Genetic modification of glaucoma associated phenotypes between AKXD-28/Ty and DBA/2J mice

ABSTRACT

The consequences of the ipd and isa mutations are modified in the AKXD-28/Ty background. These strains provide a resource for the identification of modifier genes that modulate pigment dispersion and susceptibility to pressure-induced cell death.

INTRODUCTION

Background Glaucoma is a prevalent group of retinal and optic nerve neuropathies that currently renders approximately 67 million people worldwide at risk for developing significant vision loss, including blindness. Glaucoma involves the death of retinal ganglion cells (RGCs) and their axons, and is characterized by atrophic excavation of the optic nerve. Glaucoma is usually associated with high intraocular pressure (IOP) resulting from an increased resistance to drainage of aqueous humor. Not all people with high IOP develop glaucoma, however, suggesting that other factors, such as genetic susceptibility to pressure-induced damage, interact with IOP to cause damage. The occurrence of glaucomatous damage in individuals without high IOP and the benefit of lowering IOP in some of these individuals further suggest multiple factors determine an individual's susceptibility to pressure-induced damage. The nature of the factors participating in glaucomatous events, particularly those influencing disease progression and modifying disease severity in different individuals, remain largely unknown. Increased understanding of factors contributing to glaucoma will suggest new therapeutic strategies and will likely lead to improved clinical management. Glaucomatous phenotypes have been observed in a number of mammalian species, including mice. Mice can be clinically and histologically analyzed throughout the course of a disease and their genes can be altered to study the molecular framework underlying pathology. As a consequence, mouse models are useful for identifying and characterizing the effects of causative genes necessary for glaucoma development, and for characterizing the genes and molecular pathways that participate in or modify disease progression. A collection of glaucomatous mouse strains with phenotypic differences would facilitate research to understand the complexity of glaucoma. As part of our efforts to understand glaucoma, we are screening for and characterizing glaucoma in aged mice of various strains. We are particularly interested in documenting differences in glaucoma phenotypes between strains of mice that share the same causative genes. This information will provide an experimental basis for identifying genes and mechanisms that modify the progression or severity of glaucoma. Here we report differences in genetic susceptibility to glaucoma-associated phenotypes between two related inbred strains of mice, AKXD-28/Ty (AKXD28) and DBA/2J (D2). D2 mice develop glaucoma involving a harmful increase of IOP followed by RGC loss and optic nerve damage. The increase in IOP is associated with an iris disease involving iris pigment dispersion (IPD), iris stromal atrophy (ISA), and the formation of synechiae that block aqueous humor drainage. The iris pigment dispersion and iris stromal atrophy phenotypes are caused by distinct recessive alleles at the ipd and isa loci, respectively. The IPD phenotype in D2 mice is similar to human pigment dispersion syndrome, a condition that often leads to pigmentary glaucoma, and involves degeneration of the iris pigment epithelium. Causative genes for pigment dispersion remain to be identified. The gene responsible for the ISA phenotype is tightly linked to the tyrosinase related protein 1 gene (Tyrp1),

which also regulates coat color. D2 mice have a mutant allele of this gene (Tyrp1b) and a brown coat color. In previously studied genetic backgrounds, homozygosity for D2 alleles of both isa and ipd results in iris atrophy that severely affects both the iris stroma and iris pigment epithelium, leading to a severely atrophic and largely transparent iris in old mice. AKXD28 is a recombinant inbred strain derived by inbreeding offspring from an intercross between mice of the D2 and AKR/J strains. AKXD28 mice, therefore, have a genetic background that is a mix of the D2 (glaucomatous) and AKR/J (normal eyes with no obvious disease) genomes. Due to extensive inbreeding, all AKXD28 mice are genetically identical except for the sex chromosome difference between males and females. This genetic uniformity is important for the analysis of complex diseases because it allows repeated and therefore accurate assessment of phenotypes associated with the AKXD28 mix of D2 and AKR/J genomes. AKXD28 mice inherited the glaucoma causing ipd and isa alleles from strain D2. This is evident by their brown coat color and the inheritance of D2 derived microsatellite markers flanking these loci. To further assess the phenotypic consequences of ipd and isa and whether their effect is modified in the AKXD28 genetic background, we performed a detailed characterization of the ocular phenotype in AKXD28 mice. As demonstrated here, AKXD28 mice develop an age related glaucoma involving increased IOP and optic nerve damage, and they are a useful tool for glaucoma research. The AKXD28 disease has a number of similarities to that observed in D2 mice. Importantly, however, two major differences exist between the disease in AKXD28 and D2 mice housed in the same environment. First, AKXD28 mice do not develop the IPD phenotype. The absence of the IPD phenotype is surprising considering AKXD28's inheritance of the D2 chromosomal region containing the ipd gene, and likely results from genetic differences between these strains. Understanding these differences will be important for understanding pigment dispersion, a common cause of human glaucoma. Second, although D2 and AKXD28 strains demonstrate similar magnitudes of IOP, AKXD28 mice develop more severe and more extensive retinal damage and are more prone to optic nerve head excavation than D2 mice. This suggests that compared to D2 mice, AKXD28 mice have an increased genetic susceptibility to pressure-induced damage. Identifying the genes that differ between AKXD28 and D2 mice and that modify the progression and severity of pressure-induced retinal cell death will be important for understanding mechanisms killing cells in glaucoma and may ultimately lead to improved patient care.

CONCLUSION

Conclusions We have documented the development of a disease involving iris stromal atrophy and glaucoma in aged AKXD28 mice. These results add to our understanding of the natural history of glaucoma in mice and provide a new animal model for studying glaucoma involving increased IOP. Furthermore, careful phenotypic comparisons between the AKXD28 and D2 strains suggests that the AKXD28 genome contains genetic modifiers that suppress pigment dispersion and increase susceptibility to pressure-induced retinal damage. These results provide a basis for future research to identify glaucoma modifier genes and to dissect the molecular mechanisms by which they act.