Modeling the Progression of Diabetic Retinopathy Using the BXD79 Mouse Strain

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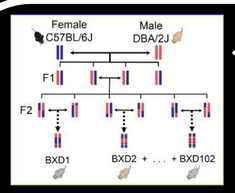
Purpose

- Diabetic retinopathy (DR) is a microvascular disease associated with diabetes mellitus (DM) complications
- Alterations in blood flow, vasodilation, & blood sugar can negatively affect the vasculature & neurons of the retina, resulting in blindness
- Animal models elicit a better understanding of the development, genetics, & mechanisms of multiple retinal degenerative diseases seen in humans
- Despite the complex etiology making DR difficult to model in animals, a spontaneous model of DR--the BXD79 mouse--has been uncovered
- This model displays naturally occurring phenotypes of hyperglycemia, obesity, vascular leakage, cataracts, and retinal degeneration
- This ongoing study seeks to investigate the etiology and pathology of DR in the BXD79 model.

Methods



- The BXD79 strain was found from an AMD genetic study; however, observed to be different in phenotype
- Single nucleotide polymorphism analysis (SNPs), reveals 9 predicted deleterious SNPs linked to many AMD & DR genes. More specifically the genes involved in angiogenesis, *Vegf*, *Kdr*, & *Flt1*.
- BXD79 & C57B/6J (wildtype) mice underwent functional examinations--electroretinograms (ERG), optokinetic nystagmography (OKN), optical coherence tomography (OCT), & fluorescein angiography (FA)--every 3 months beginning at 6 months of age until 18 months with tissues being observed using fluorescent immunohistochemistry (fIHC).

Conclusions

- Excessive sugar along with other DR-related phenotypes loosen tight junctions of the inner retinal vascular endothelial leading to vascular leakage & edema, respectively
- Functional test results (Fig. A & B) suggest a progressive reduction in retinal function, & disruption of retinal & vascular integrity (Fig. C & D) from 9 to 18 months
- fIHC reveal minimal mislocalization of inner/outer segment proteins, thus appearing normal (Fig. E). However, a loss of ganglion cell bodies & dendrites (Fig. F), thinning of the inner plexiform layer (Fig. H), and upregulation of KDR (fig. I & J)
- The combination of genetic mutations contributing to neovascularization & ganglion cell layer death can likely be linked to *Vegfa* and VEGF receptors *Flt1* and *Kdr*.

Support

Research to Prevent Blindness

irrf International Retinal Research Foundation

Knights Templar Eye Foundation, Inc. "A Masonic Charity"

National Eye Institute

Results/Discussion

ERG

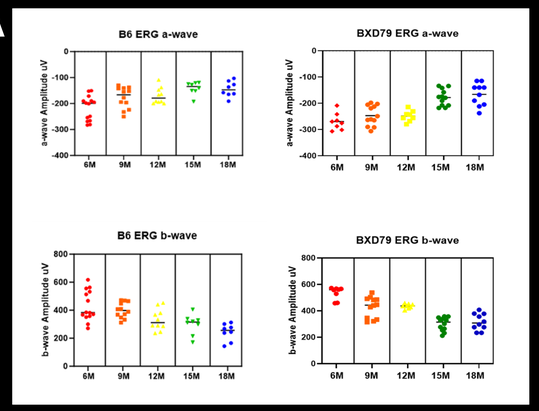


Fig A. Electroretinograms (ERGs) of wildtype (WT) & BXD79 from ages 6-18 months accessing retinal function. Data reveals dysfunction starting around 9 months in BXD79.

OKN

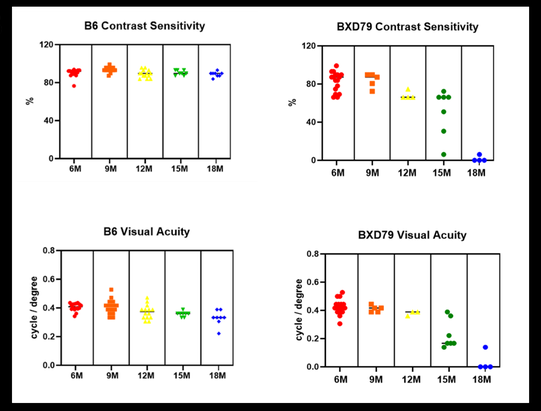
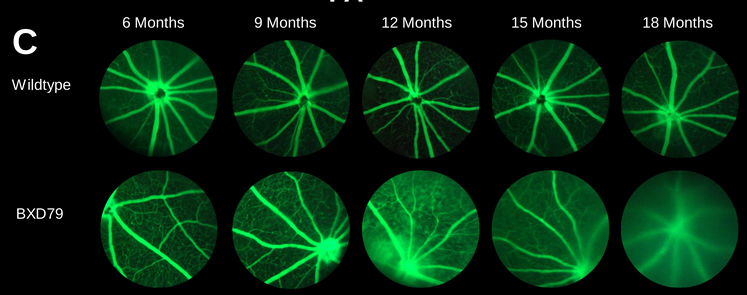


Fig B. Optokinetic nystagmography (OKN) of WT & BXD79 ages 6-18 months accessing visual acuity & contrast sensitivity. Data reveals loss of function starting at 9 months, persisting to 18 months in BXD79.

FA



OCT

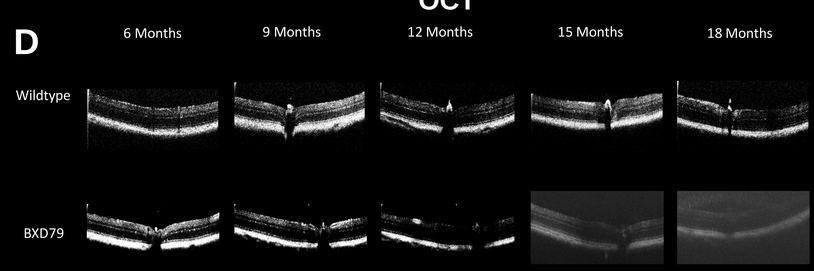


Fig C-D. C) Fluorescent angiography (FA) of WT & BXD79 (6-18 months) examining the vasculature of the retina. Vascular abnormalities & leakage are seen in BXD79 around 9 months.
D) Optical coherence tomography (OCT) of WT & BXD79 (6-18 months) accessing the retinal layers reveals retinal thinning around 12 months.

fIHC

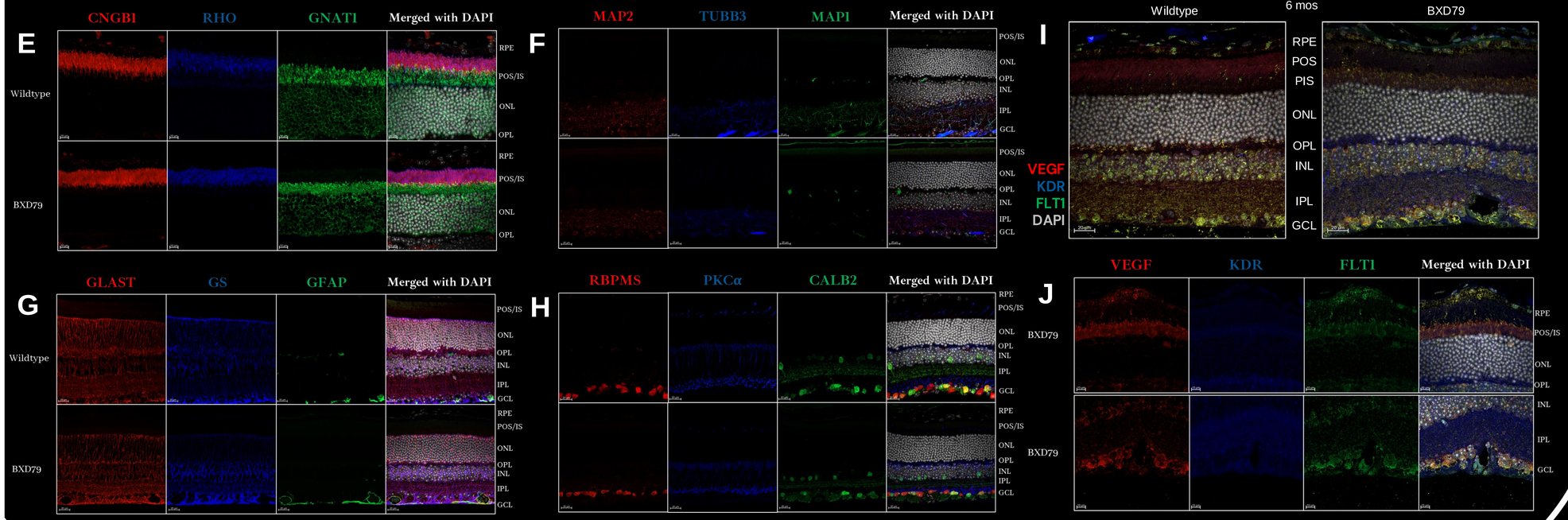


Fig. E-J. Fluorescent immunohistochemistry (fIHC) of WT & BXD79 at 18 months examining the localization of proteins in the retina. Data depicts fairly normal photoreceptors (E); however, ganglion cell body & dendrite loss (F), increased retinal stress with the upregulation of GFAP (G), retinal thinning (H), & upregulation of KDR (I-J) can also be observed. Scale bars = 20 μm.