniparental heterodisomy.

Uniparental isodisomy of chromosome 1 has been inadvertently detected in studies of recessive disease. Estimates of the prevalence...
of uniparental disomy have been made by extrapolating data from such studies; however, these figures vary dramatically. Currently, the prevalence of chromosome 1 uniparental disomy is unknown, but this phenomenon appears to be a relatively rare occurrence. These observations are consistent with our findings in which no additional cases of uniparental disomy were detected in a cohort of 830 patients with Stargardt disease.

To our knowledge, this is the first reported case of Stargardt disease caused by uniparental disomy. Although uncommon, this mode of inheritance should be considered in patients with Stargardt disease and an apparently homozygous mutation of the ABCA4 gene.

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