ABSTRACT

Using a bioinformatics approach to identify genes that have possible candidacy of association with retinitis pigmentosa: GeneWeaver

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Retinitis pigmentosa (RP) is a retinal degenerative disorder that affects about 1 in 3,000 people. The disease is genetic in cause, and currently there is no cure. The genetic cause of the disease may be contributed to one of several different genes, underscoring the complex genetic underpinnings of this disease. The information required to determine which genes are potentially causative for RP may exist, but it is difficult to determine which genes are most suitable for study because of the immense wealth and breadth of available information. In other words, large-scale heterogeneous species-specific data often obfuscates the true causative genetic background of RP. In this study we describe a method of identifying genes that may contribute to RP using the bioinformatics techniques of graph theory and database utilization. We report a potential ranked list of genes in which disruptions are likely causative of RP.

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USING A BIOINFORMATICS APPROACH TO IDENTIFY GENES THAT HAVE POSSIBLE CANDIDACY OF ASSOCIATION WITH RETINITIS PIGMENTOSA: GENEWEAVER

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CHAPTER ONE

Introduction

Retinitis pigmentosa (RP) is a congenital hereditary disease that affects the photoreceptor cells in the retina, an expanse of cells in the back of the eye. Light that enters the eye hits the retina and excites the photoreceptors; this excitation causes signals to be sent to the brain to produce vision. First described in 1857 by Dr. F. C. Donders, RP causes the photoreceptors in the retina to gradually die, causing severe visual impairment and even blindness. Currently there is no treatment available to cure RP, but the identification of associated genes opens up the possibility of developing new treatments.

The Anatomy of RP

The eye is made up of many parts that work together to produce the experience of vision. The path of light in the eye can be seen in Figure 1. Light first enters the eye through the cornea, which is a clear film over the eye. The cornea works to focus the rays of light through the pupil, the hollow opening of the eye. The light waves then travel to the back of the eye where they reach the retina.

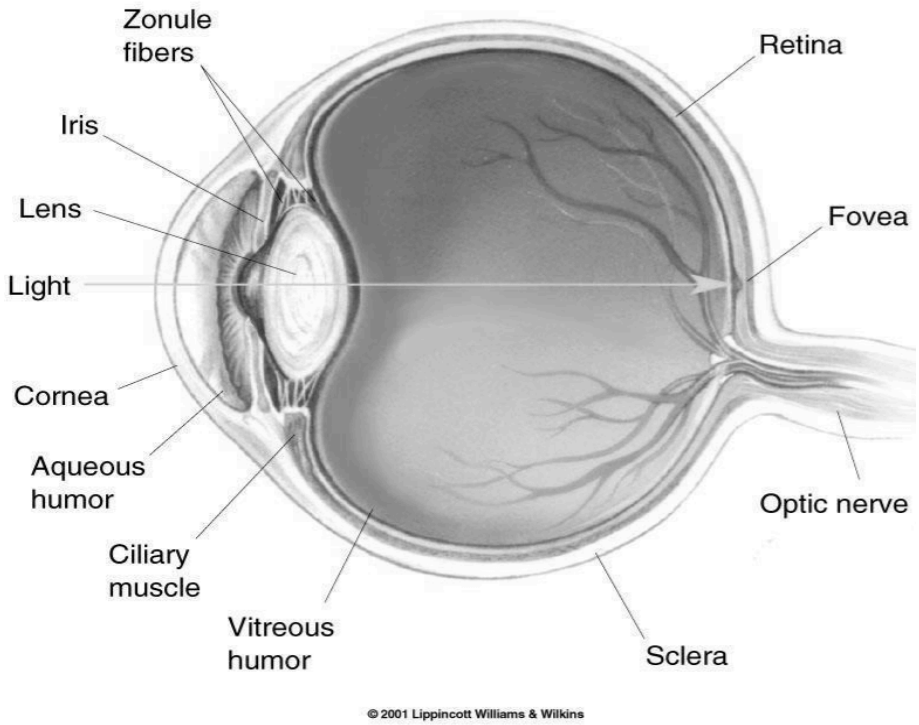


Figure 1: Cross Section of the Eye

From the front of the retina to the back, retinal cells are morphologically classified as ganglion cells, amacrine cells, bipolar cells, horizontal cells, and receptor cells. Receptor cells can be divided into the rods and cones. Rods and cones contain retinal-opsin complexes that are composed of a retinal molecule covalently bonded to an opsin protein. When retinal absorbs one photon of light, opsin undergoes a conformational change. Hyperpolarization of the receptor cell sends an electrical signal out of the receptor cell. This signal travels to the bipolar cells and then to the ganglion cells with the help of the horizontal and amacrine cells. The ganglion cells merge to form the optic nerve, and signals travel from there to the brain. The collaboration of signals from all of the receptor cells in both eyes creates the experience of vision. The retinal layers can be seen in Figure 2.

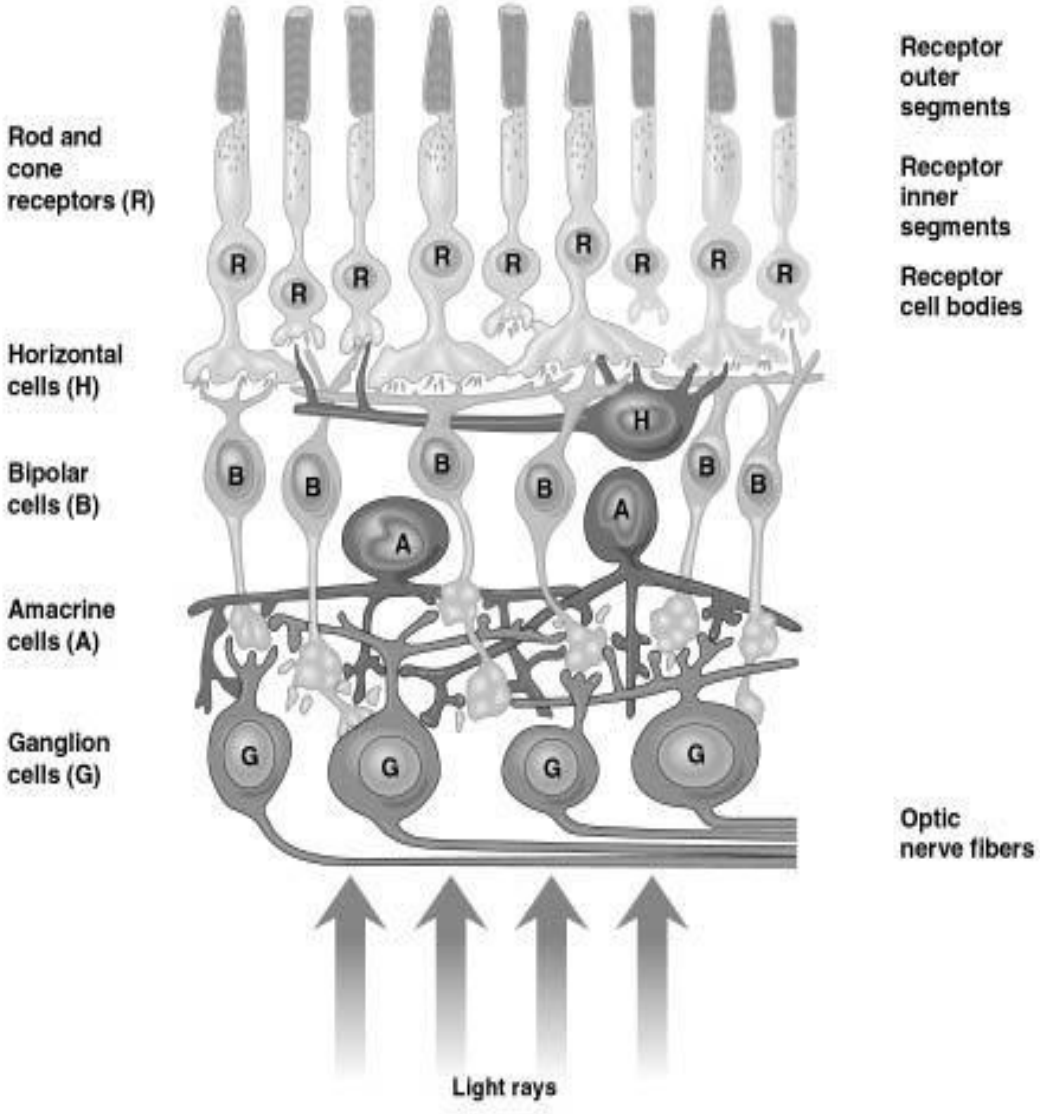


Figure 2: Organization of the Retina

RP causes gradual retinal degeneration. In early stages, rod cells die, and in final stages, cone cells die. Due to the heterogeneous nature of the disease, many possible explanations may account for rod and cone death. Rod cells are located on the periphery of the retinal field and thus account for peripheral vision. Cone cells are located primarily in the center of the visual field and thus account for central, or focal, vision. Additionally,

rod cells mediate achromatic contrast vision while cone cells mediate chromatic acuity vision. Fundus images of the back of the eye of a typical individual and an individual with RP can be seen in Figure 3. It is important to note the characteristic clumps of damaged pigment cells in the left image.

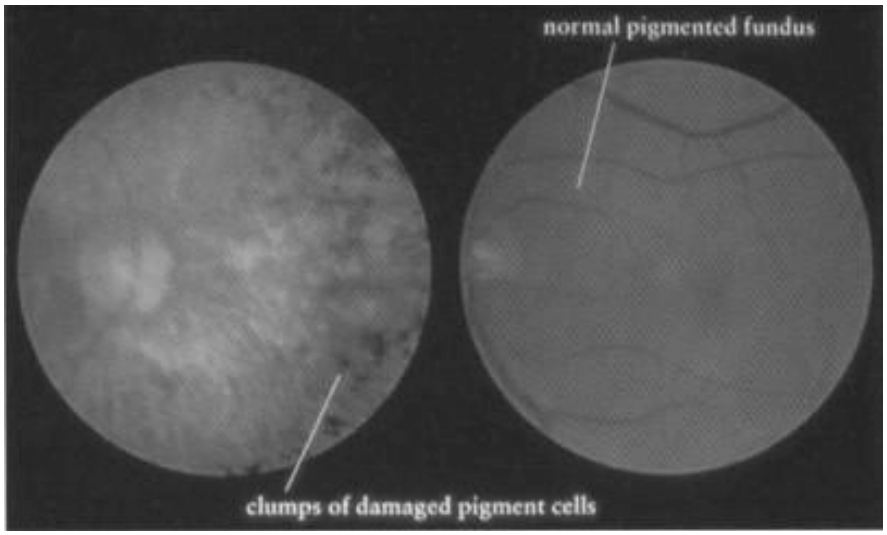


Figure 3: Comparison of the Fundus Image of an RP Eye (left) and a Normal Eye (right)

Symptoms of RP include loss of peripheral vision, otherwise known as tunnel vision, lowered perception of contrast, night blindness, lowered visual acuity, and in final stages total blindness. Onset of the disease varies, as well as disease severity; some individuals develop symptoms at an early age and others later in life. However, physiological symptoms in the retina are almost always present by age 6, even if the individual does not notice impaired vision. A percentage of individuals develop legal blindness due to the narrowing of the visual field, or total blindness. A representation of the visual experience of an individual with RP as compared to an individual with normal vision can be seen in Figure 4. Note the severe loss of peripheral vision in the left image.

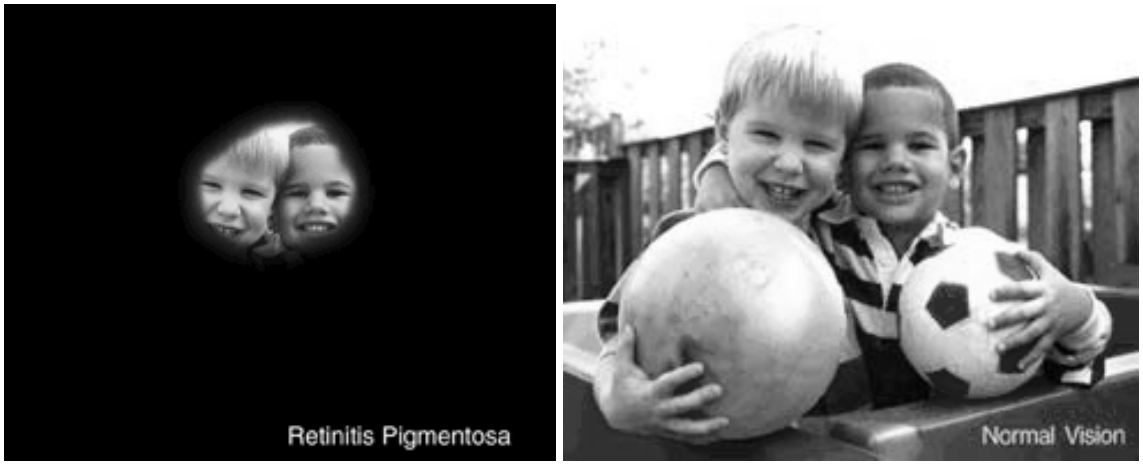


Figure 4: The Visual Experience of an Individual with RP (left) and an Individual with Normal Vision (right)

In humans, RP has been linked to various mutations in over 100 genes. In addition to humans, there are several model organisms that mimic the human RP condition: *Danio rerio* (zebrafish), *Drosophila melanogaster* (fruit fly), *Mus musculus* (mouse), *Rattus norvegicus* (rat), *Macaca mulatta* (macaque), *and Canis familiaris* (dog). A full list of genes that have been associated with RP in humans can be found in Appendix A. The majority of the genetic causes of RP were discovered using a combination of methods that include genome sequencing, linkage analysis, molecular analysis, homozygosity mapping, bioinformatics analysis, pedigree analysis, and animal models.

Treatment

Since there is no cure for RP, contemporary treatments exist only to slow the progression of the disease and have uneven palliative outcomes. Treatments include vitamin supplements of Vitamin A and DHA, or diets rich in these substances, such as oily fish. More holistic approaches include non-traditional treatments such as acupuncture.

Other treatment options for RP are currently being developed. One such treatment of RP is to use stem cell therapy to replace those cells that die due to RP with healthy photoreceptor cells. Particularly, bone marrow stem cells may be used to support retinal blood vessels that would otherwise deteriorate. In addition, stem cells can be used to provide nutrients for the dying photoreceptor cells, encouraging their survival. Stem cells may also be used to increase the number of synaptic connections from those photoreceptor cells remaining in the eye. There are some dangers to stem cell therapy, however. Stem cells currently do not have a high rate of survival when implanted, or they may be killed by the body's immune response. In addition, tumor formation may occur due to stem cells.

Neuroprotection is also being developed as a treatment for RP using growth factors or anti-apoptotic factors. Replacements for dead photoreceptor cells such as tissue transplants and retinal prostheses are also being developed.

Another future possibility of RP treatment is gene therapy. Gene therapy involves introducing non-mutated copies of a gene into an individual using a transporting vector. One vector that has shown success is the adeno-associated virus (AAV) vector. Another form of gene therapy involves introducing a gene silencing procedure into the individual to inhibit expression of the mutated gene. This can be done using ribozymes and RNA interference (RNAi). This treatment modality, however, can only succeed if the underlying genetic causes of RP can be understood, which is problematic given our current understanding of RP's genetic landscape.

Bioinformatics Approaches

The complexity of developing treatments for RP is derived mainly from the fact that even though there are numerous genes thought to be associated with RP, there is no singular causative agent. This may also imply that there are other mechanisms or genes associated with RP that have yet to be identified. Automated or semi-automated bioinformatics techniques can be used to compare large, heterogeneous data sets associated with RP. This also enables us to potentially find robust model organisms where RP can be studied.

There are several tools available to explore complex genetic traits and the convergent functional genomics associated with cross-species analysis. This thesis uses the GeneWeaver platform to integrate the numerous sets of genes associated with RP.

GeneWeaver (www.geneweaver.org) is an online database that stores and analyzes lists of genes, called gene sets, and can be annotated to a variety of categorizations. While public users can enter a gene set into GeneWeaver, most gene sets are derived directly from experimentation (GWAS, Microarray, etc.) or publications. For example, PubMed, a database for scientific literature, can be used to find articles that describe gene sets, and these gene sets can be entered into GeneWeaver. GeneWeaver retains information about the gene set name, figure label, description, access, source article, species, and per-gene scores. GeneWeaver stores sets as bipartite graphs that can be manipulated using numerous graph theory approaches, including finding the maximal or near-maximal cliques in the data structure. As can be seen in Figure 5, gene sets become associated with one another by the common genes they share. In part A of Figure 5, phenotypes, or gene sets, 1, 2, and 3 form a maximal clique in the sense that they all

contain genes a and c. Gene sets 2, 3, and 4 form a maximal clique because they all contain gene d. Gene sets 2 and 3 form a maximal clique in that they both contain genes a, c, d, and f. This information can then be organized into a hierarchical graph as shown in part B of Figure 5.

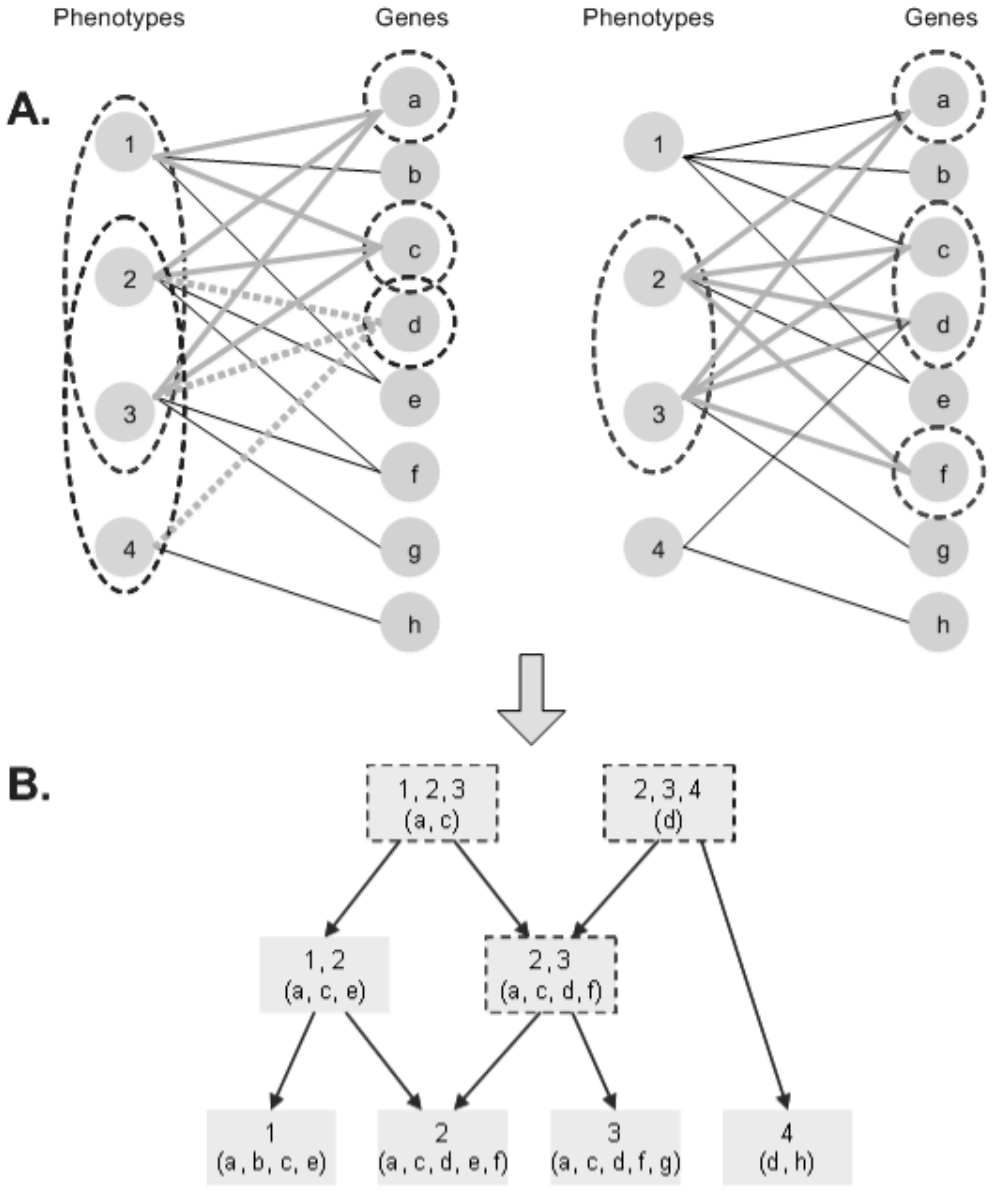


Figure 5: (A) Example of a Bipartite Graph in GeneWeaver (B) Hierarchical Organization of Information Contained in the Bipartite Graph

Once organized into a bipartite graph, gene sets can be manipulated in many different ways. For instance, a particular gene set may be used to find gene sets that are largely similar; in other words, gene sets that contain many of the same genes. This is done by GeneWeaver's identifying the other gene sets within the maximal cliques that a gene set of interest occupies.

The Jaccard index can be used to determine the degree of similarity between two gene sets. Jaccard indexes are more meaningfully visualized using the Jaccard Overlap Tool, which represents the overlap of two gene sets using a Venn diagram-like image. Figure 6 gives an example of the results of a Jaccard Overlap. Each gene set is represented as a circle, and the degree of overlap coincides with the degree of similarity between the two gene sets. This tool is especially useful when wanting to find genes that belong to gene sets that are similar to gene sets of the phenotype of interest, but are not themselves connected to the phenotype of interest. The most important gene sets are those that have a majority overlap, which is seen on the left in Figure 6. Uninformative gene sets typically have little overlap, such as can be seen in the middle image of Figure 6. Gene sets of trivial importance have one gene set engulfed by another, such as can be seen on the right in Figure 6. The notations above each image signify (number of unique genes in the left gene set (number of genes in both gene sets) number of unique genes in the right gene set). Additionally, the Jaccard Overlap Tool provides the p-value of the Jaccard index of a gene set pair.

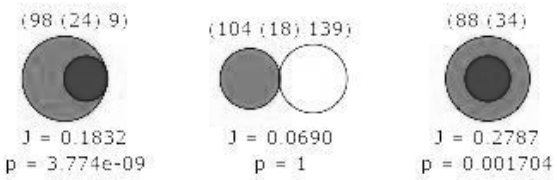


Figure 6: Examples of Jaccard Overlap Results

GeneWeaver also has the capability to combine gene sets using a Boolean Algebra tool. Users can combine all the genes of multiple gene sets into one gene set, unique genes of multiple gene sets into one gene set, or some other combination that falls between these two extremes. Users can also use the Boolean Algebra tool to subtract one gene set from another, in order to isolate those genes that are unique to one gene set.

Prioritization of these genes can then be determined using a program that, through union of shared gene sets, ranks genes by centrality. The more central a gene is, the more associations with other genes it has through inclusion in the same gene sets. Genes of higher centrality are considered to be of higher importance in determining possible association with the phenotype of interest.

Corroboration of the importance of these genes in particular organs and body structures can be assessed using the metadatabase GeneCards (www.genecards.org), which compiles vast amounts of information about a gene, such as the gene's transcripts, domains, and pathways. GeneCards presents the expression of proteins as microarray, RNAseq, and SAGE data. Microarray data, provided by BioGPS, is acquired by microarray, which involves introducing labeled molecules to an array of capture DNA to determine the levels of binding between the labeled molecules and the capture DNA. More bound species indicates a higher intensity of signal and an inferred greater expression of that DNA's protein. In the case of GeneCards, the DNA from a particular

tissue, for instance the retina, take the role of capture DNA, and a labeled molecule that will bind to the gene of interest is used to capture. RNAseq, or RNA sequencing, is a method of determining the levels of RNA present in a particular sample, in this case the tissue of the retina, which can indicate the levels of a certain protein in the sample. SAGE, or serial analysis of gene expression, is a method of linking cDNA fragments serially and then sequencing the concatemer to determine levels of cDNA, and thus levels of inferred protein, in a sample. GeneCards also provides information about the diseases associated with a particular gene, provided by the partner database MalaCards (www.malacards.org).

The pathways associated with a gene can be obtained from Pathway Commons (www.pathwaycommons.org), a database that displays the genes that a particular gene is associated with biologically. Pathway Commons can be used to understand the roles that a particular gene plays in the body and what systems a gene might affect. In this study, a gene's association with genes that have processes in the retina could suggest possible involvement of that gene in retinal diseases such as RP.

CHAPTER TWO

Methods

Summary of Research Process

The project herein describes a process that can be used to identify genes that have possible association with RP through comparing similar gene sets and identifying genes in those similar gene sets that are currently not associated with RP. These genes can then be further studied to determine their relation to RP. A schematic of the project's procedure can be found in Figure 7, with those steps involving GeneWeaver shaded gray. First, the PubMed database is used to find journal articles that describe genes associated with RP, in humans and other model organisms. These genes are entered as gene sets into GeneWeaver, and a union gene set is created for each organism using the Boolean Algebra Tool. Then, the View Similar Gene Sets function can be used in GeneWeaver to find gene sets similar to the union human organism gene set. The gene sets are organized into two groups, one of gene sets of eye phenotypes and one of gene sets of non-eye phenotypes. These similar gene sets are then compared to the union human gene set through the Jaccard Overlap Tool in GeneWeaver to discern which gene sets are most similar. The Boolean Algebra tool is used to create new gene sets that isolate those genes that are in a gene set similar to an RP gene set but are not in that RP gene set; in other words, those genes that are unique non-RP eye disease genes and unique non-RP non-eye disease genes. All the genes in these gene sets are analyzed by an algorithm to determine their centrality. GeneCards is used to discern which of the most central genes have

protein expression in the retina and to research any diseases the gene is associated with, through MalaCards. Pathway Commons is used to gain more insight into the pathways in which the genes are involved. The result is two annotated lists of ranked genes, one related to non-RP eye phenotypes and one related to non-RP non-eye phenotypes, that have not previously been associated with RP but have a good probability of being implicated in the disease. These genes can be then used as targets for further study in model organisms to determine whether or not mutations in these genes are indeed causative. Using these approaches therefore allows for exploration of a broad range of genes and disease phenotypes in relation to RP.

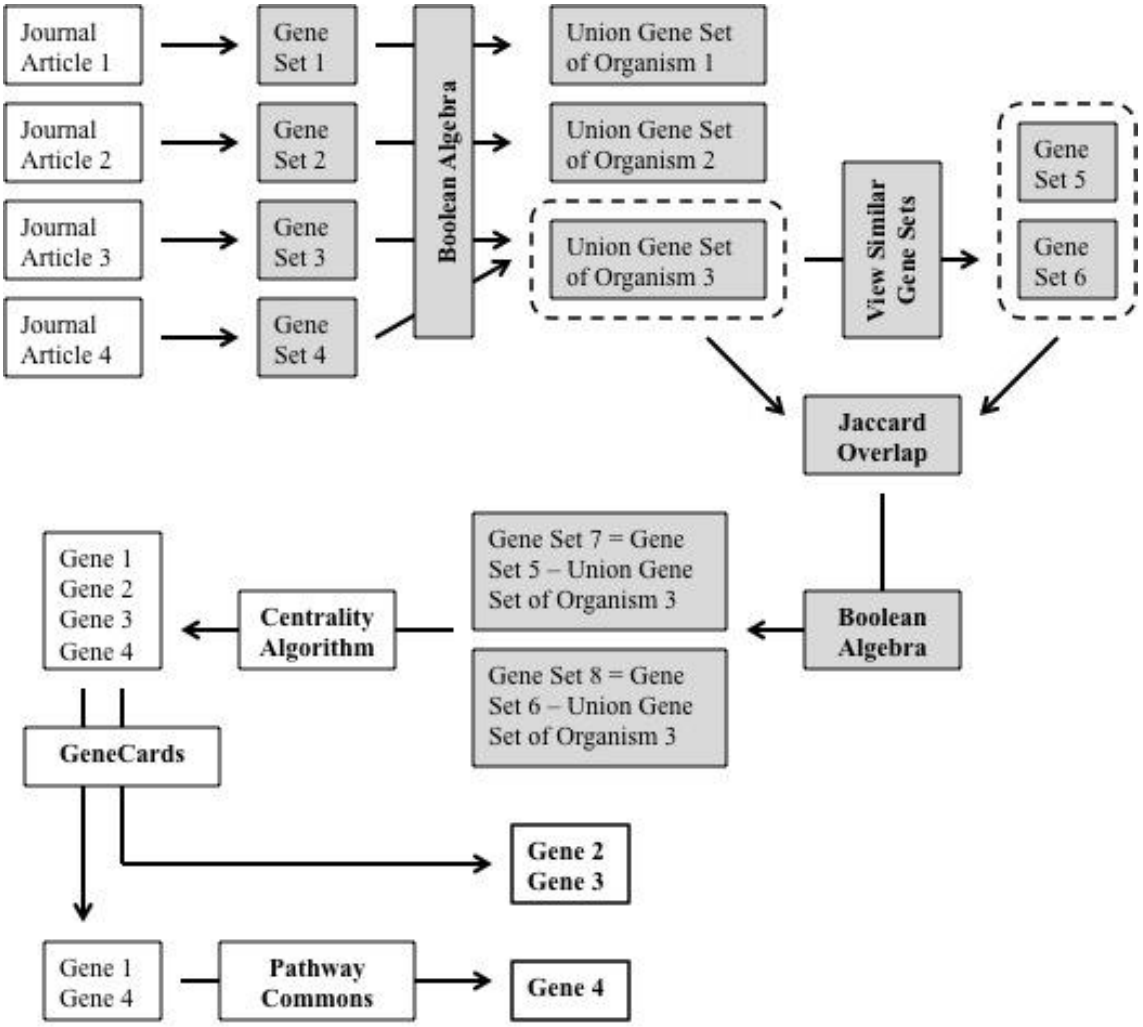


Figure 7: Schematic of Methods

Building Gene Sets

To collect gene sets that pertained to RP, PubMed was searched for papers that described genes associated with RP. Each paper found corresponded to one gene set. Journal articles were found for the organisms *Homo sapiens* (human), *Danio rerio* (zebrafish), *Drosophila melanogaster* (fruit fly), *Mus musculus* (mouse), *Rattus norvegicus* (rat), *Macaca mulatta* (macaque), *and Canis familiaris* (dog). There were 568 hits for *Homo sapiens*, 45 hits for *Canis familiaris*, 49 hits for *Drosophila melanogaster*,

9 hits for *Macaca mulatta*, 118 hits for *Mus musculus*, 23 hits for *Rattus norvegicus*, and 21 hits for *Danio rerio*. A list of search terms used in PubMed can be found in Appendix B, and the genes included in the union human organism RP gene set can be found in Appendix A.

Gene sets were entered into GeneWeaver using the "Upload GeneSet" function. Each gene set was uploaded with a name, figure label, description, access restrictions, PubMed ID, and genes. The genes were listed using gene symbol identifiers. A total of 58 gene sets were uploaded to GeneWeaver. The uploaded gene sets can be found in Appendix C.

Using the Boolean Union tool, all gene sets of a particular organism were merged into one comprehensive organism gene set. A total of 7 organism gene sets were made, corresponding to the 7 organisms for which gene sets were found.

Finding and Comparing Similar Gene Sets

Gene sets similar to each organism gene set were found using the "View Similar Gene Sets" function, which finds maximal cliques within bipartite graphs to identify similar gene sets. For those gene set similar to the comprehensive human gene set, the gene sets were organized into projects based on disease or characteristic. One project was made for non-RP eye disease gene sets; the list of 78 gene sets in this project can be found in Appendix D. A total of 17 projects were made for non-RP non-eye disease gene sets, consisting of brain, cell, diabetes, ear, genitalia, hand and foot, head, kidney, liver, mental, metabolism, motor, nose, skin, vascular weight, and other. These 17 projects contained 162 gene sets in total. The complete list of the non-eye similar gene sets can be found in Appendix E.

Each individual project was compared with the union human gene set using the Jaccard Overlap Tool, which calculates the Jaccard index of a pair of gene sets. The Jaccard index is calculated by dividing the number of genes that occur in both gene sets, or the intersection of the two gene sets, with the total number of genes in both gene sets, or the union of the two gene sets. This yields a number from 0 to 1 with a higher number indicating more similarity between the two gene sets. Those gene sets that had majority overlap were set aside, and a Boolean subtraction was done to separate the genes that were unique to the non-RP gene set. This produced 18 gene sets that contain the unique non-RP non-eye genes, found in Appendix F, and 7 gene sets that contain the unique non-RP eye disease genes, found in Appendix G. The Jaccard Overlap data for the unique non-eye non-RP gene sets can be found in Appendix H, and the Jaccard Overlap data for the unique eye non-RP gene sets can be found in Appendix I.

Ranking Genes by Centrality

The unique non-eye non-RP gene sets yielded 298 unique non-eye non-RP genes, and the unique eye non-RP gene sets yielded 66 unique eye non-RP genes. These genes were ranked by order of centrality using a gene graph program. The nonzero centrality values for the unique non-eye non-RP genes can be found in Appendix J and the nonzero centrality values for the unique eye non-RP genes can be found in Appendix K. Centrality is a measure of connectedness of genes; the more genes a particular gene is connected to by way of gene sets, the more centrality it has. If one considers part A of Figure 5 again (can be seen in Figure 8), gene d has high centrality because it is connected to many gene sets that are themselves connected to many genes. In contrast, gene h has low centrality because it is connected to only one gene set, and that gene set is

connected to only one other gene. In Figure 7, genes that exist within the same gene set are linked together by an edge, and the gene with the most edges linked to it is the most central. As can be seen in Figure 8, gene d has 6 edges connecting it to other genes; this indicates that gene d has high centrality. Gene h only has one edge connecting it to other genes; this indicates that gene h has low centrality.

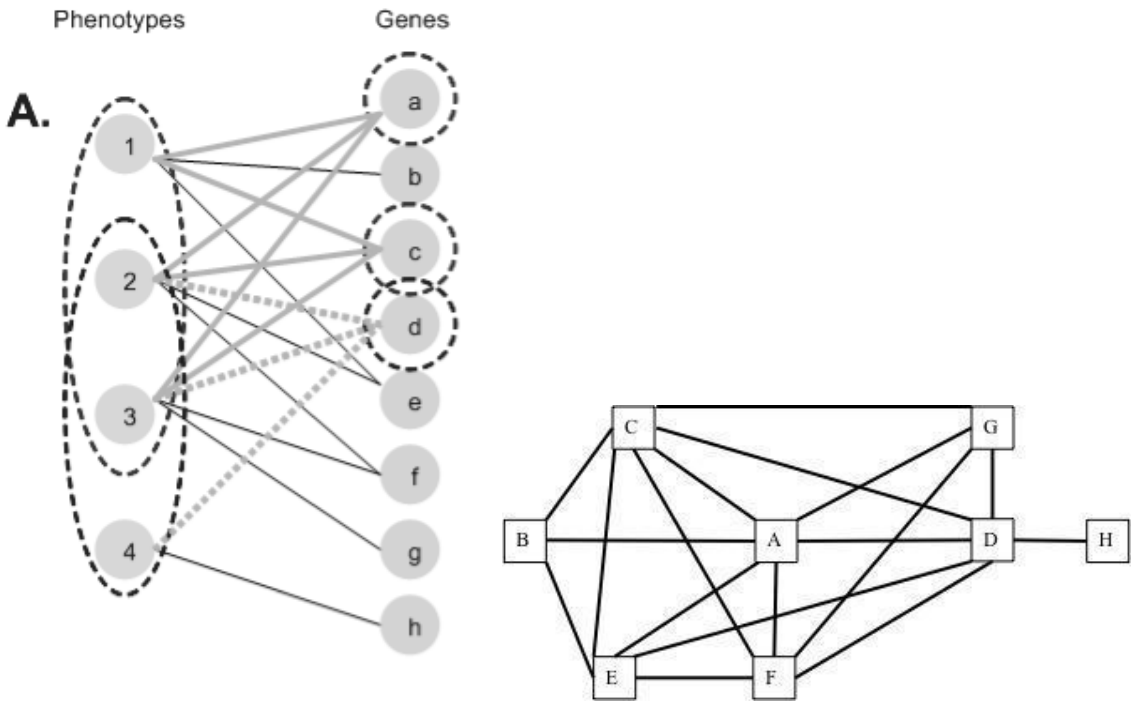


Figure 8: Example of a Graphical Representation of Centrality in Genes

Finding Further Evidence of Possible RP Causality

The eight most central genes from the non-RP non-eye disease centrality list, those with a centrality greater than 0.5, were considered in GeneCards. The seven most central genes from the non-RP eye disease centrality list were also considered in GeneCards; these genes had a centrality greater than 0.23. The microarray, RNAseq, and SAGE data were considered for each gene. The compiled data for the non-eye disease

genes can be seen in Appendix L, and the data for the eye disease genes can be seen in Appendix M.

Diseases associated with the 15 genes were also considered. Disease information was collected both from GeneCards and from the gene's initial gene set in GeneWeaver. Those genes that were already associated with abnormalities of the retina were set aside as probable for RP causation. Those genes that had not been previously related to abnormalities of the retina were further explored by analyzing their associated pathways for retinal activity in Pathway Commons. The information gathered pertaining to the diseases and pathways associated with a gene can be seen in Appendix L for non-eye disease genes and Appendix M for eye disease genes.

CHAPTER THREE

Results and Discussion

The ‘View Similar Gene Sets’ command on the comprehensive human RP gene set produced 162 gene sets pertaining to non-eye phenotypes and 79 gene sets pertaining to eye phenotypes. The Jaccard Overlap tool found majority overlap between the comprehensive human RP gene set and 18 non-eye disease gene sets, and between the comprehensive human RP gene set and 7 eye disease gene sets. Unique genes were isolated from these gene sets using the Boolean Algebra tool. 298 genes were isolated from the 18 non-eye disease gene sets, and 66 genes were isolated from the 7 eye disease gene sets.

For the unique eye disease non-RP genes, microarray data found that all the genes’ proteins were expressed in the retina. Most genes’ proteins were expressed using SAGE. The diseases associated with most of the unique non-eye disease non-RP genes indicated that they have no involvement with eye abnormalities. However, the disease associated with RAB3GAP1, Warburg Micro Syndrome, has abnormal retinal phenotypes. Similarly, the disease associated with TBCE, Kenny-Coffey Syndrome, also has abnormal retinal phenotypes, and the gene BL3GCT has been previously associated with macular degeneration, a disease very similar to RP.

Microarray data showed that almost all of the unique eye non-RP genes have their proteins expressed in the retina. SAGE reported that most genes have their proteins expressed in the retina. One anomaly was that the gene CYP4V2 does not have its protein expressed in microarray data. This is unusual because the CYP4V2 gene is linked with

Bietti Crystalline Corneoretinal Dystrophy, as listed by GeneCards, and night blindness, as stated by the gene's original gene set. The lack of expression may be due to the fact that the protein expression of this gene is too low to detect using current methods, or that GeneCards simply has no data on the gene's protein expression to display. This may also be the reason why RNAseq reported no protein expressed for any of the 15 genes and why SAGE reported no protein expressed for some of the eye disease genes.

All but one of the unique eye phenotype non-RP genes considered were associated with abnormal retinal phenotypes. However, SDR16C5, a gene involved in vitamin A and retinol metabolic processing, has not been linked to any eye diseases. Retinol, a form of vitamin A, is a precursor to the protein retinal, which isomerizes when exposed to light to interact with bound opsins on the retina to produce vision. The importance of vitamin A in RP has already been indicated; Hartong and colleagues described a possible treatment for RP in a 2006 paper that involved vitamin A supplements. This suggests that SDR16C5 is a good candidate for possible association with RP.

Those genes out of the 15 that had not been previously associated with any retinal phenotype (PAX6, HADH, MPI, UGT1A1, B3GAT3, PQBP1) were further researched using Pathway Commons to determine if the genes were involved in any pathways that specifically affected the retina. It was found that none of these genes were involved in any pathways that affected the retina. PAX6 is a transcription regulator in the eye, but because its protein is so essential for proper development of the eye, any disruptions of the gene would have much wider effects than solely in the retina. HADH's protein is a 3-hydroxyacyl-CoA-dehydrogenase involved in the beta-oxidation pathway in

mitochondria; its effects are therefore too broad and the gene is unlikely to be associated with an abnormal retinal phenotype specifically. The broadness of effect also applies to the other 4 genes. MPI encodes a phosphomannose isomerase is involved in producing D-mannose derivatives necessary for glycosylation. UGT1A1 encodes a UDP-glucoronsyltransferase involved in metabolism of lipophilic molecules. B3GAT3 also encodes a glucoronyltransferase involved in the linkage of proteoglycans. PQBP1 encodes a polyglutamine-binding protein, a transcription activator.

CHAPTER FOUR

Conclusion

We have effectively identified putative genes associated with strong evidence for possible association with the disease retinitis pigmentosa. The best candidate gene associated with RP is SDR16C5, due to its involvement in metabolic processing of vitamin A and retinol. The genes with the next strongest salience are those that have been previously associated with retinal eye diseases other than RP, in order of decreasing rank as determined by centrality: CYP4V2, ELOVL4, LRP2, CHM, and ACO2. The genes with the next strongest salience are those that are associated with abnormal retinal phenotype syndromes, in order of decreasing rank by centrality: RAB3GAP1, TBCE, and B3GALTL. The genes with the least salience are those that are not associated with any abnormal retinal phenotypes, but are important nonetheless due to their inclusion in gene sets similar to those gene sets associated with RP and their high centrality values. These genes are, in order of decreasing rank by centrality: PAX6, HADH, MPI, UGT1A1, B3GAT3, and PQBP1.

Some considerations must be taken for the efficacy of the methods used in this study, particularly the use of centrality to prioritize genes. Since centrality prioritizes genes by their degree of connectedness to other genes through gene sets in GeneWeaver, some bias necessarily is present due to the identity of the gene sets that have been entered into GeneWeaver. In other words, if a user is interested in a particular phenotype, then there may be an artificially high number of gene sets for that phenotype. Therefore, centrality values may be skewed toward genes associated with that phenotype.

Additionally, since centrality is a degree of connectedness, the most central genes commonly are housekeeping genes, or genes that are indicated in broad biological processes. Such broad action of these genes is not specific enough for association with a specific phenotype to be probable. Indeed, many of the unique non-eye non-RP genes with high centrality were such housekeeping genes.

In determining whether or not the methods employed herein are effective for identifying genes for association with a particular disease, we have shown that the method succeeds in finding genes that are in gene sets similar to gene sets associated with the disease, have high centrality, and are associated biologically with the retina in some way. The true determinant of the efficacy of this method for finding new genes to associate with a disease lies in direct observational studies of gene perturbations *in vivo*; if a model organism exhibits an abnormal retinal phenotype due to a gene identified in this study being disrupted, then exceptionally strong evidence would be provided for the gene's association with RP. Therefore, the next phase of this study requires *in vivo* research in model organisms.

If the genes identified in this study prove to be associated with RP, it would demonstrate that the methods implemented in this study might be applicable to other diseases with a genetic basis. In particular, it would provide evidence for the rationale that genes residing in a gene set similar to a disease gene set could be associated with that disease simply because of the two gene sets' similarity. That is to say, that using properties of an emergent graph derived from the base bipartite may be informative to rank genes for potential risk or study.

As a tool for conducting bioinformatics, GeneWeaver's effectiveness could be improved if it provided broader tools for convergent functional genomics and analysis of secondary data. GeneWeaver's usability could be increased by providing a method for searching genes within a finite group of multiple gene sets, or multiple projects. This would increase the manipulability of data sets and heighten control over data. Additionally, in order to the genes unique to one of multiple gene sets, two functions must be carried out. Provision of a one-step process for Boolean subtraction would simplify data manipulation further. One of the least manageable issues of GeneWeaver is the fact that one can only sometimes navigate to gene sets created using the Boolean Algebra Tool. In order to ensure that a gene set can be reached through GeneWeaver's website, one must first assign it to a project, which is only accessible to the registered user who owns the project. Correcting the issue of navigation to Boolean Algebra-created gene sets would significantly increase the accessibility of data on GeneWeaver.

We have demonstrated that the utilization of graph theory to perform convergent functional genomics for the identification genes that could be associated with RP does produce a ranked list of genes that are good candidates for further affirmative study. If further research involving these genes produces a model organism with phenotypes similar to RP, then the effectiveness of the methods used here will be further supported.

APPENDICES

APPENDIX A

LIST OF GENES ASSOCIATED WITH RP

ABCA4
ABHD12
ADH1B
ADH4
ADH7
AKR1C1
AKR1C2
ALB
ALDH1A1
ALDH1A2
ALDH1A3
ALDH2
ALDH3A1
ALPK3
APOB
AREG
AREGB
ARL2BP
ARL6
ATXN2
BBS1
BBS2
BBS4
BBS5
BBS7
BBS9
BBS10
BBS12
BCMO1
BCS1L
BEST1
BLOC1S3
BTC
C1QTNF5
C2orf71
C5AR2
C8orf37
CA4
CC2D2A

CDH23
CDHR1
CDSN
CEP290
CERKL
CLN3
CLRN1
CNGA1
CNGB1
CNGB3
COQ2
CRB1
CRX
CTSD
CYP26A1
DCUN1D1
DHDDS
DHPS
DHRS3
DHX38
E2F1
EMC1
EYS
FAM161A
FLVCR1
FSCN2
GPR98
GPR125
GUCA1B
HBEGF
HGSNAT
HK1
HOOK1
IDH3B
IFT140
IMPDH1
IMPG2
IQCB1
KCNA4
KIAA1549
KLHL7
KLK1
LRAT
MAK
MAPRE2
MERTK

MKKS
MKS1
MVK
MYO7A
NEK2
NPHP4
NR2E3
NRL
NUDT19
OFD1
PANK2
PCDH15
PDE6A
PDE6B
PDE6G
PDZD7
PEX1
PEX2
PEX7
PEX26
PHYH
PLK1S1
PMM2
PROM1
PRPF3
PRPF4
PRPF4B
PRPF6
PRPF8
PRPF31
PRPH
PRPH2
RBP1
RBP3
RDH5
RDH10
RDH11
RDH12
REG3A
RGL4
RGR
RHBDD2
RHO
RHOD
RLBP1
RNF7

ROM1
RP1
RP2
RP9
RPE65
RPGR
SAG
SEMA4A
SLC7A14
SLC9A3R1
SLC25A4
SNRNP200
SPATA7
STK19
TAAR5
TOPORS
TRIM32
TTC8
TTC19
TULP1
UQCRB
UQCRQ
USH1C
USH1G
USH2A
WDPCP
ZBTB18
ZNF513

APPENDIX B

LIST OF SEARCH TERMS USED TO FIND ARTICLES IN PUBMED

gene[Title/Abstract] AND associated[Title/Abstract] AND "retinitis pigmentosa"[Title/Abstract]
725 hits
Filters activated: Humans
568 hits

("retinitis pigmentosa"[Title/Abstract])AND((dog[Title/Abstract])AND(gene[Title/Abstract]))
45 hits

((gene) AND Drosophila[Title/Abstract]) AND "retinitis pigmentosa"[Title/Abstract]
49 hits

("retinitis pigmentosa"[Title/Abstract])AND(("macaca mulatta"[Title/Abstract])OR(primate[Title/Abstract]))AND(gene[Title/Abstract]))
6 hits

("retinitis pigmentosa"[Title/Abstract])AND(("macaca mulatta"[Title/Abstract])OR(monkey[Title/Abstract]))AND(gene[Title/Abstract]))
3 hits

("retinitis pigmentosa"[Title/Abstract])AND(("mus musculus"[Title/Abstract])OR(mouse[Title/Abstract]))AND(gene[Title/Abstract])AND(associated[Title/Abstract])
118 hits

("retinitis pigmentosa"[Title/Abstract])AND(("rattus norvegicus"[Title/Abstract])OR(rat[Title/Abstract]))AND(gene[Title/Abstract])AND(associated[Title/Abstract])
23 hits

((gene) AND zebrafish[Title/Abstract]) AND "retinitis pigmentosa"[Title/Abstract]
21 hits

APPENDIX C

RP GENE SETS ENTERED INTO GENEWEAVER

Organism	*Number of Genes*	*Gene Set Number*	*Title*
Dog	2 Genes	GS232730	Mutation in CNGB1 in Dog model of Human
Dog	2 Genes	GS232762	rAAV virus used to alleviate forms of retinitis pigmentosa (RP) in dogs
Dog	1 Genes	GS232763	Mutation in CNGA1 causes form of retinitis pigmentosa (RP) in dogs
Dog	1 Genes	GS232764	Dog model of retinitis pigmentosa (RP) with mutation in RHO
Dog	1 Genes	GS236310	Genome-wide association study finds mutation in SAG gene that causes form of retinitis pigmentosa (RP) in dogs
Dog	1 Genes	GS237598	Dog model of retinitis pigmentosa (RP) with mutation in PDE6B
Dog	1 Genes	GS246020	Dog model of retinitis pigmentosa (RP) with mutation in C2orf71 gene
Dog	1 Genes	GS246021	Mutation in RPGRIP1 gene causes form of retinitis pgimentosa (RP) in dogs
Dog	1 Genes	GS246022	Frameshift mutation in SLC4A3 causes form of retinitis pigmentosa (RP) in dogs
Dog	1 Genes	GS246023	Dog model of retinitis pigmentosa (RP) with mutation in PDE6A
Dog	6 Genes	GS246024	Candidate genes to affect gene expression in dogs with retinitis pigmentosa (RP)
Dog	1 Genes	GS246025	Mutation in PRCD associated with retinitis pigmentosa (RP) in dogs
Fly	8 Genes	GS222071	Fly models display mutations in various genes that lead to retinitis pigmentosa (RP)
Fly	1 Genes	GS222262	DLin-7 mutations cause retinal degeneration and retinitis pigmentosa (RP) in Drosophila model
Fly	1 Genes	GS222263	Rumi mutation may cause retinitis pigmentosa (RP) in Drosophila
Fly	27 Genes	GS222264	Genes affecting retinal degeneration in Drosophila
Fly	1 Genes	GS222279	Mutation in Prp31 gene in Drosophila leads to retinitis pigmentosa (RP)

Human	25 Genes	GS123142	Retinaldehyde interacting genes (MeSH
Human	70 Genes	GS221898	HP
Human	14 Genes	GS221900	RetNet genes linked to retinitis pigmentosa (RP)
Human	1 Genes	GS221923	Capture panel of retinitis pigmentosa (RP) genes used to diagnose Italian probands
Human	49 Genes	GS221924	Multiplex ligation-dependent probe amplification (MLPA) and array-based comparative genomic hybridization (aCGH) used to study mutations in USH2A gene that cause retinitis pigmentosa (RP)
Human	54 Genes	GS221925	Capture panel of retinitis pigmentosa (RP) genes used to diagnose Chinese probands
Human	1 Genes	GS221926	Capture panel of retinitis pigmentosa (RP) genes used to diagnose Irish probands
Human	24 Genes	GS221927	Targeted exome capture identifies mutation in CRB1 gene that causes retinitis pigmentosa (RP)
Human	1 Genes	GS221931	Targeted exome capture and sequencing identifies novel PRPF31 mutations in autosomal dominant retinitis pigmentosa (RP) in Chinese families
Human	7 Genes	GS221932	Sanger sequencing and western blot used to study mutations in PRPH2 that cause retinitis pigmentosa (RP)
Human	62 Genes	GS221933	Set of genes involved in pre-mRNA splicing linked to retinitis pigmentosa (RP) by targeted sequence capture and next-generation massively parallel sequencing (NGS)
Human	1 Genes	GS221934	Mutations of 60 known causative genes in 157 families with retinitis pigmentosa (RP) based on exome sequencing
Human	1 Genes	GS221935	Whole exome sequencing finds mutation in RDH11 that causes new syndrome with retinitis pigmentosa (RP)
Human	70 Genes	GS222261	Direct sequencing identifies new mutation in C5L2 that leads to retinitis pigmentosa (RP)
Human	1 Genes	GS222407	UnionofRP-genesets
Monkey	1 Genes	GS222405	Genes associated with retinitis pigmentosa (RP) on OMIM database
Monkey	6 Genes	GS222408	Mutations in RNR gene associated with retinitis pigmentosa (RP) using Northern blot and reverse transcription PCR
Mouse	1 Genes	GS221897	Macaque model of retinitis pigmentosa (RP) with mutation in mertk gene

Mouse	1 Genes	GS221953	Mutations in genes associated with retinitis pigmentosa (RP) in Macaques
Mouse	2 Genes	GS222077	Mouse model of PDEβ gene mutation that causes retinitis pigmentosa (RP)
Mouse	1 Genes	GS222298	RHBDD2 gene mutation in Mouse model leads to retinitis pigmentosa (RP)
Mouse	1 Genes	GS222301	Mouse model made by knock-in of mutation in RHO gene causes retinitis pigmentosa (RP)
Mouse	1 Genes	GS222302	Mutation in MFRP gene causes photoreceptor degeneration in Mouse model
Mouse	1 Genes	GS222303	Whole exome sequencing identifies mutations in KIZ associated with retinitis pigmentosa (RP)
Mouse	1 Genes	GS222304	Knockout Mouse models with CRX mutation have retinitis pigmentosa (RP)
Mouse	2 Genes	GS222305	Mutation in Nr2e3 in Mouse model associated with retinitis pigmentosa (RP)
Mouse	2 Genes	GS222307	Retinitis pigmentosa (RP) Mouse model with Pde5a mutation
Mouse	1 Genes	GS222308	Mouse model of retinitis pigmentosa (RP) with mutation in Rp2
Mouse	1 Genes	GS222310	Mouse model with mutation in CERKL exhibits retinitis pigmentosa (RP)
Rat	1 Genes	GS222072	Mutation in FAM161A Mouse model leads to retinitis pigmentosa (RP)
Rat	2 Genes	GS222306	Mutation in RPGR leads to retinitis pigmentosa (RP) in Mouse model
Rat	1 Genes	GS222309	Rat model of mutation in RHO leads to retinitis pigmentosa (RP)
Rat	1 Genes	GS222328	Rat model with mutation in CERKL exhibits retinitis pigmentosa (RP)
Rat	1 Genes	GS222329	Mutation in FAM161A rat model leads to retinitis pigmentosa (RP)
Rat	1 Genes	GS222330	Gene therapy on rat model of retinitis pigmentosa (RP) with mutation in MERTK
Zebrafish	1 Genes	GS221954	Rat model of retinitis pigmentosa (RP) with mutation in Rho
Zebrafish	1 Genes	GS221955	GDNF-deficient rat model of retinitis pigmentosa (RP)
Zebrafish	1 Genes	GS221956	Whole genome sequencing in patients with retinitis pigmentosa (RP) reveals pathogenic DNA structural changes and NEK2 as a new disease gene
Zebrafish	1 Genes	GS221957	Study of mutations of RP2 gene in zebrafish models
Zebrafish	1 Genes	GS221958	DHDDS mutation shown to cause retinitis

			pigmentosa (RP) by whole-exome sequencing and zebrafish model
Zebrafish	1 Genes	GS221959	Mutation in Prpf4 causes retinitis pigmentosa (RP) by causing splicing errors shown by zebrafish model

APPENDIX D

EYE DISEASE GENES SIMILAR TO THE UNION GENE SET OF HUMAN RP GENES

Organism	*Number of Genes*	*Gene Set Number*	*Title*
Human	47 Genes	GS200701	GO:0009583 detection of light stimulus
Human	167 Genes	GS170916	HP:0008056 Aplasia/Hypoplasia affecting the eye
Mouse	26 Genes	GS181543	GO:0001917 photoreceptor inner segment
Mouse	35 Genes	GS183129	GO:0006776 vitamin A metabolic process
Mouse	48 Genes	GS186787	GO:0006721 terpenoid metabolic process
Human	124 Genes	GS204243	GO:0006766 vitamin metabolic process
Mouse	40 Genes	GS192982	GO:0001523 retinoid metabolic process
Mouse	40 Genes	GS179281	GO:0016101 diterpenoid metabolic process
Mouse	52 Genes	GS167572	MP:0001006 abnormal retinal cone cell morphology
Mouse	172 Genes	GS169334	MP:0009389 abnormal extracutaneous pigmentation
Mouse	623 Genes	GS164446	MP:0005195 abnormal posterior eye segment morphology
Mouse	167 Genes	GS166016	MP:0001324 abnormal eye pigmentation
Mouse	125 Genes	GS163943	MP:0005201 abnormal retinal pigment epithelium morphology
Mouse	23 Genes	GS169166	MP:0008456 abnormal retinal rod cell outer segment morphology
Mouse	569 Genes	GS165809	MP:0002864 abnormal ocular fundus morphology
Mouse	135 Genes	GS163942	MP:0005200 abnormal eye pigment epithelium morphology
Mouse	63 Genes	GS186788	GO:0006720 isoprenoid metabolic process
Human	61 Genes	GS175740	HP:0010747 Medial flaring of the eyebrow
Mouse	553 Genes	GS167217	MP:0001325 abnormal retina morphology
Human	18 Genes	GS198372	GO:0042572 retinol metabolic process

Human	140 Genes	GS174906	HP:0000545 Myopia
Human	55 Genes	GS172097	HP:0000580 Pigmentary retinopathy
Mouse	48 Genes	GS169803	MP:0003730 abnormal photoreceptor inner segment morphology
Mouse	459 Genes	GS163138	MP:0005253 abnormal eye physiology
Human	1162 Genes	GS176203	HP:0000478 Abnormality of the eye
Human	54 Genes	GS203639	GO:0006721 terpenoid metabolic process
Human	51 Genes	GS176559	HP:0000483 Astigmatism
Mouse	47 Genes	GS164793	MP:0008587 short photoreceptor outer segment
Human	59 Genes	GS172311	HP:0100691 Abnormality of the curvature of the cornea
Mouse	92 Genes	GS170195	MP:0008515 thin retinal outer nuclear layer
Mouse	388 Genes	GS170108	MP:0003727 abnormal retinal layer morphology
Human	43 Genes	GS196051	GO:0016101 diterpenoid metabolic process
Human	41 Genes	GS209924	GO:0001523 retinoid metabolic process
Mouse	323 Genes	GS163432	MP:0006069 abnormal retinal neuronal layer morphology
Mouse	73 Genes	GS167219	MP:0001327 decreased retinal photoreceptor cell number
Mouse	96 Genes	GS164692	MP:0004021 abnormal rod electrophysiology
Mouse	95 Genes	GS166313	MP:0008450 retinal photoreceptor degeneration
Human	187 Genes	GS174247	HP:0000539 Abnormality of refraction
Human	37 Genes	GS202821	GO:0001750 photoreceptor outer segment
Human	36 Genes	GS199929	GO:0006776 vitamin A metabolic process
Mouse	45 Genes	GS185984	GO:0001750 photoreceptor outer segment
Mouse	89 Genes	GS170245	MP:0004022 abnormal cone electrophysiology
Mouse	139 Genes	GS169804	MP:0003731 abnormal retinal outer nuclear layer morphology
Mouse	24 Genes	GS186963	GO:0045494 photoreceptor cell maintenance
Mouse	112 Genes	GS167220	MP:0001326 retinal degeneration
Human	42 Genes	GS174449	HP:0001123 Visual field defect
Mouse	190 Genes	GS166394	MP:0003728 abnormal retinal photoreceptor layer morphology
Mouse	223 Genes	GS169032	MP:0005551 abnormal eye electrophysiology

Mouse	182 Genes	GS163581	MP:0001004 abnormal retinal photoreceptor morphology
Human	36 Genes	GS174701	HP:0000556 Retinal dystrophy
Mouse	106 Genes	GS166716	MP:0003729 abnormal photoreceptor outer segment morphology
Human	541 Genes	GS172354	HP:0004328 Abnormality of the anterior segment of the eye
Human	25 Genes	GS123142	Retinaldehyde interacting Genes (MeSH:D012172) in CTD
Human	471 Genes	GS173079	HP:0000496 Abnormality of eye movement
Human	411 Genes	GS172195	HP:0000504 Abnormality of vision
Human	308 Genes	GS172100	HP:0000587 Abnormality of the optic nerve
Mouse	123 Genes	GS193540	GO:0007601 visual perception
Mouse	123 Genes	GS193046	GO:0050953 sensory perception of light stimulus
Human	513 Genes	GS172353	HP:0004329 Abnormality of the posterior segment of the eye
Human	510 Genes	GS174836	HP:0001098 Abnormality of the fundus
Human	361 Genes	GS173991	HP:0000505 Visual impairment
Human	323 Genes	GS172843	HP:0000481 Abnormality of the cornea
Human	205 Genes	GS209987	GO:0050953 sensory perception of light stimulus
Human	204 Genes	GS210485	GO:0007601 visual perception
Human	397 Genes	GS172134	HP:0000639 Nystagmus
Human	274 Genes	GS172372	HP:0000648 Optic atrophy
Human	356 Genes	GS175500	HP:0000517 Abnormality of the lens
Human	342 Genes	GS174378	HP:0000518 Cataract
Human	386 Genes	GS176202	HP:0000479 Abnormality of the retina
Human	136 Genes	GS171855	HP:0000597 Ophthalmoparesis
Human	120 Genes	GS171657	HP:0000613 Photophobia
Human	169 Genes	GS173988	HP:0000501 Glaucoma
Human	95 Genes	GS176989	HP:0008047 Abnormality of the vasculature of the eye
Human	89 Genes	GS176988	HP:0008046 Abnormality of the retinal vasculature
Human	79 Genes	GS175373	HP:0011486 Abnormality of corneal thickness
Human	78 Genes	GS172553	HP:0100689 Decreased corneal thickness

Human	95 Genes	GS176616	HP:0000662 Night blindness
Human	201 Genes	GS171631	HP:0008051 Abnormality of the retinal pigment epithelium
Human	124 Genes	GS175492	HP:0000512 Abnormal electroretinogram

APPENDIX E

NON-EYE DISEASE GENE SETS SIMILAR TO THE UNION GENE SET OF HUMAN RP GENES

Organism	*Number of Genes*	*Gene Set Number*	*Title*
Human	83 Genes	GS200700	GO:0009582 detection of abiotic stimulus
Human	169 Genes	GS171752	HP:0001713 Abnormality of cardiac ventricle
Human	99 Genes	GS175130	HP:0000750 Delayed speech and language development
Human	390 Genes	GS175537	HP:0011277 Abnormality of the urinary system physiology
Mouse	98 Genes	GS181416	GO:0060271 cilium morphogenesis
Human	146 Genes	GS170968	HP:0000156 High-arched palate
Human	178 Genes	GS176151	HP:0000256 Macrocephaly
Human	110 Genes	GS176907	HP:0009804 Reduced number of teeth
Human	110 Genes	GS173939	HP:0006101 Finger syndactyly
Human	174 Genes	GS171806	HP:0005656 Positional foot deformities
Mouse	74 Genes	GS193065	GO:0044441 cilium part
Human	173 Genes	GS175117	HP:0001883 Talipes
Mouse	72 Genes	GS181684	GO:0042384 cilium assembly
Mouse	35 Genes	GS183129	GO:0006776 vitamin A metabolic process
Human	195 Genes	GS222320	Genes associated with high risk of intellectual disability.
Human	49 Genes	GS173812	HP:0000738 Hallucinations
Human	1488 Genes	GS174131	HP:0002011 Abnormality of the central nervous system
Mouse	48 Genes	GS186787	GO:0006721 terpenoid metabolic process
Human	94 Genes	GS201986	GO:0034754 cellular hormone metabolic process
Human	141 Genes	GS172281	HP:0000822 Hypertension
Human	124 Genes	GS204243	GO:0006766 vitamin metabolic process
Human	232 Genes	GS170999	HP:0000082 Abnormality of renal physiology
Human	75 Genes	GS198474	GO:0042384 cilium assembly
Mouse	40 Genes	GS179281	GO:0016101 diterpenoid metabolic process
Mouse	40 Genes	GS192982	GO:0001523 retinoid metabolic process
Human	115 Genes	GS172148	HP:0010442 Polydactyly
Human	1218 Genes	GS170964	HP:0000152 Abnormality of head and neck

Mouse	172 Genes	GS169334	MP:0009389 abnormal extracutaneous pigmentation
Human	66 Genes	GS200476	GO:0005932 microtubule basal body
Human	111 Genes	GS173651	HP:0009142 Duplication of bones involving the upper extremities
Human	111 Genes	GS171465	HP:0004275 Duplication of hand bones
Human	1203 Genes	GS171168	HP:0000234 Abnormality of the head
Human	110 Genes	GS172484	HP:0009997 Duplication of phalanx of hand
Human	64 Genes	GS172899	HP:0011815 Cephalocele
Human	64 Genes	GS174379	HP:0002084 Encephalocele
Human	877 Genes	GS174646	HP:0000951 Abnormality of the skin
Human	1222 Genes	GS171998	HP:0001939 Abnormality of metabolism/homeostasis
Human	101 Genes	GS175263	HP:0001161 Polydactyly (hands)
Human	86 Genes	GS172352	HP:0000137 Abnormality of the ovary
Human	56 Genes	GS171189	HP:0000142 Abnormality of the vagina
Human	98 Genes	GS170997	HP:0000080 Abnormality of genital physiology
Human	69 Genes	GS176657	HP:0000054 Micropenis
Human	97 Genes	GS198206	GO:0060271 cilium morphogenesis
Human	52 Genes	GS173419	HP:0000147 Polycystic ovaries
Human	80 Genes	GS173031	HP:0004362 Abnormality of the enteric ganglia
Human	80 Genes	GS175635	HP:0002251 Aganglionic megacolon
Human	136 Genes	GS175674	HP:0007360 Aplasia/Hypoplasia of the cerebellum
Human	51 Genes	GS176598	HP:0000668 Hypodontia
Human	1098 Genes	GS176613	HP:0000271 Abnormality of the face
Human	50 Genes	GS171995	HP:0001764 Small feet
Mouse	63 Genes	GS186788	GO:0006720 isoprenoid metabolic process
Human	1206 Genes	GS176817	HP:0011446 Abnormality of higher mental function
Human	1068 Genes	GS171815	HP:0001574 Abnormality of the integument
Human	61 Genes	GS175740	HP:0010747 Medial flaring of the eyebrow
Human	18 Genes	GS198372	GO:0042572 retinol metabolic process
Human	72 Genes	GS176835	HP:0000426 Prominent nasal bridge
Human	110 Genes	GS171784	HP:0001399 Hepatic failure
Human	41 Genes	GS172634	HP:0010468 Aplasia/Hypoplasia of the testes
Human	41 Genes	GS171758	HP:0001714 Ventricular hypertrophy
Human	41 Genes	GS173096	HP:0000678 Dental crowding
Human	40 Genes	GS172506	HP:0008734 Decreased testicular size
Human	53 Genes	GS171415	HP:0000138 Ovarian cysts
Human	53 Genes	GS176772	HP:0001007 Hirsutism
Human	66 Genes	GS176153	HP:0100820 Glomerulopathy
Human	736 Genes	GS173290	HP:0011354 Generalized abnormality of skin

Human	259 Genes	GS176172	HP:0001251 Ataxia
Human	1055 Genes	GS171274	HP:0100543 Cognitive impairment
Human	950 Genes	GS172054	HP:0001507 Growth abnormality
Human	72 Genes	GS172350	HP:0000135 Hypogonadism
Human	33 Genes	GS173487	HP:0000873 Diabetes insipidus
Human	58 Genes	GS199931	GO:0006775 fat-soluble vitamin metabolic process
Human	32 Genes	GS171753	HP:0001712 Left ventricular hypertrophy
Human	70 Genes	GS175439	HP:0009136 Duplication involving bones of the feet
Human	985 Genes	GS171833	HP:0000119 Abnormality of the genitourinary system
Human	31 Genes	GS173433	HP:0001769 Broad foot
Human	69 Genes	GS172825	HP:0001829 Polydactyly (feet)
Human	43 Genes	GS171083	HP:0001328 Specific learning disability
Human	54 Genes	GS203639	GO:0006721 terpenoid metabolic process
Human	66 Genes	GS176263	HP:0100259 Postaxial polydactyly
Human	40 Genes	GS172205	HP:0100326 Immunologic hypersensitivity
Human	51 Genes	GS176730	HP:0000100 Nephrotic syndrome
Human	38 Genes	GS171754	HP:0001711 Abnormality of the left ventricle
Human	37 Genes	GS175617	HP:0002099 Asthma
Human	110 Genes	GS210006	GO:0044441 cilium part
Human	61 Genes	GS175264	HP:0001162 Postaxial polydactyly (hands)
Human	24 Genes	GS172226	HP:0001772 Talipes equinovalgus
Human	23 Genes	GS172830	HP:0001827 Genital tract atresia
Human	23 Genes	GS171180	HP:0000148 Vaginal atresia
Human	886 Genes	GS175016	HP:0001626 Abnormality of the cardiovascular system
Human	128 Genes	GS171905	HP:0004297 Abnormality of the biliary system
Human	20 Genes	GS172225	HP:0001773 Short, broad feet
Human	20 Genes	GS172877	HP:0002370 Poor coordination
Human	43 Genes	GS196051	GO:0016101 diterpenoid metabolic process
Human	124 Genes	GS174854	HP:0001410 Decreased liver function
Human	41 Genes	GS209924	GO:0001523 retinoid metabolic process
Human	16 Genes	GS173875	HP:0002141 Gait imbalance
Human	16 Genes	GS176906	HP:0009806 Nephrogenic diabetes insipidus
Human	36 Genes	GS199929	GO:0006776 vitamin A metabolic process
Human	116 Genes	GS172063	HP:0000107 Renal cysts
Human	413 Genes	GS173146	HP:0011282 Abnormality of the hindbrain
Human	413 Genes	GS175169	HP:0001317 Abnormality of the cerebellum
Human	413 Genes	GS173147	HP:0011283 Abnormality of the metencephalon
Human	69 Genes	GS203640	GO:0006720 isoprenoid metabolic process

Human	55 Genes	GS175055	HP:0001080 Biliary tract abnormality
Human	550 Genes	GS171251	HP:0003549 Abnormality of connective tissue
Human	84 Genes	GS175531	HP:0000003 Multicystic kidney dysplasia
Human	341 Genes	GS176245	HP:0011443 Abnormality of coordination
Human	837 Genes	GS171848	HP:0000598 Abnormality of the ear
Human	95 Genes	GS195352	GO:0072372 primary cilium
Mouse	244 Genes	GS179362	GO:0005929 cilium
Human	636 Genes	GS172032	HP:0000366 Abnormality of the nose
Mouse	102 Genes	GS178598	GO:0072372 primary cilium
Human	51 Genes	GS171787	HP:0001395 Hepatic fibrosis
Human	237 Genes	GS196129	GO:0005929 cilium
Human	598 Genes	GS176718	HP:0000078 Abnormality of the genital system
Mouse	37 Genes	GS181873	GO:0043954 cellular component maintenance
Human	170 Genes	GS173476	HP:0002311 Incoordination
Human	78 Genes	GS206917	GO:0031513 nonmotile primary cilium
Mouse	87 Genes	GS190034	GO:0031513 nonmotile primary cilium
Human	38 Genes	GS198664	GO:0043954 cellular component maintenance
Human	496 Genes	GS175539	HP:0007256 Abnormality of pyramidal motor function
Human	382 Genes	GS173810	HP:0002597 Abnormality of the vasculature
Human	511 Genes	GS173020	HP:0000818 Abnormality of the endocrine system
Human	401 Genes	GS174217	HP:0005105 Abnormal nasal morphology
Human	532 Genes	GS172360	HP:0004323 Abnormality of body weight
Human	695 Genes	GS177031	HP:0011442 Abnormality of central motor function
Human	489 Genes	GS171226	HP:0000812 Abnormal internal genitalia
Human	469 Genes	GS174505	HP:0000708 Behavioural/Psychiatric Abnormality
Human	590 Genes	GS172031	HP:0000364 Hearing abnormality
Human	576 Genes	GS172030	HP:0000365 Hearing impairment
Human	442 Genes	GS175423	HP:0010461 Abnormality of the male genitalia
Human	435 Genes	GS173024	HP:0000811 Abnormal external genitalia
Human	423 Genes	GS175332	HP:0000032 Abnormality of male external genitalia
Human	389 Genes	GS171126	HP:0000022 Abnormality of male internal genitalia
Human	280 Genes	GS176231	HP:0010938 Abnormality of the external nose
Human	381 Genes	GS175333	HP:0000035 Abnormality of the testis

Human	384 Genes	GS171708	HP:0000359 Abnormality of the inner ear
Human	381 Genes	GS175714	HP:0011389 Functional abnormality of the inner ear
Human	385 Genes	GS176836	HP:0000422 Abnormality of the nasal bridge
Human	368 Genes	GS170971	HP:0000407 Sensorineural hearing impairment
Human	273 Genes	GS172516	HP:0001347 Hyperreflexia
Human	248 Genes	GS176844	HP:0000429 Abnormality of the nasal alae
Human	316 Genes	GS175597	HP:0011013 Abnormality of carbohydrate metabolism/homeostasis
Human	220 Genes	GS171139	HP:0005288 Abnormality of the nares
Human	288 Genes	GS175335	HP:0000036 Abnormality of the penis
Human	284 Genes	GS175594	HP:0011014 Abnormal glucose homeostasis
Human	209 Genes	GS175990	HP:0000463 Anteverted nares
Human	220 Genes	GS171791	HP:0000370 Abnormality of the middle ear
Human	182 Genes	GS176955	HP:0000431 Wide nasal bridge
Human	209 Genes	GS173206	HP:0003241 Genital hypoplasia
Human	199 Genes	GS176660	HP:0000050 Hypoplastic genitalia
Human	120 Genes	GS172358	HP:0003117 Abnormality of circulating hormone level
Human	158 Genes	GS171900	HP:0011452 Functional abnormality of the middle ear
Human	157 Genes	GS171968	HP:0000405 Conductive hearing impairment
Human	177 Genes	GS171047	HP:0008736 Hypoplasia of penis
Human	171 Genes	GS173019	HP:0000819 Diabetes mellitus
Human	103 Genes	GS173741	HP:0100699 Scarring
Human	100 Genes	GS176744	HP:0000987 Atypical scarring of skin
Human	156 Genes	GS172363	HP:0004324 Increased body weight
Human	148 Genes	GS172295	HP:0001513 Obesity
Human	85 Genes	GS173666	HP:0005978 Type II diabetes mellitus
Human	77 Genes	GS173703	HP:0000842 Hyperinsulinemia

APPENDIX F

HUMAN UNIQUE NON-RP NON-EYE DISEASE GENE SETS

Organism	*Number of Genes*	*Gene Set Number*	*Title*	*Parent Gene Set*
Human	21 Genes	GS246070	Unique non-RP HP:0001711 abnormality of the left ventricle	GS171754
Human	16 Genes	GS246068	Unique non-RP HP:0001712 left ventricular hypertrophy	GS171753
Human	25 Genes	GS246066	Unique non-RP HP:0001714 ventricular hypertrophy	GS171758
Human	44 Genes	GS246063	Unique non-RP HP:0000987 atypical scarring of skin	GS176744
Human	47 Genes	GS246061	Unique non-RP HP:0100699 scarring	GS173741
Human	1 Genes	GS246059	Unique non-RP HP:0002141 gait imbalance	GS173875
Human	5 Genes	GS246057	Unique non-RP HP:0002370 poor coordination	GS172877
Human	20 Genes	GS246055	Unique non-RP GO:0006776 vitamin A metabolic process	GS183129
Human	5 Genes	GS246053	Unique non-RP GO:0042572 retinol metabolic process	GS198372
Human	5 Genes	GS246051	Unique non-RP HP:0001773 short, broad feet	GS172225
Human	9 Genes	GS246049	Unique non-RP HP:0001772 talipes equinovalgus	GS172226
Human	139 Genes	GS246047	Unique non-RP HP:0003241 genital hypoplasia	GS173206
Human	8 Genes	GS246041	Unique non-RP HP:0001827 genital tract atresia	GS172830
Human	21 Genes	GS246039	Unique non-RP HP:0000842 hyperinsulinemia	GS173703
Human	1 Genes	GS246035	Unique non-RP HP:0009806 nephrogenic diabetes insipidus	GS176906
Mouse	16 Genes	GS246033	Unique non-RP GO:0043954 mouse cellular component maintenance	GS181873
Human	29 Genes	GS246037	Unique non-RP HP:0005978 type II diabetes mellitus	GS173666
Human	17 Genes	GS232732	Unique non-RP GO:0043954	GS198664

			human cellular component maintenance	

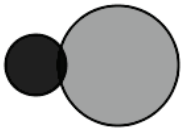
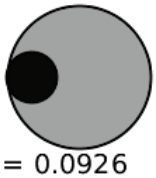
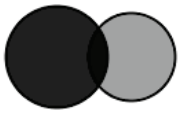
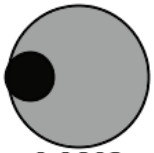
APPENDIX G

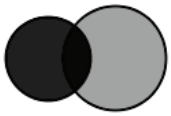
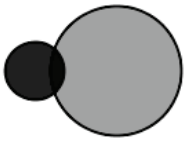
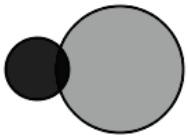
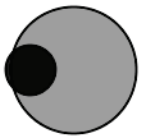
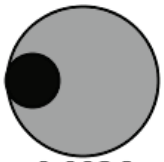
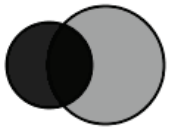
HUMAN UNIQUE NON-RP EYE DISEASE GENE SETS

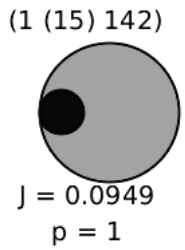
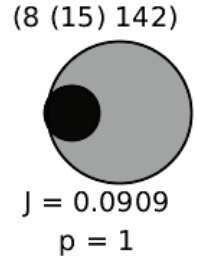
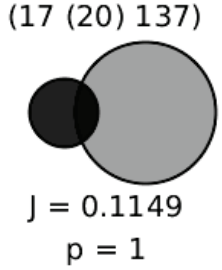
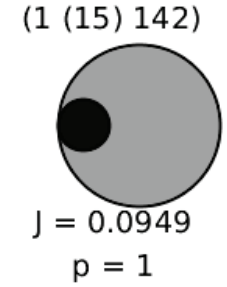
Organism	*Number of Genes*	*Gene Set Number*	*Title*	*Parent Gene Set*
Human	19 Genes	GS246510	Unique Eye HP:0100689 decreased corneal thickness	GS172553
Human	24 Genes	GS246508	Unique Eye HP:0000662 night blindness	GS176616
Human	20 Genes	GS246506	Unique Eye HP:0011486 abnormality of corneal thickness	GS175373
Human	4 Genes	GS246501	Unique Eye GO:0045494 photoreceptor cell maintenance	GS186963
Human	13 Genes	GS246499	Unique Eye HP:0000556 retinal dystrophy	GS174701
Human	8 Genes	GS246497	Unique Eye MP:0008456 abnormal retinal rod cell outer segment morphology	GS169166
Human	5 Genes	GS246495	Unique eye GO:0042572 retinol metabolic process	GS198372

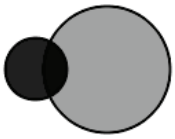
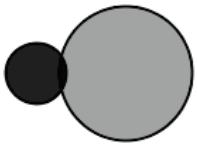
APPENDIX H

JACCARD OVERLAP OF NON-EYE NON-RP GENE SETS WITH GOOD SIMILARITY WITH THE HUMAN ORGANISM GENE SET

Gene set ALL HUMAN RP (left circle)	*Gene set (right circle)*
(26 (15) 142)  J = 0.0820 p = 1	GS171758: HP:0001714 Ventricular hypertrophy
(5 (15) 142)  J = 0.0926 p = 1	GS172877: HP:0002370 Poor coordination
(140 (69) 88)  J = 0.2323 p = 9.369e-05	GS173206: HP:0003241 Genital hypoplasia
(5 (13) 144)  J = 0.0802 p = 1	GS198372: GO:0042572 retinol metabolic process

(48 (55) 102)  J = 0.2683 p = 0.02704	GS173741: HP:0100699 Scarring
(17 (15) 142)  J = 0.0862 p = 1	GS171753: HP:0001712 Left ventricular hypertrophy
(22 (16) 141)  J = 0.0894 p = 1	GS171754: HP:0001711 Abnormality of the left ventricle
(9 (15) 142)  J = 0.0904 p = 1	GS172226: HP:0001772 Talipes equinovalgus
(5 (15) 142)  J = 0.0926 p = 1	GS172225: HP:0001773 Short, broad feet
(30 (55) 102)  J = 0.2941 p = 0.1441	GS173666: HP:0005978 Type II diabetes mellitus

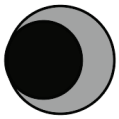
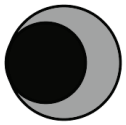
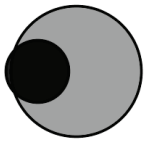
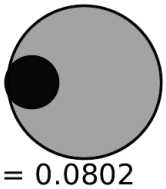
	GS176906: HP:0009806 Nephrogenic diabetes insipidus
	GS172830: HP:0001827 Genital tract atresia
	GS181873: GO:0043954 cellular component maintenance
	GS173666: HP:0005978 Type II diabetes mellitus
	GS173875: HP:0002141 Gait imbalance

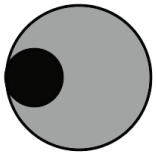
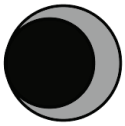
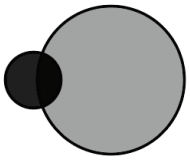
(17 (21) 136)  J = 0.1207 p = 1	GS198664: GO:0043954 cellular component maintenance
(21 (12) 145)  J = 0.0674 p = 1	GS183129: GO:0006776 vitamin A metabolic process
(22 (55) 102)  J = 0.3073 p = 0.2537	GS173703: HP:0000842 Hyperinsulinemia

APPENDIX I

JACCARD OVERLAP OF EYE NON-RP GENE SETS WITH GOOD SIMILARITY

WITH THE HUMAN ORGANISM GENE SET

Gene set ALL HUMAN RP (left circle)	*Gene set (right circle)*
(21 (58) 99)  J = 0.3258 p = 0.4499	GS175373: HP:0011486 Abnormality of corneal thickness
(20 (58) 99)  J = 0.3277 p = 0.4706	GS172553: HP:0100689 Decreased corneal thickness
(13 (23) 134)  J = 0.1353 p = 1	GS174701: HP:0000556 Retinal dystrophy
(5 (13) 144)  J = 0.0802 p = 1	GS198372: GO:0042572 retinol metabolic process

(4 (20) 137)  J = 0.1242 p = 1	GS186963: GO:0045494 photoreceptor cell maintenance
(25 (70) 87)  J = 0.3846 p = 0.06233	GS176616: HP:0000662 Night blindness
(10 (13) 144)  J = 0.0778 p = 1	GS169166: MP:0008456 abnormal retinal rod cell outer segment morphology

APPENDIX J

UNIQUE NON-EYE NON-RP GENES RANKED BY CENTRALITY

Gene	*Centrality*
RAB3GAP1	0.875103237
HADH	0.840754885
TBCE	0.71556664
MPI	0.65110293
B3GALTL	0.587766807
UTG1A1	0.576264558
B3GAT3	0.536268838
PQBP1	0.50027138
A1S9T	0.477033685
TIM14	0.471067416
NHP2P	0.466257005
ZNF-HX	0.401437111
DHC1b	0.399826293
RISC	0.384754115
TGMX	0.374236775
RAB23	0.370055156
HS6ST	0.35820306
WARBM2	0.35766047
RAD6A	0.355539337
RIS2	0.351628522
GLA	0.3389059
STE24	0.338521917
OCRL	0.321126096
GDE	0.313528742
EZH2	0.310214266
SJS	0.299156636
URA1	0.295227679
MCOPCT2	0.29248471
XGALT1	0.291855106
RDH#2	0.289664528
NELIN	0.282467869
HCAP	0.280615625
NAF-1	0.27046435

ORC6	0.269022405
BRESEK	0.259330283
MVA2	0.248563701
ORNT1	0.248302829
MAN2B1	0.245688852
CDC18L	0.242334862
MIPOL1	0.238496747
LHCGR	0.23597904
RETSAT	0.232426484
CENP-31	0.22479558
MDDGB1	0.222604331
NLGN2	0.222231202
NDN	0.221847335
SMTPHN	0.220046098
ARVD9	0.219237176
GLUD	0.215523901
LAMB2	0.208691241
ORC4	0.205049328
VPS33B	0.202246676
EM9	0.200934623
PP1G	0.200491799
LIG4	0.199964507
LZTFL1	0.195374076
MRX76	0.19380187
BSCL	0.191934034
SLC39A13	0.191363364
FP13812	0.190306486
ORC1L	0.188367391
DXS423E	0.187469368
NELF	0.186879618
TMEM216	0.18383521
SPH1	0.171073773
NXP1	0.17079185
MCOPS7	0.168545764
JPH2	0.16452793
KIFC3	0.163079998
PRLMNS	0.16226277
UROS	0.159864793
POR	0.156753998
UGT1-08	0.150249579
UGT1A10	0.150249579

UGT-1I	0.150249579
UGT1-07	0.150249579
CMT4B	0.148951091
PERK	0.147930649
SUV3	0.147307339
TBS	0.14415238
PLZF	0.141910004
NY-REN-55	0.139735657
OPN1	0.139432664
COL5A1	0.13818585
SEF2-1A	0.137837769
RAB4B	0.134406408
MTR	0.132990105
TSPYL	0.129092933
PPN	0.127136362
PMX1	0.125995537
FRAS1	0.125014558
EBR1	0.120170808
PCTT	0.120006849
HHF5	0.119330775
NKX2E	0.117029744
KAL5	0.114933401
CAVIN	0.114928023
WNT7A	0.112053297
PRKBB	0.110903045
BPTP3	0.108958151
MDDGB5	0.108341827
HSAPXL	0.106750069
COL4A1	0.106299006
LHX4	0.10602954
WNT5A	0.10557031
HOXHB9	0.105198979
CRBPII	0.104999357
BSCL2	0.103735849
MyHC-peri	0.102816192
XLDPP	0.102429531
PTF1-p48	0.10182557
SSAT	0.100712817
GPR73L1	0.099523674
ABC1	0.098886014
MNK	0.09877369

SEB	0.096888939
ARCI2	0.096874574
HHF3	0.096044859
XHL	0.094713969
PLEC1	0.094626336
BDB	0.093799539
RDH8	0.09344525
RAD51L2	0.093272254
COFS	0.09227972
UGT1A3	0.091663775
SNRNP-N	0.089593641
KAT6B	0.089585034
dJ20C7.5	0.089193341
FH1	0.088888471
FREM2	0.088641191
SS-5-R	0.088299858
CMT2J	0.088081907
CMH18	0.085681839
CDLS	0.085224045
MDDGA6	0.084484758
HMG-R	0.083380903
C2orf37	0.083250882
TIP-40	0.082530305
BBS16	0.081919566
SLOS	0.080069255
GAA	0.079052809
COL3A1	0.077651711
HOXA13	0.077507155
CYP26C1	0.076268017
KIAA1543	0.076046701
SSK1	0.075447347
CAV3	0.075368172
ATFB12	0.074725906
LMNC	0.072803562
BEY1	0.072006149
RECQL3	0.071591059
FBN	0.070852446
ACTB	0.070631803
LCA4	0.070582478
TANC	0.069477141
UBR1	0.068084031

KIF7	0.067422888
SDR9C4	0.067306922
B2T	0.067229967
CRTR	0.066637568
NDNL1	0.065970057
NFJ	0.064665183
NSD1	0.063713676
LDS3	0.061581549
MRXSJ	0.060950253
BBDS	0.059900324
COL1A2	0.059891683
TFQTL2	0.059266938
BMPR-II	0.059176482
PAPA	0.058565389
B(p51B)	0.058119656
PLCD1	0.057798608
KCNJ11	0.057010299
CD104	0.054926731
HIgR	0.054583411
SYNS2	0.054223972
EP300	0.05369642
MCT	0.052683214
LISX	0.052665102
ZNF469	0.052375191
RBP4	0.052146402
PGFS	0.052024897
NPI	0.051822538
CD49f	0.051718934
FND2	0.051382845
GHR	0.051318226
FHI	0.051217683
SOX2	0.048370785
LDS1A	0.048172523
MLL4	0.047969625
PPARgamma	0.047374771
HNF-1B	0.047264719
DCDC4B	0.046837782
MAN1	0.046789508
CREBBP	0.044981966
MYCD	0.041905771
MDPK	0.040769799

TCF-1	0.04033641
MEN2B	0.040189027
cTnI	0.038278885
RIIC	0.038039611
EBS2	0.03745732
ECM1	0.037277633
ACTC1	0.036942153
COL1A1	0.036612988
ATA	0.036408825
FGF8	0.030878194
RAB40AL	0.029244548
MCOPCB5	0.027558651
TRKA	0.025206648
BMP2B1	0.021105358
SRXY1	0.010469956

APPENDIX K

UNIQUE NON-EYE NON-RP GENES RANKED BY CENTRALITY

Gene	*Centrality*
CYP4V2	0.365887688
ELOVL4	0.348349891
PAX6	0.314684519
LRP2	0.301931889
SDR16C5	0.289664528
CHM	0.282705782
ACO2	0.241347464
RETSAT	0.232426484
LMX1B	0.214722186
IFT122	0.207349059
CHRDL1	0.195578036
TMEM216	0.18383521
PDE6H	0.179566282
UNC119	0.178060978
HBB	0.174377863
CABP4	0.170286139
OAT	0.152460318
GUCY2F	0.14778216
NYX	0.132687402
HRAS	0.130213478
KCNJ13	0.123717664
AHI1	0.114589203
CNGA3	0.104399573
GUCY2D	0.101648227
GRN	0.101231461
VSX1	0.099716345
HSD3B7	0.095206594
RDH8	0.09344525
ERCC6	0.09227972
RPGRIP1	0.090619855
LCA5	0.086459038
SDCCAG8	0.081919566
OTX2	0.078858599

COL3A1	0.077651711
RECQL4	0.07503534
AIPL1	0.070582478
DHRS9	0.067306922
ADAM9	0.066696094
PITPNM3	0.066294322
GRM6	0.064950607
DFNB31	0.06381481
CACNA1F	0.060990481
RIMS1	0.059355666
GRK1	0.058155651
CNNM4	0.055196738
NTRK2	0.054436419
ZNF469	0.052375191
RBP4	0.052146402
RP1L1	0.046837782
GNAT1	0.040937339
KCNV2	0.028976162
BMP4	0.021105358

APPENDIX L

CENTRALITY AND ASSOCIATED DISEASES AND PATHWAYS FOR THE MOST CENTRAL UNIQUE NON-EYE DISEASE NON-RP GENES

Gene Symbol	*Centrality*	*Microarray*	*RNAseq*	*SAGE*
RAB3GAP1	0.875103237	yes		yes
HADH	0.840754885	yes		yes
TBCE	0.71556664	yes		yes
MPI	0.65110293	yes		
B3GALTL, B3GLCT	0.587766807	widely expressed		
UGT1A1	0.576264558	yes		yes
B3GAT3	0.536268838	yes		yes
PQBP1	0.50027138	yes		yes

Gene Symbol	*GeneCards Disorders*	*Original Gene Set Name*	*Pathway Commons Information*
RAB3GAP1	Warburg Micro Syndrome	GS173206: HP:0003241 genital hypoplasia	
HADH	Hyperinsulinism	GS173703: HP:0000842 hyperinsulinemia	Beta-oxidation, transcriptional activators for liver-specific genes
TBCE	Kenny-Coffey Syndrome	GS173206: HP:0003241 genital hypoplasia	
MPI	Glycosylation	GS173703: HP:0000842 hyperinsulinemia	Glycosylation
B3GALTL, B3GLCT	Peters Plus Syndrome, Macular Degeneration	GS173206: HP:0003241 genital hypoplasia	
UGT1A1	Cligler-Najjar Syndrome, Gilbert Syndrome, Lucey-Driscoll Syndrome	GS183129: GO:0006776 vitamin A metabolic process	UDP-glucuronosyltransferase

B3GAT3	Larsen-Like Syndrome	GS171754: HP:0001711 abnormality of the left ventricle, GS171753: HP:0001712 left ventricular hypertrophy, GS171758: HP:0001714 ventricular hypertrophy, GS172226: HP:0001772 talipes equinovalgus	Proteoglycan linkage
PQBP1	Renpenning Syndrome	GS173206: HP:0003241 genital hypoplasia	Transcription activation

APPENDIX M

CENTRALITY AND ASSOCIATED DISEASES AND PATHWAYS FOR THE MOST CENTRAL UNIQUE EYE DISEASE NON-RP GENES

Gene Symbol	*Centrality*	*Microarray*	*RNAseq*	*SAGE*
CYP4V2	0.365887688			yes
ELOVL4	0.348349891	yes		
PAX6	0.314684519	yes		yes
LRP2	0.301931889	yes		
SDR16C5	0.289664528	yes		yes
CHM	0.282705782	yes		yes
ACO2	0.241347464	yes		yes

Gene Symbol	*GeneCards Disorders*	*Original Gene Set Name*
CYP4V2	Bietti Crystalline Corneoretinal Dystrophy	GS176616: HP:0000662 night blindness
ELOVL4	Stargardt Disease	GS169166: MP:0008456 abnormal retinal rod cell outer segment morphology
PAX6	Aniridia, Peters Plus Syndrome, Keratitis	GS175373: HP:0011486 abnormality of corneal thickness, GS172553: HP:0100689 decreased corneal thickness
LRP2	Donnai-Barrow	GS174701: HP:0000556 retinal dystrophy
SDR16C5	NONE	GS198372: GO:0042572 retinol metabolic process, GS183129: GO:0006776 vitamin A metabolic process
CHM	Choroideremia	HP:0000662 night blindness
ACO2	Infantile Retinal Degeneration, Optic Atrophy	HP:0000556 retinal dystrophy

BIBLIOGRAPHY

Achor, L. Joseph. 2015. “Vision: The Eye.” Baylor University, January 14.

Bubier, Jason A., and Elissa J. Chesler. 2012. “Accelerating Discovery for Complex Neurological and Behavioral Disorders through Systems Genetics and Integrative Genomics in the Laboratory Mouse.” *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics* 9 (2): 338–48. doi:10.1007/s13311-012-0111-3.

Bubier, Jason A., Jeremy J. Jay, Christopher L. Baker, Susan E. Bergeson, Hiroshi Ohno, Pamela Metten, John C. Crabbe, and Elissa J. Chesler. 2014. “Identification of a QTL in Mus Musculus for Alcohol Preference, Withdrawal, and Ap3m2 Expression Using Integrative Functional Genomics and Precision Genetics.” Genetics 197 (4): 1377–93. doi:10.1534/genetics.114.166165.

Bubier, Jason A., Charles A. Phillips, Michael A. Langston, Erich J. Baker, and Elissa J. Chesler. 2015. “GeneWeaver: Finding Consilience in Heterogeneous Cross-Species Functional Genomics Data.” *Mammalian Genome: Official Journal of the International Mammalian Genome Society* 26 (9-10): 556–66. doi:10.1007/s00335-015-9575-x.

Cerami et al. Pathway Commons, a web resource for biological pathway data. Nucl. Acids Res. (2010) doi: 10.1093/nar/gkq1039

“Disorders of Vision.” 2015. Accessed October 26. http://www.ssc.education.ed.ac.uk/resources/vi&multi/bowmandutton/bowmandutton3.html.

Donders, Franciscus C., 1855. “Torpeur de la rétine congénital e héréditarie.” *Annales d’Oculistique* 34:270—3.

Donders, F. C. 1857. “Beiträge zur pathologischen Anatomie des Auges.” *Archiv für Ophthalmologie* 3 (1): 139–65. doi:10.1007/BF02720685.

Goldstein, E. 2013. *Sensation and Perception*. Cengage Learning.

Goyal, S., M. Jäger, P. N. Robinson, and V. Vanita. 2015. “Confirmation of TTC8 as a Disease Gene for Nonsyndromic Autosomal Recessive Retinitis Pigmentosa (RP51).” *Clinical Genetics*, July. doi:10.1111/cge.12644.

Hamel, Christian. 2006. “Retinitis Pigmentosa.” *Orphanet Journal of Rare Diseases* 1: 40. doi:10.1186/1750-1172-1-40.

Hartong, Dyonne T, Eliot L Berson, and Thaddeus P Dryja. 2006. "Retinitis Pigmentosa." *The Lancet* 368 (9549): 1795–1809. doi:10.1016/S0140-6736(06)69740-7.

Lancet D, Safran M, Olender T, Dalah I, Iny-Stein T, Inger A, Harel A and Stelzer G. GeneCards tools for combinatorial annotation and dissemination of human genome information GIACS Conference on Data in Complex Systems April, 2008

Marcos, I., A. Ruiz, S. Borrego, C. Ayuso, M. Baiget, and G. Antiñolo. 2001. "[Molecular analysis of the RPE65 gene in 72 Spanish families with autosomal recessive retinitis pigmentosa]." *Medicina Clínica* 117 (4): 121–23.

Mi, Huaiyu, Anushya Muruganujan, John T. Casagrande, and Paul D. Thomas. 2013. "Large-Scale Gene Function Analysis with the PANTHER Classification System." *Nature Protocols* 8 (8): 1551–66. doi:10.1038/nprot.2013.092.

Mitamura, Yoshinori, Sayaka Mitamura-Aizawa, Toshihiko Nagasawa, Takashi Katome, Hiroshi Eguchi, and Takeshi Naito. 2012. "Diagnostic Imaging in Patients with Retinitis Pigmentosa." *The Journal of Medical Investigation: JMI* 59 (1-2): 1–11.

Rappaport N, Twik M, Nativ N, Stelzer G, Bahir I, Iny Stein T, Safran M and Lancet D. MalaCards: A Comprehensive Automatically-Mined Database of Human Diseases, Curr. Protoc. Bioinform. 47:1.24:1.24.11.24.19. (Sept 2014)

"Retinitis Pigmentosa | Blindness.org." 2016. Accessed April 13. http://www.blindness.org/retinitis-pigmentosa.

Wang, Chunxia, Katsuhiro Hosono, Masafumi Ohtsubo, Kentaro Ohishi, Jie Gao, Nobuo Nakanishi, Akiko Hikoya, Miho Sato, Yoshihiro Hotta, and Shinsei Minoshima. 2014. "Interaction between Optineurin and the bZIP Transcription Factor NRL." *Cell Biology International* 38 (1): 16–25. doi:10.1002/cbin.10174.

Wang, Feng, Yandong Wang, Bin Zhang, Li Zhao, Vera Lyubasyuk, Keqing Wang, Mingchu Xu, et al. 2014. "A Missense Mutation in HK1 Leads to Autosomal Dominant Retinitis Pigmentosa." *Investigative Ophthalmology & Visual Science* 55 (11): 7159–64. doi:10.1167/iovs.14-15520.

Xu, Jian, and Qinghua Peng. 2015. "Retinitis Pigmentosa Treatment with Western Medicine and Traditional Chinese Medicine Therapies." *Journal of Ophthalmology* 2015: 421269. doi:10.1155/2015/421269.