Molecular Vision 2020; 26:173-187 <http://www.molvis.org/molvis/v26/173>
Received 11 October 2019 | Accepted 4 March 2020 | Published 6 March 2020

Using BXD mouse strains in vision research: A systems genetics approach

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We illustrate the growing power of the BXD family of mice (recombinant inbred strains from a cross of C57BL/6J and DBA/2J mice) and companion bioinformatic tools to study complex genome-phenome relations related to glaucoma. Over the past 16 years, our group has integrated powerful murine resources and web-accessible tools to identify networks modulating visual system traits—from photoreceptors to the visual cortex. Recent studies focused on retinal ganglion cells and glaucoma risk factors, including intraocular pressure (IOP), central corneal thickness (CCT), and susceptibility of cellular stress. The BXD family was exploited to define key gene variants and then establish linkage to glaucoma in human cohorts. The power of this experimental approach to precision medicine is highlighted by recent studies that defined cadherin 11 (*Cdh11*) and a calcium channel (*Cacna2d1*) as genes modulating IOP, *Pou6f2* as a genetic link between CCT and retinal ganglion cell (RGC) death, and *Aldh7a1* as a gene that modulates the susceptibility of RGCs to death after elevated IOP. The role of three of these gene variants in glaucoma is discussed, along with the pathways activated in the disease process.

Since the first wave of whole genome sequencing in the early 2000s [1-7], teams of investigators have developed open genetic, genomic, and transcriptomic resources to study the eye, visual system, and blinding diseases [8-12]. Over this same period, the costs of generating high-quality phenome and genome data have been decreased, and data quality and throughput have improved greatly. We are now at the point that is practical to consider in-depth analyses across large cohorts of human populations and rodent models. In the case of isogenic cohorts of mice and rats, the analysis of single genomes can be extended to multiple time points during development, aging, and in the progression of blinding diseases, making it possible to study gene-by-environmental and gene-by-treatment effects in ways that have high translational relevance to human clinical disease. A second major advance is our ability to systematically define and validate causal gene variants with increasing precision, power, and efficiency [13,14]. We can then move on to the more important stage of research to probe linked molecular and cellular networks associated with variation in the eye and visual system structure, function, disease, and treatment. For the first time, we can, in principle, combine a systems approach across the entire visual system (from the cornea to the cortex to visually guided behavior) using global omics and genetic methods, including epigenomic, proteomic, metabolomic, and lipidomic methods. When this omics combination is coupled with classic genetics (i.e., genetically diverse populations), it is referred to as systems genetics; essentially systems biology but in a rich genetics and omics context [2,3,15].

Progress in systems genetics was driven by the development of greatly expanded families of fully isogenic replicable cohorts [16,17], in particular the BXD strain set (parental strains, the C57BL/6J mouse and the DBA/2J mouse, Figure 1) [18,19], the AXB/BXA strain set (parental strains, the AJ mouse and the C57BL/6J mouse) [20], and the collaborative cross (CC,) [21,22]. In addition, the CC is used to create the mouse diversity outbred strains [23,24]. These recombinant inbred strains have been used in studies of the visual system, focusing mainly on the retina [17,25-28]. Table 1 lists the attributes of each strain and the strain set–specific tools available for data analysis. Each recombinant inbred strain has its advantages. The AXB strains were used extensively to map quantitative trait loci (QTLs) modulating cell number in the retina [29,30]. The disadvantage of this strain set is that there are a limited number of strains (now in cryopreservation) and only one data set for transcriptome analysis of the whole eye. The CC has the advantage of an extremely diverse genetic background with eight parental mouse strains contributing to the overall genetic diversity. Seventy-five strains are available from the Jackson Laboratory; however, this strain set is not widely used in vision research. All of the recombinant inbred strains have the distinct advantage of resampling the same genetic background. This ability to resample decreases the contribution of environmental variance and dramatically

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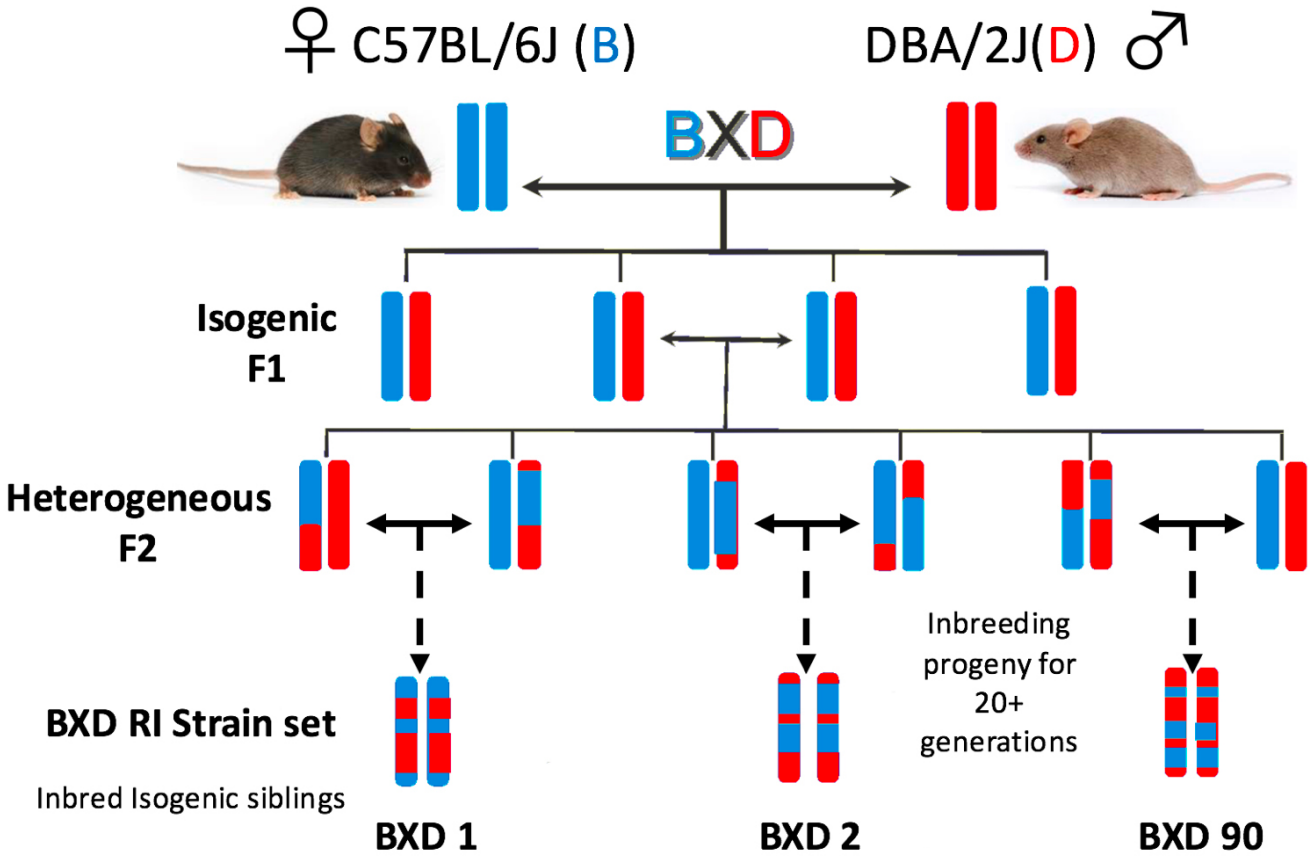


Figure 1. The breeding strategy for creating the BXD recombinant inbred strains is shown. The parental strains were C57BL/6J female mice and DBA/2J male mice. The mice were bred to produce an F1 cross, and the F1 mice were bred again to produce an F2 generation. The mice were inbred through brother-sister mating for at least 20 generations to produce inbred sub-strain populations. Currently, 150 BXD strains are available.

enhances the ability to accurately map QTLs. The fact that mice cannot be resampled in the mouse diversity panel is a decidedly distinct disadvantage.

At the present time, the BXD family is one of the preeminent platforms for systems biology to study the visual system and neurodegeneration [12,15,27,31-34]. The BXD family consists of 150 strains that segregate at more than 6 million sequence variants—a level comparable to many human cohorts used in genome-wide association studies (GWASs) [19]. There are several advantages vis-à-vis studies of human

Table 1. Comparison of Strain Sets Commonly Used in Vision Research.

Features	BXD	AXB	CC	Diversity outbred
Number of parental strains	2	2	8	8
Number of Strains	202	25*	75	Unlimited
Resampling	Yes	Yes	Yes	No
Fully sequenced	No	No	Yes	No
Fully mapped genome	Yes	Yes	Yes	No
Bioinformatic tools	GeneNetwork	GeneNetwork	SPARCC**	No
Eye transcriptome datasets	2	1	0	0
Retina transcriptome datasets	4	0	0	0

*Cryopreserved Jackson Laboratories **Simulated Power Analysis in the Realized Collaborative Cross [1,119]

cohorts: efficient experimental procedures and therapeutics, access to cells and tissues at any time point under many controlled conditions, high statistical power (resampling individual isogenic genotypes), high mapping precision (often better than 2 mega-bases), the ability to study gene-by-environmental interactions, and faster exploration and testing of the potential and the limitations of precision medicine.

The BXD family (Figure 1) was derived by crossing two of the most widely used inbred strains of mice: C57BL/6J (B6) and DBA/2J (D2). The B6-by-D2 offspring (BXD) were then inbred along separate lines until each line was fully inbred. Each of the 150 BXD progeny strains is essentially immortal and a fully inbred sibling. Some of these strains have been used for nearly 25 years for rigorous quantitative analysis of the visual system and the retina structure [35], cortical plasticity [27,36], as well as for studies of eye and retinal transcriptomes [1,37].

The development of the BXD family was begun by Benjamin A. Taylor in about 1973. He generated the two sets of these strains (BXD1 to BXD32 [38], and then BXD33 to BXD42 [18]) at the Jackson Laboratory. BXD43 through BXD102 were generated by Lu Lu, Jeremy Pierce, and colleagues in the late 1990s and early 2000s using advanced intercross progeny [39]. Recent efforts by our group have increased the number of BXD progeny to 150 living strains. All are currently available from either the Jackson Laboratory or the University of Tennessee Health Science Center. All have been fully sequenced (this is publicly available) [19].

The BXD family incorporates a comparatively high level of genetic diversity and can serve as a robust animal model for some human ophthalmic diseases and developmental abnormalities. The use of sophisticated molecular, imaging, and phenotyping methods across such a large set of fully sequenced and isogenic (reproducible) lines of mice opens up new opportunities in an experimental version of precision medicine. We focus on the eye, retina, and primary visual system. The BXD family of strains offers a unique resource for the vision research community with several advantages. Across the strains, there is a relatively high level of diversity in phenotypes. For example, the total population of retinal ganglion cells per eye varies from about 50,800 ± 1,100 in BXD27 to 75,800 ± 2,000 in BXD32 [40]. The practicality of resampling each genome many times—for example, to gain precise estimates of RGC numbers—greatly reduces non-genetic sources of variance and boosts the effective heritability of traits. This makes it possible to map and even clone the most stubborn and noisiest phenotypes. Initial studies by our group explored the genetic diversity within the BXD family to define genetic, molecular, and phenotypic networks active in the eye (Table 2).

Table 2. BXD Microarray Databases Available on GeneNetwork.

Retina RNA
DoD CDMRP Retina Affy MoGene 2.0 ST (May 2015) RMA Gene Level
DoD CDMRP Retina Affy MoGene 2.0 ST (May 2015) RMA Exon Level
Full HEI Retina Illumina V6.2 (April 2010)
HEI Retina Normal Illumina V6.2 (April 2010)
DoD Retina After Blast Affy MoGene 2.0 ST (May 2016) RMA Gene Level
DoD Retina Blast vs. Normal Affy MoGene 2.0 ST (May 2016) RMA Gene Level
DoD Retina after Blast Affy MoGene 2.0 ST (May 2016) RMA Exon Level
ONC HEI Retina (April 2012) RankInv
HEI ONC vs Normal HEI Retina Illumina V6.2 (Sept 2011) RankInv
Eye RNA
Eye M430v2 (September 2008) RMA
Eye M430v2 No Mutant/Mutant (April 2012) RMA
Eye M430v2 Mutant *Gpnmb* (September 2008) RMA
Eye M430v2 WT *Gpnmb* (September 2008) RMA
Eye M430v2 Mutant *Tyrp1* (September 2008) RMA
Eye M430v2 WT *Tyrp1* (September 2008) RMA
Eye M430v2 WT WT (September 2008) RMA
Howell et al., 2011, DBA/2J Glaucoma Optic Nerve Head M430 2.0 (December 2012) RMA
Howell et al., 2011, DBA/2J Glaucoma Retina M430 2.0 (December 2012) RMA

We have developed companion open access data resources and analytic tools that make the statistical and mapping methods far more accessible to a large community of vision research scientists who have matched expertise in molecular and cellular biology (for detailed instruction on the use of these resources, see Geisert et al. [1]). For example, we generated, collected, and curated multiple gene expression data sets (Table 2). Normative and experimental data sets facilitate the study of ocular diseases and injury in eyes [1] and the retinas [11,27,37,41]. The complete eye data set is the Eye M430v2 (Sep08) RMA which contains data from 68 BXD RI strains, the parental strain, the reciprocal F1 crosses, 35 strains from the mouse diversity panel, and eye data from six knockout mouse lines. The other data sets are subsets taken from the original data. One of the parental strains contains mutations in two genes (*Tyrp1* and *Gpnmb*) that contribute to pigment dispersion and ultimately, to glaucoma [42-44]. The derivative data sets are split subsamples based on the presence or absence of mutations in these two genes. For example, the Eye M430v2 no Mutant/Mutant (Aug12) RMA data set contains array data for eyes from 57 BXD strains, none of which have mutations in *Tyrp1* or *Gpnmb.*

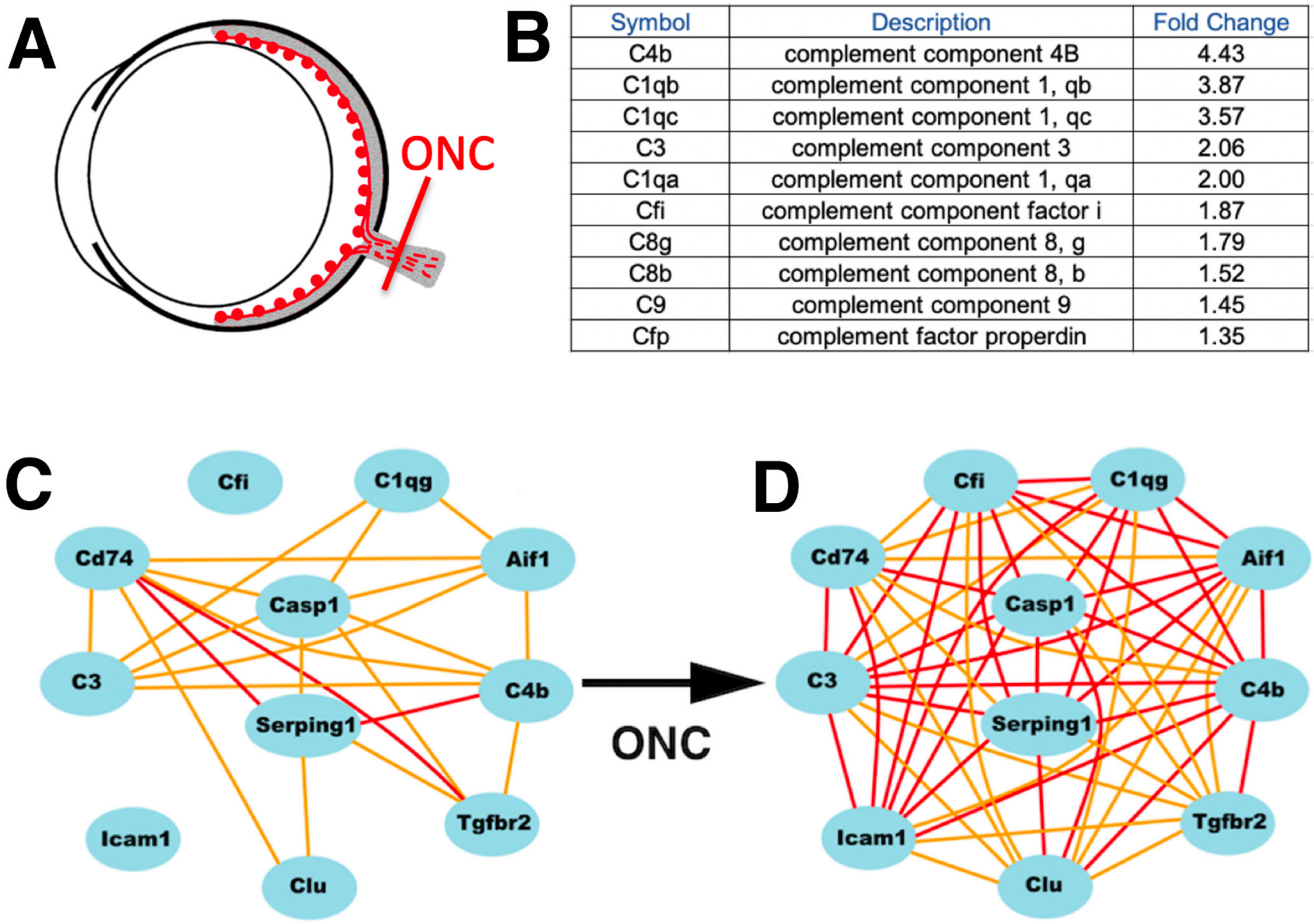
There are also several different retinal transcriptome data sets. The most recent exploits the Affymetrix Mouse Gene 2.0 ST Exon array (Santa Clara, CA) to estimate change in gene expression between the healthy retina and the retina 5 days after the eye was exposed to a 50 psi blast injury ((Table 2) [37,41]. These Affymetrix data sets include the DoD Retina Normal Affy MoGene 2.0 ST (May15) RMA Gene Level (the data set was made using healthy retinas from 59 different mouse strains), DoD Retina Normal Affy MoGene 2.0 ST (May15) RMA Exon Level (the data set explores 59 strains at the exon level), DoD Retina After Blast Affy MoGene 2.0 ST (March16) RMA Gene Level (the data set consists of gene-level data from the retinas of 54 strains 5 days following blast injury), DoD Retina After Blast Affy MoGene 2.0 ST (March16) RMA Exon Level (the 5-day blast injury data are also presented at the exon level), and DoD Retina Blast versus Normal Affy MoGene 2.0 ST (April15) RMA Gene Level. The other data sets were run on the Illumina V6.2 array (San Diego, CA), and the difference in gene expression between healthy retinas and retinas 2 days after optic nerve crush was examined [11,27]. The arrays in the Illumina data set include Full HEI Retina Illumina V6.2 (April10) RankInv (the data set represents gene-level expression data from the healthy retinas from 75 BXD strains), HEI Retina Normal Illumina V6.2 (April10) RankInv (the data set is similar to that for the full retina with the removal of data from six strains with high levels of glial fibrillary acidic protein (GFAP) expression), and ONC HEI Retina (April12) RankInv (the data set consists of retinal samples 2 days after optic nerve crush). These BXD data sets provide a large resource that is especially useful for characterizing molecular and genetic networks in the eye, and for tracking down sequence variants related to the injury or disease susceptibility [1,11,45,46]. Furthermore, all the retinal mRNA profile data from healthy and injured conditions are accessible by the public on GeneNetwork, along with a sophisticated array of bioinformatic tools.

Defining genetic networks active in the eye and the retina: The eye and retina transcriptome data sets provide powerful tools for defining the genetic profiles of specific ocular tissues and cell types [1,47,48]. In the HEI Eye Data Set, signature transcript profiles can define the genes expressed in the cornea to retinal ganglion cells [1]. The large microarray data sets also allow us to define genetic networks active within the retina and the changes in these networks that occur after injury [11,49]. One example is the activation of an innate immune network within the retina following optic nerve crush or blast injury to the eye. Using four comprehensive and complementary transcriptome data sets (the healthy retina and the retina 2 days after optic nerve crush, along with the healthy retina and the retina 5 days after blast injury, gn2.GeneNetwork.org), we examined changes that occur in gene expression profiles after optic nerve crush or after blast injury. Our group found an innate immune network that is rapidly activated after injury to the retina [11,41]. This work added to the previous work of others that showed members of the complement cascade are involved in retinal injury and glaucoma [50-53]. The importance of this complement network in glaucoma was revealed by knocking out *C1qa* on a DBA/2J background. In these animals, pigmentary dispersion glaucoma and elevated intraocular pressure (IOP) occur, but the expected loss of axons in the optic nerve is dramatically mitigated [53]. Thus, C1QA, and potentially, the complement cascade, plays a pivotal role in the degeneration of axons within the optic nerve of the DBA/2J glaucoma mouse model.

An examination of the changes in the expression of *C1qa* and *C4* following optic nerve crush or blast injury led to the identification of a genetic network activated by injury. The prominent genes in this network are members of the innate immune system. Defining the activation of these genetic pathways was made possible by the large number of BXD strains in these data sets [1,11]. The power of this research effort allows us to define genetic networks in the healthy mouse retina and genetic networks activated by injury (based on 61 BXD strains). If we look at the distribution of *C4b* across the BXD RI strain set, we can see that selected animals have high levels of expression. If we compare the top 100 correlates of *C4b* in the injured retina to those in the healthy

retina, then there is clear upregulation of the expression of these genes, and the genes are more highly correlated than observed in the healthy retina database (Figure 2). Examining cellular markers in the activated network, it appears that retinal microglia are the main cellular component of the innate immune response in the retina [11]. Defining the innate immune genetic network in the retina illustrates the power of the BXD strain set to examine the coordinated activation of genomic elements.

Systems biology of ocular phenotypes: One of the primary uses of the BXD family is to map QTLs that modulate ocular phenotypes or functional aspects of the visual system. Our group has conducted studies on several morphometric features, beginning with ganglion cell number [35], eye size, lens weight, and retinal area [54]. Examination of one of the targets of the retina, the lateral geniculate nucleus (LGN), in the BXD strains, led to interesting correlations between the number of RGC neurons and the number of neurons in the lateral geniculate nucleus. The study of the LGN is a good example of how systematically generating quantitative data across the BXD family can lead to substantial revisions in our understanding of the visual system [55]. Before the LGN



Symbol	Description	Fold Change
C4b	complement component 4B	4.43
C1qb	complement component 1, qb	3.87
C1qc	complement component 1, qc	3.57
C3	complement component 3	2.06
C1qa	complement component 1, qa	2.00
Cfi	complement component factor i	1.87
C8g	complement component 8, g	1.79
C8b	complement component 8, b	1.52
C9	complement component 9	1.45
Cfp	complement factor properdin	1.35

Figure 2. The activation of the innate immune network following ONC is illustrated. **A**: Following damage to the optic nerve, the retina responds with the retinal ganglion cells undergoing degeneration and the microglia and macroglia (astrocytes and Müller cells) responding to the insult. **B**: One of the responses is upregulation of components of the innate immune system. The genes that are upregulated by injury are shown. There is also an increased correlation across the BXD strains from the healthy retina (**C**) to the retina 2 days after injury (**D**). The network map for selected genes from the innate immune system illustrates the increased correlation in the retina 2 days after optic nerve crush (ONC). In the mouse, C1q is represented by three separate genes, and all three genes (*C1qa*, *C1qb*, and *C1qc*) behave similarly. The colored lines indicate the Pearson correlation between the genes with the red lines representing r>0.7 and the orange lines representing r>0.5. Selected genes from the innate immune network are shown in two plots. Notice the increased correlation in the genes of the innate immune network following ONC. These data demonstrate the power of comparing and contrasting two different data sets: the healthy retina and the retina after ONC.

work, it was universally thought that the numbers of RGC neurons and neurons in the LGN were jointly titrated during development to some optimal functional stoichiometry—for example, to a relative tightly adjusted ratio between RGC neurons and their principal targets in the LGN. However, Seecharan and colleagues [55] refuted this neat numerical matching hypothesis. Across 56 strains, the correlation between the numbers of RGC and LGN neurons is merely 0.01, strong evidence that interconnected neurons in these two regions are not jointly controlled by either genetic or developmental mechanisms. Other families of inbred strains were used to examine other cell types within the retina [30,48,56-61]. Finally, recent studies used the BXD strain set to examine the regenerative capacity of axons in the optic nerve [62]. All of the phenotypic data are available on GeneNetwork under BXD Phenotypes.

The tools and databases presented in GeneNetwork were used to examine genetic regulation of factors associated with glaucoma risk in humans [63]. Glaucoma affects millions of people worldwide [64,65] and is the second leading cause of blindness in the United States [66]. Adult-onset glaucoma is a collection of diseases with multiple risk factors and genes that ultimately affect the loss of RGCs [67-69]. The severity of primary open angle glaucoma (POAG) is dependent on the interaction of multiple genes, age, and environmental factors [70]. The primary risk factor is elevated IOP [71]. There are known genetic mutations that affect IOP that result in inherited glaucoma [72,73]. Since the Ocular Hypertension Treatment Studies (OHTS) [63] and others' subsequent independent findings [74,75], several phenotypic risk factors for POAG have been identified. Two of these glaucoma risk factors are IOP and central corneal thickness (CCT). We identified genes modulating these phenotypic factors in the mouse and examined human glaucoma to determine the potential role of these genes in human populations. As an alternative approach to human GWASs, we used mouse model systems to define genes regulating ocular phenotypes and potential links between these ocular traits and glaucoma risk [76]. These mouse models aid not only in defining genes involved in glaucoma risk but also in understanding the disease mechanism along with potential therapeutic interventions [77,78].

Regulation of IOP: The BXD family was used in three studies to examine QTLs modulating IOP in the mouse [12,25,28]. We know a considerable amount about the regulation of IOP from the production of aqueous humor to the outflow pathways [79,80]. We also know that IOP is a complex trait affected by different tissues in the eye each of which may be regulated by multiple genes. Interestingly, until recently few studies [81-86] had identified genomic loci in humans modulating healthy IOP. Recent work using the eye phenotypic data from the UK Biobank identified several genes modulating IOP in human populations [87-89]. Lu et al. [28] examined the regulation of IOP in BXD strains relative to pigment dispersion (transillumination deficit), time of day, and age. The study found that IOP across the full array of BXD strains was independent of transillumination defects or the time of day. There was no single genomic locus identified in this study that was found to modulate IOP in this set of BXD strains. The second study by Chintalapudi et al. [25] examined 65 BXD strains and found a significant QTL peak on chromosome 5. Within this QTL, one gene (*Cacna2D1*) was identified as a likely candidate for modulating IOP in the mouse. When the , National Eye Institute Glaucoma Human genetics collaBORation Heritable Overall Operational Database (NEIGHBORHOOD) GWAS was examined, calcium channel, voltage-dependent, alpha 2/delta subunit 1 (CACNA2D1-HGNC: 1399 Entrez Gene: 781 Ensembl: ENSG00000153956 OMIM: 114204) had a nominal association with POAG ($p<0.001$). This protein was also found to be highly expressed in the ciliary body and displayed expression in the trabecular meshwork. The identification of this candidate gene, *Cacna2d1*, provided a promising new target for therapeutic intervention to modulate IOP in POAG. The third study by King et al. [12] used 38 BXD strains, none of which carried the two mutations (*Tyrp1* and *Gpnmb*) that result in pigment dispersion and elevated IOP. The genome-wide interval map identified one significant peak on chromosome 8 that lies in a gene desert. Within this region, there are only four annotated genes: *Gm15679* (predicted gene 15,679), *Cdh8* (cadherin 8), *Cdh11* (cadherin 11), and *Gm8730* (predicted gene 8730). Defining good candidate genes within the QTL requires a genomic element that eventually affects protein function. There are several possibilities: an increase or decrease in the amount of transcript produced by each strain, resulting in differences of protein expression or a difference in RNA levels (specifically non-coding RNAs or microRNAs). Another possibility is there is a mutation in the transcript that affects its function. For a protein, this would represent a non-synonymous single nucleotide polymorphism (SNP) that has a deleterious effect on protein function. For RNA, it would represent a sequence change that alters the function of the RNA. Using the tools available on GeneNetwork, we were able to identify candidate genes, particularly those associated with so-called cis-QTLs [1] or with nonsynonymous SNPs changing protein sequence and affecting protein function [47]. There are only two strong candidate genes, *Cdh11* and *Cdh8*. Neither has cis-QTLs in eye or retinal data sets [1,37]. Both have non-synonymous SNPs. Based on expression levels and on Sorting Intolerant from Tolerant (SIFT) analysis (a test designed to define SNPs

that affect protein function), *Cdh11* was the single strongest candidate. Examining human RNA sequencing (RNA-seq) data for the trabecular meshwork [90], we found expression of *CDH11* is 55 times higher than that of *CDH8*. Cadherin 11 was also found in structures associated with the control of IOP. In sections of the mouse eye stained for cadherin 11, there was antibody-specific staining of the trabecular meshwork, the endothelial cells of the canal of Schlemm, and other structures within the angle of the eye. The expression pattern of cadherin 11 in the cells of the trabecular meshwork and the canal of Schlemm is appropriate for a protein involved in regulation of IOP. After we found these results in the mouse, two human GWASs identified cadherin 11 (*CDH11*-HGNC: 1750 Entrez Gene: 1009 Ensembl: ENSG00000140937 OMIM: 600023) as a gene involved in the regulation of IOP in humans [87,88]. Recent studies demonstrated that *CDH11* is also a glaucoma risk factor [91]. These data revealed that cadherin 11 is a modulator of IOP and a risk for glaucoma.

Cadherins play an important role in cell–cell adhesion [92-94], and trabecular meshwork cells express several family members, including VE-cadherin (cadherin 5), K-cadherin (cadherin 6), OB-cadherin (cadherin 11), cadherin 19, and N-cadherin (cadherin 2) [95-97]. In the trabecular meshwork, cadherins can be modulated by TGFβ [98]. In culture, treating trabecular meshwork cells with Wnt3a causes an increase in cadherin 11 expression, resulting in enhanced cell–cell adhesion. The levels of cadherin 11 can also be affected by the wingless (Wnt)/β-catenin pathway [99]. Wnt signaling is known to increase membrane associated cadherin 6 [100]. The TGFβ and Wnt/β-catenin pathways interact with each other in modulating cadherin expression, specifically cadherin 2, cadherin 6, and cadherin 11. The upregulation of these cadherins in cultured trabecular meshwork cells enhances the adhesion between the cells resulting in an increase in resistance across the culture cell monolayers. The interaction between the Wnt signaling pathway and cadherins appears to be important in the regulation of IOP. The Clark group [101] found that increasing TGFβ elevates IOP while the Wnt pathway maintains IOP homeostasis. We have shown that *Cdh11* modulates IOP in the mouse [34]. Others have implicated CDH11 in IOP regulation in humans [87,88]. It appears to be part of an integral network involved in TGFβ and the Wnt/β-catenin signaling that modulates cell adhesion between trabecular meshwork cells. These interactions play an important role in the regulation of IOP and potentially form the basis of the role of *CDH11* in glaucoma [91].

Susceptibility of RGCs to injury: To define genomic elements modulating the susceptibility of RGCs to injury, we examined axon loss in 49 BXD strains that had magnetic beads injected into the anterior chamber of one eye blocking the trabecular meshwork and elevating IOP [49]. When the number of axons in the healthy retina and the number of axons following elevated IOP were used to generate genome-wide interval maps, they revealed the same suggestive QTLs on proximal chromosome 3. Neither the healthy nerve nor the optic nerve after elevated IOP had QTLs that reached a level of statistical significance ($p>0.05$). To define genomic loci that could modulate the susceptibility of RGCs to death, the loss of axons per strain was calculated by subtracting the mean number of axons in bead-injected eyes from the mean number of axons in healthy eyes for each strain. The genome-wide interval map revealed a single statistically significant genomic locus on chromosome 18 (54 to 56 Mb). Within this locus, there were no non-synonymous SNPs that could account for the allelic differences between the C57BL/6J and DBA/2J mice. One gene, *Aldh7a1*, had a significant linkage related score (LRS = 31, $p<0.01$, Probe 17,354,434). *Aldh7a1* was the single cis-eQTL within this interval.

The distribution of the ALDH7A1 protein in retinal sections or flatmounts reveals it is within RGCs that are colabeled with RGC markers TUJ1 or RBPMS [48,102]. ALDH7A1 staining was relatively ubiquitous in the cell body and axons but absent from the nucleus. These results are in line with other studies that demonstrated mitochondrial and cytosolic localization of ALDH7A1 in humans and rodents [103-105].

It is interesting to speculate about the potential role of ALDH7A1 in glaucoma risk. ALDH7A1 is involved in the metabolism of acetaldehyde to acetic acid. This process also involves metabolism of NAD. This coregulation of NAD may have a direct effect on axon and neuronal survival. These data suggest that allelic differences in ALDH7A1 may affect mitochondria function resulting in the susceptibility of RGCs to death. Previous work revealed that mitochondrial function is critical for RGC survival. The prime example is an interesting murine mutation that affects Wallerian degeneration in the peripheral nervous system [106] and the central nervous system [107]. The mutation disrupting healthy axon degeneration is a chimeric protein made up of Ube4b and Nmnat1 that produces the Wallerian Degeneration Slow (Wlds) protein. The effect of Wlds on axonal degeneration is due to local activity in the axon itself. The chimeric protein localizes not only to the nucleus but also in small axonal pools [108], causing a local increase in NAD^+. In a rat model of glaucoma, Wlds was shown to protect axons from degeneration, but did not appear to alter the fate of the neuronal cell bodies [109]. In the D2 mouse model of glaucoma, supplementing the diet with NAD or overexpressing *Nmnat1* partially protects

against glaucomatous degeneration [110]. When the mutation in WLDs was put on the D2 background, and the mouse was supplemented with NAM (nicotinamide, a NAD precursor), there was almost complete rescue from the effects of glaucoma with 94% of the treated eyes not developing glaucoma [78]. It is possible that the interactions of ALDH7A1 with NAD are in part responsible for the glaucoma risk inferred by specific mutations in this protein.

Central corneal thickness and glaucoma: The BXD strains were used to define a genetic link between CCT and glaucoma risk [12]. CCT is one of the most heritable ocular phenotypes, and it is also a risk for developing POAG [111-113]. Thinner corneas are associated with an increased risk of developing POAG, and this risk is independent of the confounding effects of CCT on intraocular pressure measurements [63,75]. A thinner CCT is also associated with increased severity of visual field loss and more rapid progression of the disease [66,70,114]. *Pou6f2* was identified as a gene that modulates CCT in the mouse, and in the NEIGHBORHOOD human glaucoma database, *POU6F2* (HGNC: 21694 Entrez Gene: 11281 Ensembl: ENSG00000106536 OMIM: 609062) is a risk factor for human glaucoma [91,115,116].

CCT was measured in 61 BXD RI strains (Figure 3), and a single significant QTL (Figure 3) was identified on chromosome 13 (13 to 19 Mb). Within this QTL, there was only one candidate gene *Pou6f2* that contained non-synonymous SNPs in the mouse. The syntenic regions in the human were examined by Wiggs and colleagues in the NEIGHBORHOOD database [117] to determine if there are potential risk factors for glaucoma in this region. The top 50 SNPs were all associated with one gene (*POU6F2*). The highest statistically significant level was a probability of 10^{-6} for SNP rs76319873. This combined approach identified *Pou6f2* as a gene that modulates CCT in the mouse and a risk factor for primary open angle glaucoma [91].

POU6F2 was first described as a novel POU-domain transcription factor in the retina [118], and it identified a subpopulation of RGCs. We have independently confirmed these findings and found that *Pou6f2* is part of a genetic network found in mouse RGCs [48]. The first hint of the link

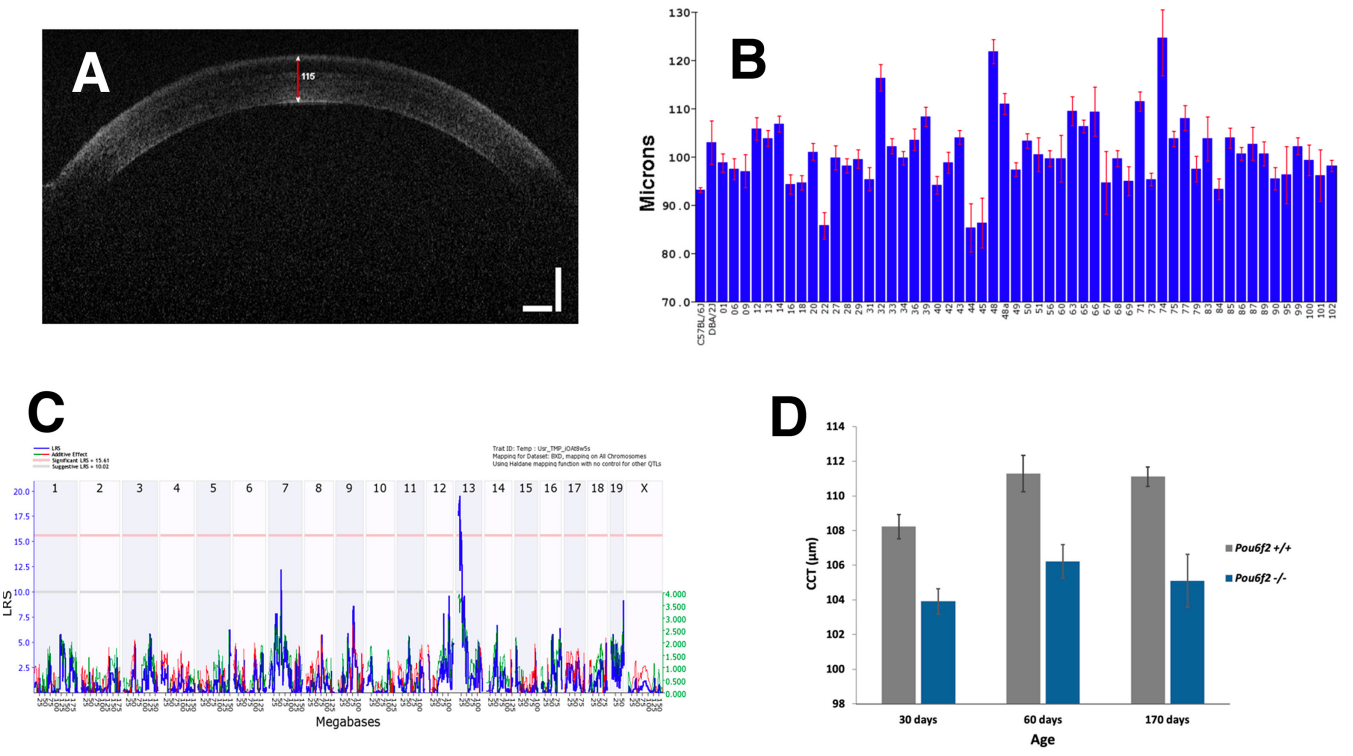


Figure 3. Central corneal thickness was measured using optical coherence tomography (OCT) in **A**. **B**: The difference in the central corneal thickness (CCT) can be seen in the 61 BXD strains measured. **C**: Interval map of the CCT across the mouse genome. The total linkage related score (LRS) is indicated with a blue line. The red line illustrates the contribution from the B6 allele and the green line the contribution from the D2 allele. Across the top of the figure, the genome is indicated from chromosome 1 to chromosome X. On the y-axis is the LRS. Notice one statistically significant quantitative trait locus (QTL) peak on chromosome 13 (above the pink line, p = 0.05) and additional suggestive peaks (above the gray line). **D**: Mice with a null mutation in *Pou6f2* (n = 6) had thinner corneas than wild-type (n = 6) littermates.

between *Pou6f2* modulating CCT in the mouse and the potential role of the gene in glaucoma is revealed during the development of the eye. *POU6F2* is expressed in RGC progenitor cells and the cornea. In the embryonic eye, strong POU6F2 staining was observed in neuroblasts destined to become RGCs. There is also staining of the developing cornea and corneal stem cells [12].

In flatmounts of the mouse retina, virtually all of the POU6F2-positive cells are labeled with RNA-binding protein with multiple splicing, RBPMS (Figure 4). There are cells that are heavily labeled (approximately 16% of RPBMS RGCs) and cells that are moderately to lightly labeled (approximately 16% of the RPBMS RGCs). A few cells in the amacrine cell layer are POU6F2 positive, and all of these cells are also labeled with RBPMS, suggesting that these cells are displaced ganglion cells. In retinas 28 days following optic nerve crush, no cells in the ganglion cell layer are positive for POU6F2. As POU6F2 is found only in RBPMS positive cells, and as all of the staining for POU6F2 disappears following optic nerve crush, we conclude that POU6F2 labels only RGCs in the C57BL/6J and DBA2J mouse adult retinas.

To examine the potential role of POU6F2 in glaucoma, we compared the distribution of POU6F2-RGCs in four young D2 mice (70 days old) to four older D2 mice (8 months old). There was a 22% loss of RPBMS labeled RGCs in the aged mice, while there was a 73% loss of POU6F2 heavily labeled cells and a 10% loss of POU6F2 moderate to lightly labeled RGCs (Figure 4). These data demonstrate that heavily labeled POU6F2 RGCs are sensitive to early phases of glaucoma in the DBA/2J mouse model.

Conclusions: The BXD family and the research tools developed on GeneNetwork offer the vision research community a unique system for analyzing complex genomic interactions associated with the healthy development of the mammalian visual system and disease. The initial efforts of our group explored the genetic diversity within the BXD RI strain set and defined genetic networks active in the eye. As a result of this work, we provided the vision research community with the Hamilton Eye Institute Mouse Eye Database (HEIMED [1]). To continue our efforts in studying the complex biology and diseases of the eye, we created the HEI Retinal Database. Within this database, naturally occurring changes in the mRNA levels are defined as the phenotype, and the genomic loci modulating the differences in transcriptional control can be evaluated using traditional QTL mapping methods. Thus, the HEI Retinal Database and the DoD Normal Retina Database provide a transcriptome-wide analysis of the retina, which allows identification of the genetic variability between the BXD RI strains and the expression signatures of cells that underlie the phenotypic variation. The utility of the BXD strains and the expression databases offered on GeneNetwork is demonstrated by the identification of *Pou6f2* as a

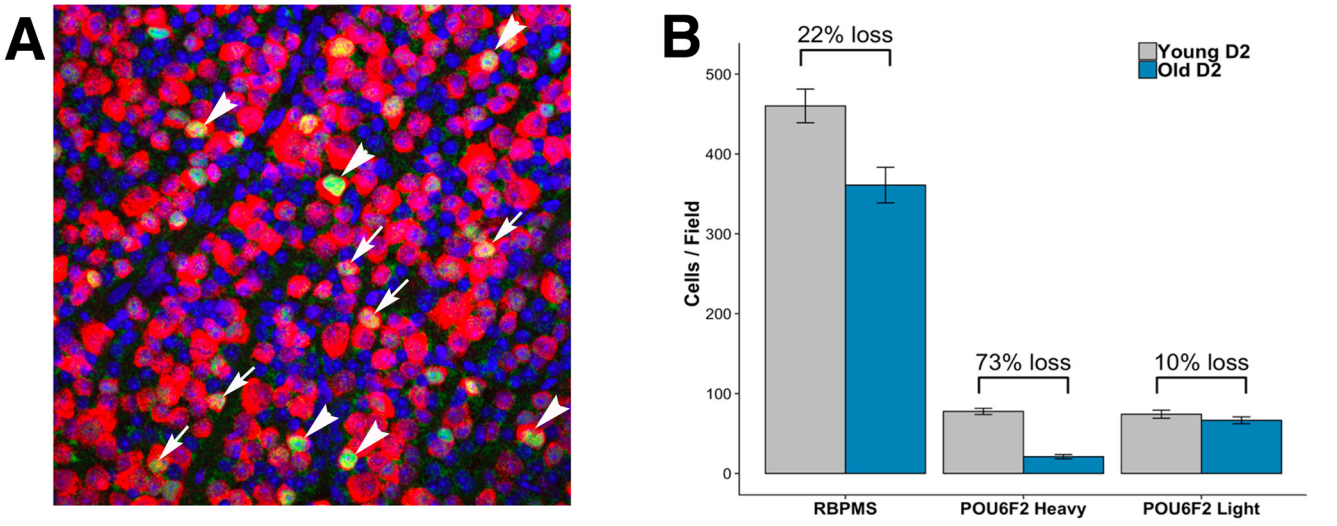


Figure 4. The selective sensitivity of POU6F2 RGC subtypes is demonstrated using the DBA/2J mouse model of glaucoma. POU6F2 (green) differentially labels ganglion cells (stained red with RBPMS). **A**: In the retina, 16.8% of the retinal ganglion cells (RGCs) are heavily labeled, and 16.1% of the RGCs are lightly labeled for POU6F2. In 8-month-old DBA/2J mice, there is a modest loss of RGCs with 22% loss of RBPMS-labeled RGCs in aged DBA/2J mice compared to young DBA/2J mice (2 months of age, young D2). The arrow heads mark heavily-labeled RGCs and the arrows indicate lightly-labeled RGCs. **B**: There was a dramatic loss of 73% of the heavily labeled POU6F2-positive cells compared to the young D2 mice. These data demonstrate the sensitivity of the heavily labeled POU6F2 RGC subtype to glaucoma.

modulator of CCT (a risk factor for POAG) and *Cdh11* as a modulator of IOP (a risk factor for POAG). Both genes were recently identified as glaucoma risk factors [91] providing a genetic link between CCT and IOP to glaucoma risk.

ACKNOWLEDGEMENTS:

This study was supported by an Unrestricted Grant from Research to Prevent Blindness, NEI grant R01EY017841 (E.E.G.), Owens Family Glaucoma Research Fund, P30EY06360 (Emory Vision Core) and DoD CDMRP Grant W81XWH-12-1-0255 from the USA Army Medical Research & Materiel Command and the Telemedicine and Advanced Technology (E.E.G.). GeneNetwork supported by NIGMS (R01GM123489), NIDA (P30DA044223) and the UT Center for Integrative and Translational Genomics, and funds from the UT-ORNL Governor's Chair (R.W.W.).

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Articles are provided courtesy of Emory University and the Zhongshan Ophthalmic Center, Sun Yat-sen University, P.R. China. The print version of this article was created on 6 March 2020. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.