Revealing Candidate Inherited Retinal Disorder Genes through Genome-wide Screening of Knockout Mice

Andy Shao[1]; Dave Clary[2]; KC Kent Lloyd[2]; Ala Moshiri[3]

1. University of Nevada Reno, Reno, Nevada, United States
2. UC Davis Mouse Biology Program, California, United States
3. Ophthalmology and Vision Science, School of Medicine, U.C. Davis, California, United States

University of Nevada, Reno School of Medicine

Introduction

Inherited retinal disorders (IRDs) are a conundrum for the ophthalmologic community as diagnosis of these debilitating diseases hinges heavily upon established knowledge of causative gene mutations. The rarity of IRDs has led to limited funding and interest for expanding the understanding of implicated genes.

Single gene knockout mice are a powerful tool the screening of candidate IRD genes. Given the breadth and standardized phenotyping of the IMPC mouse knockout project, the IMPC provides an invaluable resource for the search for candidate human IRD genes.

The aim of this study is to present a list of candidate human IRD genes using IMPC single gene knockout mice data. Furthermore, strains with vascular retinal abnormalities and concomitant hearing impairment were further stratified as candidate Familial Exudative Vitreoretinopathy and Usher Syndrome genes, respectively.

Methods

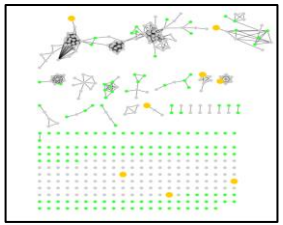
As of our interrogation, the IMPC database contained phenotypic data for approximately 7,000 mice with targeted single gene knockouts. We investigated all strains with abnormal retinal phenotypes and further enriched our search for strains with concomitant hearing or retinal vascular abnormalities.

Candidate genes were then analyzed for potential protein-protein interactions via bioinformatic analysis with STRING and PANTHER proteomics databases and cross-referenced against established IRD-causative genes as presented by the RETNET database.

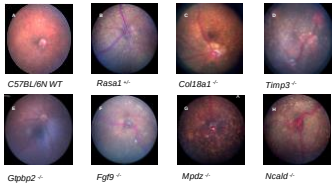
Results

Retinal Phenotype	Retinal phenotype (Novel)	Retinal Phenotype (Established)	Vascular Retinal Phenotype (Novel)	Auditory co-phenotype
179	152	27	104	12

Summary of IMPC mice strains with retinal phenotyping. Novel lines suggest no previous association with retinal pathology in mice or humans per RetNet Database and literature review. All auditory co-phenotype lines were novel for Usher Syndrome.

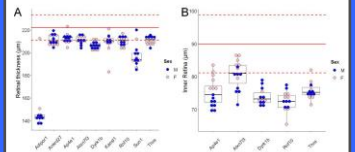


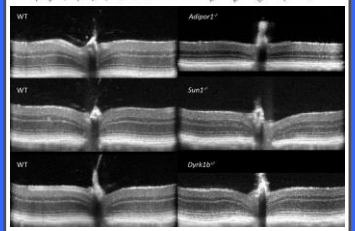
STRING Analysis of IMPC candidate (green) and RetNet (grey) genes reveals functional clusters of interest. Genes that exist in both lists are labeled (gold).



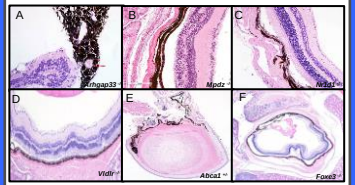
Example fundus photos from select IMPC knockout lines demonstrating vascular and pigmentary changes

Results





OCT quantification of total retinal thickness in select knockout lines. Male (blue) and female (pink) data are segregated. Wild type control data shown above (red). OCT images of select lines and WT controls are shown below.



Histological analysis demonstrating retinal abnormalities in select IMPC knockout lines. Abnormalities include vascular abnormalities, retinal atrophy, and retinal dysplasia.

PANTHER analysis of IMPC candidate genes reveals several novel pathways (right) not seen in RetNet genes (left). Further investigation of these pathways and their implicated genes has revealed novel candidate genes for vascular retinal pathology.

Conclusions

We present 153 targeted gene deletions previously unknown to cause retinal pathology. Twelve of these 153 are candidate Usher Syndrome genes. Thirteen of these 153 are candidates for heritable retinal vascular disorders such as FEVR. These genes are of interest not only for improving screening of human IRD patients, but also for elucidating novel biological mechanisms involved in retinal development.

Disclosures

No authors have financial disclosures.

Support

Funding generously provided by NIH NEI K08EY027463

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For further information

Please contact *amoshiri@ucdavis.edu*