HotSpots

Same gene, surprising difference: adult neuronal ceroid lipofuscinoses linked to CLN6, mutated in variant late-infantile form

References


Kufs disease, the major adult form of neuronal ceroid lipofuscinoses, caused by mutations in CLN6


The neuronal ceroid lipofuscinoses (NCLs) are a group of rare genetic disorders characterized by neuronal degeneration and the intracellular accumulation of autofluorescent ceroid lipopigments. The majority of NCLs present in infants and children with progressive motor dysfunction, epilepsy, and retinal failure leading to blindness and death. Interestingly, a small number of NCL cases present in adulthood, typically around the age of 30, as Kufs disease. Notably, Kufs disease differs from infantile and juvenile NCLs in that the retina is not affected and vision is preserved. Kufs disease is further classified as type A or B based on the initial presenting symptoms, the former showing myoclonic epilepsy and the latter presenting with dementia.

Historically, NCLs were diagnosed by biopsy, permitting histological identification of the characteristic lipopigments. Cases were clinically categorized by age of onset into infantile, late infantile, juvenile, and adult NCL. Owing to advances in genetics over the past two decades, the majority of cases within these subsets have been linked to specific loci and genes (1). However, traditional NCL clinical categories have shown heterogeneity versus the eight genes reported to date, and the locus of Kufs disease remained unidentified.

In this new study, Arsov et al. sought to identify the genetic basis of Kufs disease utilizing four families with autosomal recessive inheritance patterns and suggested consanguinity. They discovered causative mutations of Kufs type A disease in CLN6, a gene previously associated with variant late infantile NCL, and validated this finding in three additional Kufs type A families. It is striking that such marked differences in age of onset and clinical presentation result from mutations to the same gene in both Kufs disease and variant late infantile NCL. Arsov et al. note that previously characterized variant late infantile NCL mutations to CLN6 do not obviously differ from the nine they identify for Kufs type A disease (Fig. 1), as both groups contain missense and nonsense mutations to conserved amino acid residues throughout the CLN6 gene. In one Kufs type A family, a frameshift mutation near the end of CLN6 is shared with a previously reported variant late infantile NCL case. The authors note that modifying genes may distinguish the two groupings, or subtle functional differences based on the mutations themselves.

The identification of CLN6 mutations in Kufs patients may have come as a surprise. In this study, the locus was identified from genome-wide tagSNP genotyping of six affected and eight unaffected individuals constituting a mapping set, with no hypothesis or bias of target. A subset of markers with high heterozygosity were assessed by multipoint linkage analysis with the Merlin software package (2), identifying two regions of linkage on chromosome 15. One of these regions, overlapping in three type A Kufs families, but not with a fourth type B Kufs family, yielded 14 candidate genes for mutational analysis. Among these targets was CLN6, known to the authors as the gene mutated in variant late infantile NCL.

After identifying plausible mutations in their mapping set, Arsov et al. sequenced CLN6 in eight unrelated Kufs families of A, B and unassigned types, constituting a validation set. Homozygous or compound heterozygous mutations of CLN6 were detected in all three confirmed recessive Kufs type A families of the validation set and in one unassigned family, whereas the remaining families were wild-type or, in one type B case, heterozygous for CLN6 mutation and wild-type. Finally, 360 control chromosomes were screened by the authors for all 11 CLN6 variants identified in the study, none of which were reported in dbSNP. Arsov et al. found one nonpathogenic mutation on one of 360 control chromosomes, but detected none of the remaining 10 variants at all.

Linkage analysis of Kufs disease has not previously succeeded, in part owing to the rarity of the affliction and the difficulty of collecting sufficient donor samples from affected pedigrees. Thanks to a high tagSNP resolution provided by increasingly dense SNP genotyping platforms, and recent statistical software tools available for linkage analysis of thousands of markers in sparse inheritance trees, Arsov et al. have generated strong evidence of the genetic roots of this unusual NCL using a small number of pedigrees. With the linkage of Kufs type A disease to CLN6, there is an opportunity not only for genetic diagnosis of Kufs patients without biopsy but also for a deeper functional understanding.
CLN6

Fig. 1. Nine mutations of CLN6 identified by Arsov et al. as pathogenic for Kufs disease. Exon boundaries are defined according to protein coding sequence of reference mRNA NM_017882.2.

of NCL pathology. CLN6 is a highly conserved protein without homology to other proteins, and results in NCL lysosomal dysfunction by unknown mechanisms (3). An in-depth study of the mutations associated with Kufs type A disease versus those associated with variant late infantile NCL may shed light on the pathogenesis of this family of lysosomal storage disorders.

C Kay

Department of Medical Genetics, Centre for Molecular Medicine and Therapeutics, University of British Columbia, 950 West 28th Avenue, Vancouver, British Columbia, Canada V5Z 4H4.

e-mail: ckay@cmmt.ubc.ca