

Supplementary information for:

Simple and complex retinal dystrophies are associated with profoundly different disease networks

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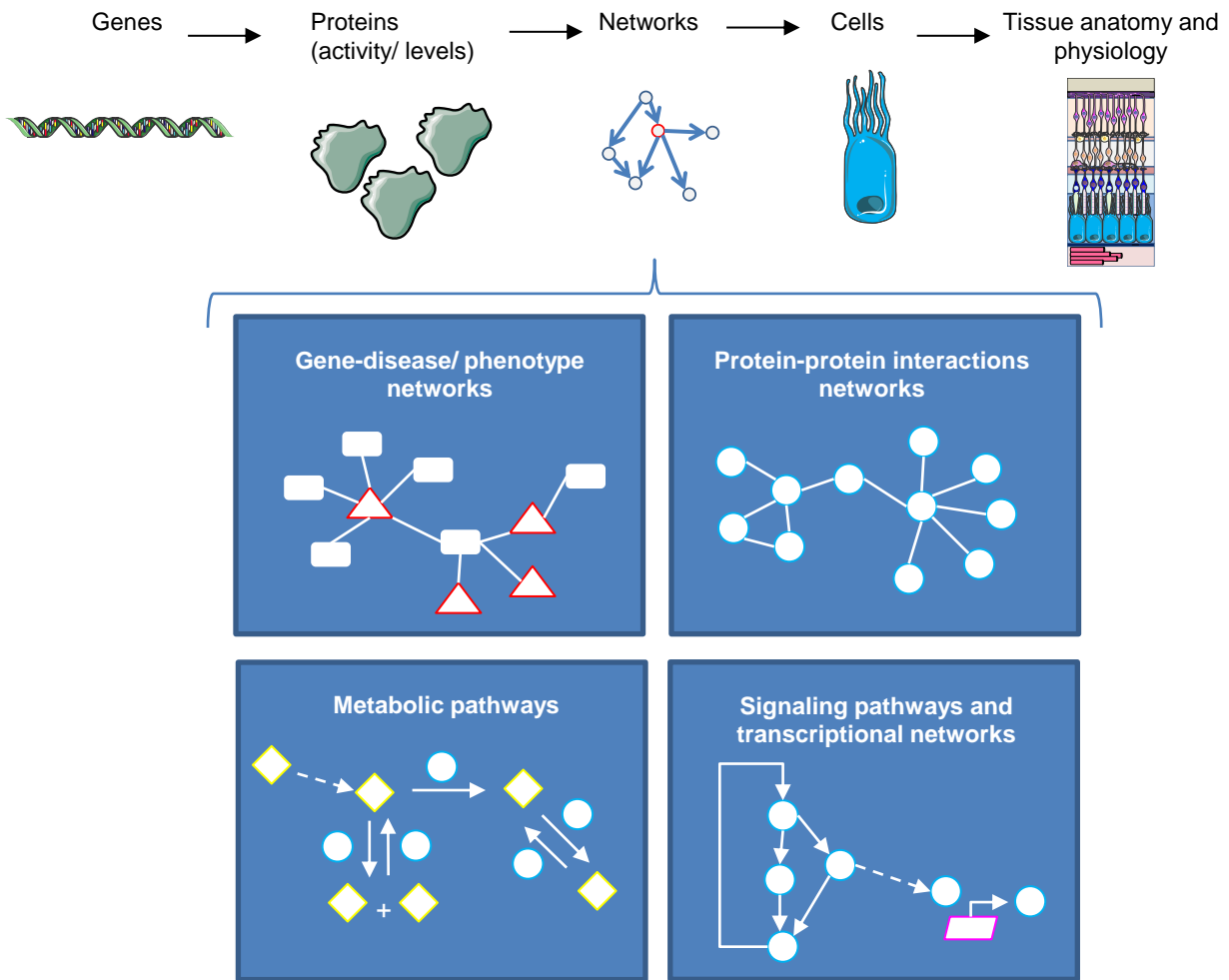
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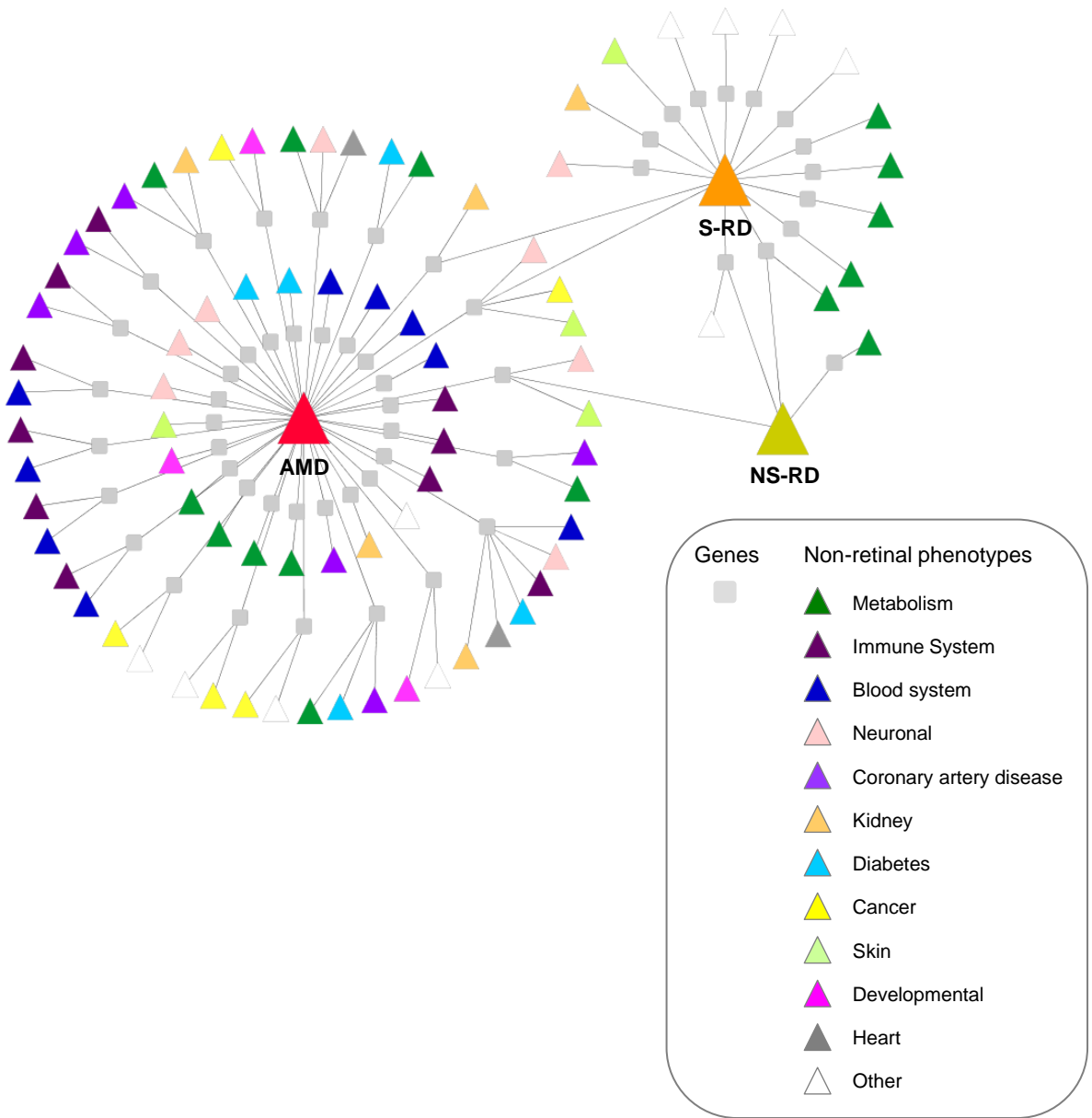


Supplementary Figure 1

Schematic diagram illustrating a gene- and network-centric approach to molecular medicine.

In this approach the disease phenotype is considered as the consequence of perturbations of complex intra- and intercellular networks caused by genetic defects that spread along the network, which ultimately affects the cellular or tissue phenotype. There are different types of networks to be considered. For example, in gene-disease networks genes participating in the same disease are linked. Protein-protein interaction networks refer the physical interactions between proteins. Metabolic, signalling and transcriptional pathways include directionality, activities and feedback mechanisms. The figure was prepared using images from Servier Medical Art by Servier (<http://www.servier.com/Powerpoint-image-bank>), which is licensed under a Creative Commons Attribution 3.0 Unported License.

Related to Figure 1b.

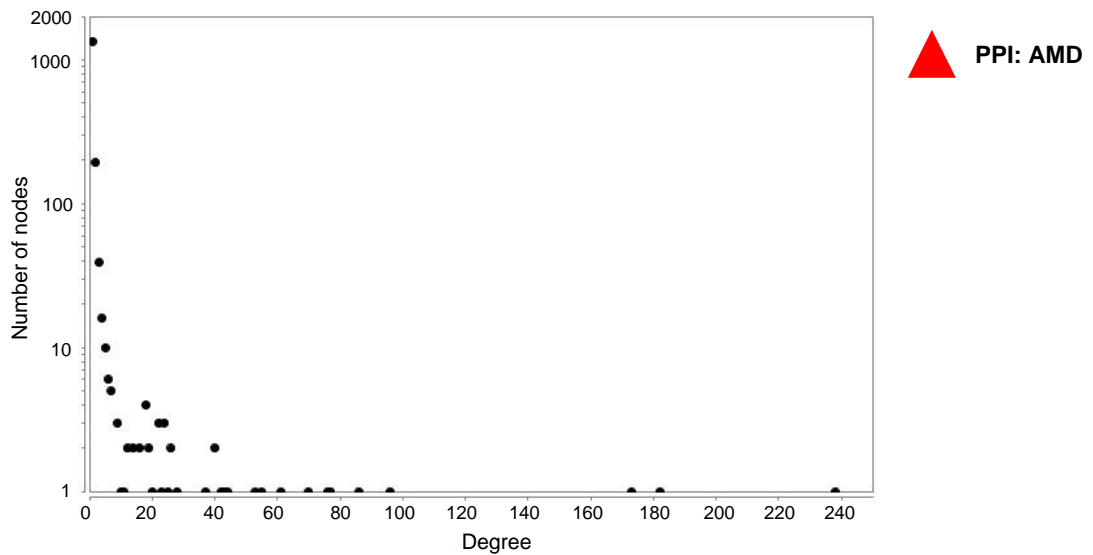
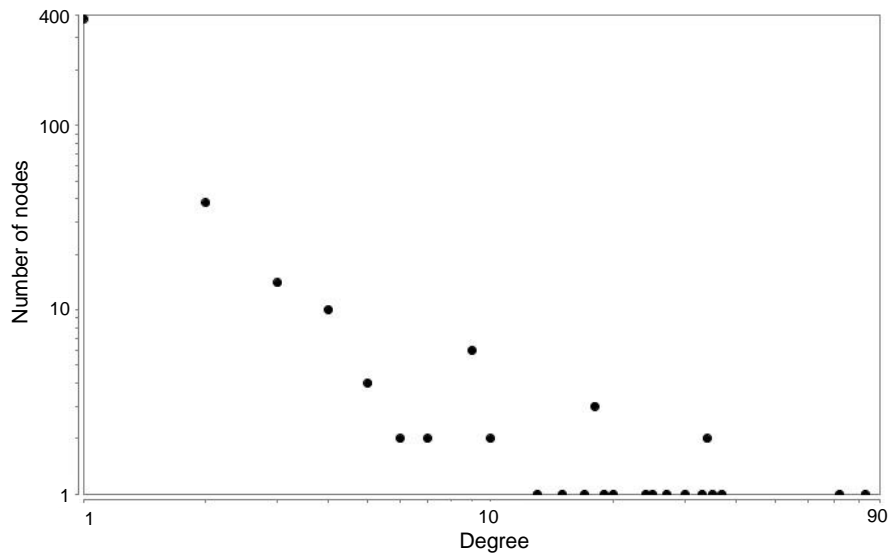
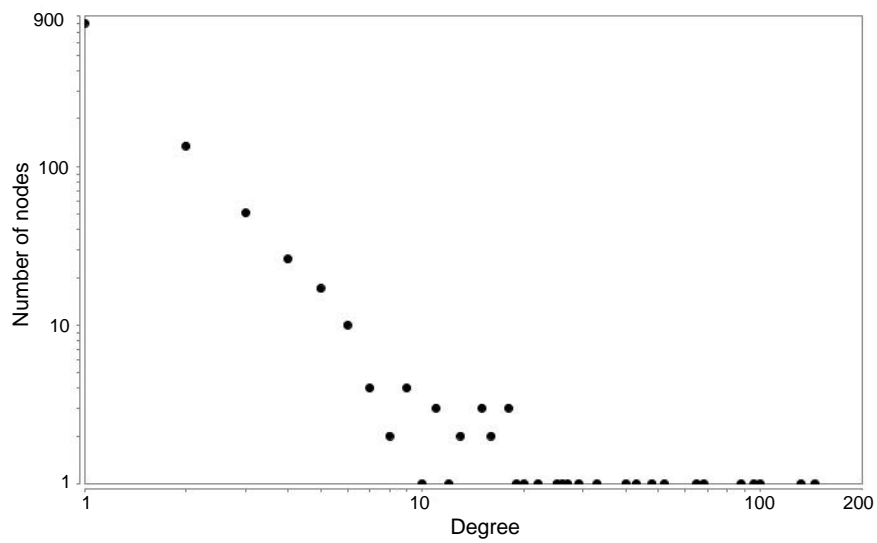


Supplementary Figure 2

RD genes associated to non-retinal phenotypes.

Network representation of the association between diseases and RD genes that additionally have a non-retinal phenotype. Boxes represent genes and triangles diseases or phenotypes. Monogenic non-syndromic RD are coloured in yellow, monogenic syndromic RD are coloured in orange, and AMD in red (see network). The remaining triangles represent disease or phenotypes that manifest in tissues outside the eye (non-vision related, see legend).

Related to Figure 1b.

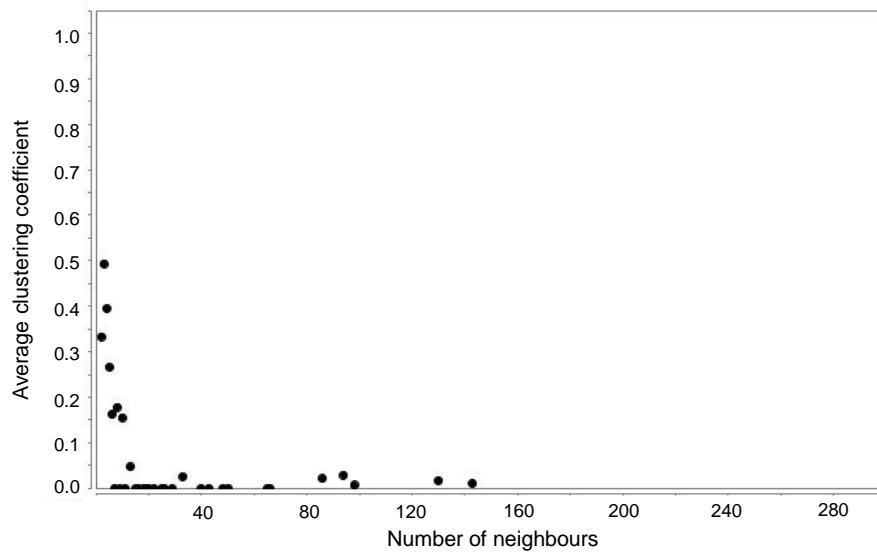


Supplementary Figure 3

Degree distribution of proteins in the three protein-protein interaction (PPI) networks.

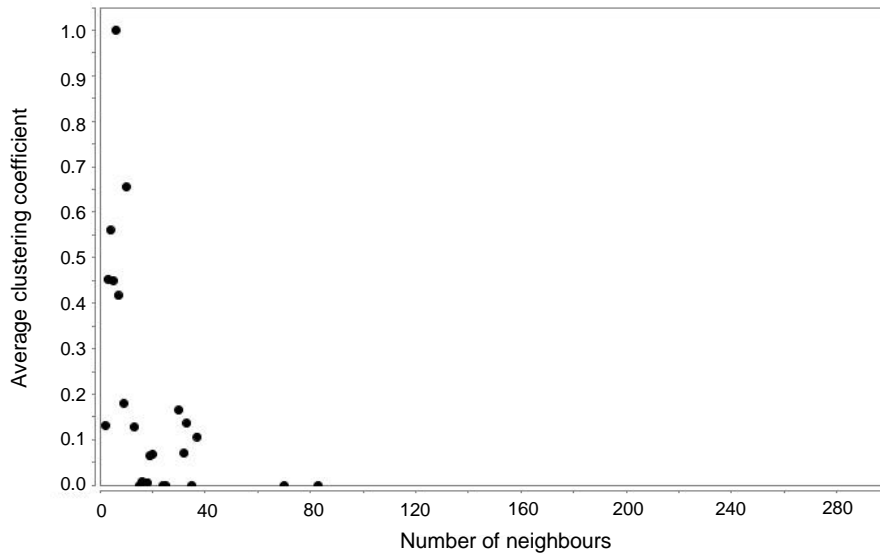
Diagrams of the degree distributions (number of interaction partners) for all nodes (proteins) in the three PPI networks (M-NS RD, M-S RD, and AMD) are depicted. The network statistics and plots were calculated using the Cytoscape 'NetworkAnalyzer' plugin.

Related to Figure 2a.



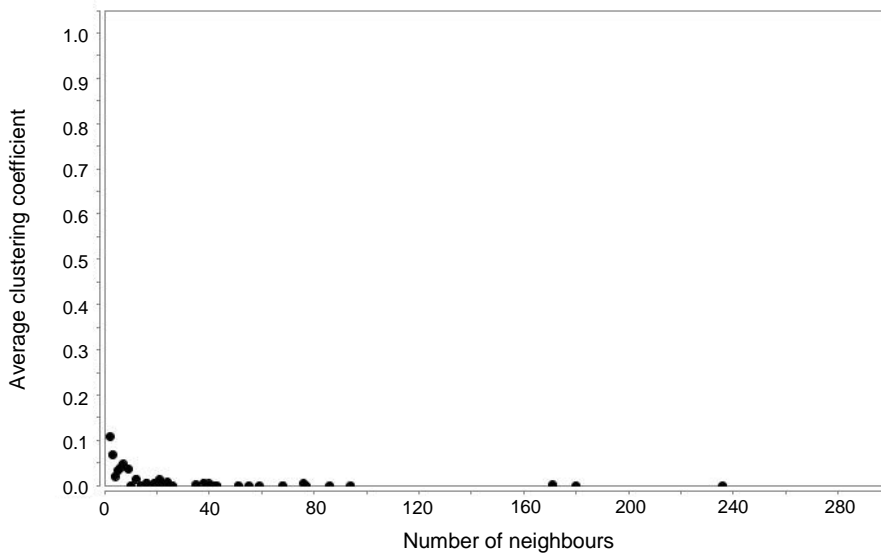
PPI: M-NS RD

Average clustering coefficient in the network: 0.081



PPI: M-S RD

Average clustering coefficient in the network: 0.052



PPI: AMD

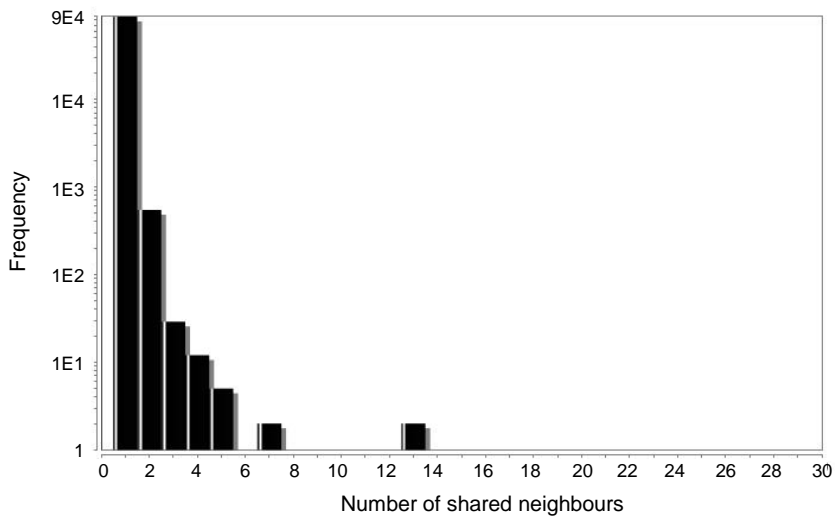
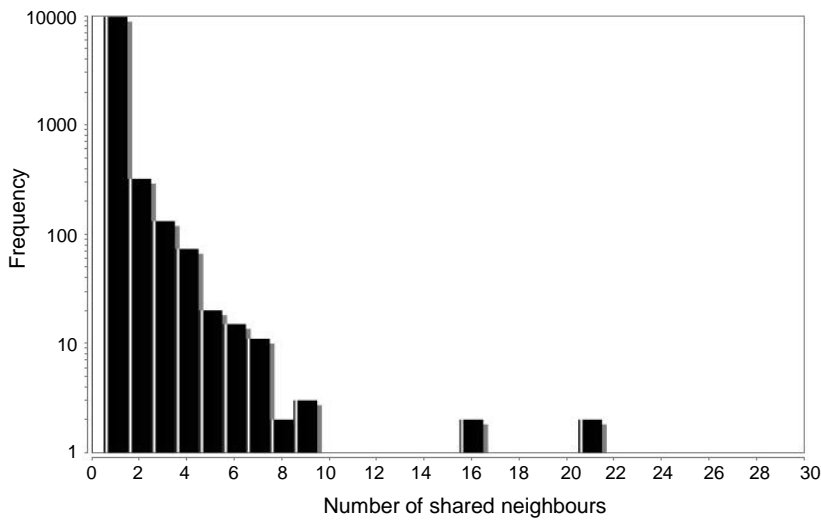
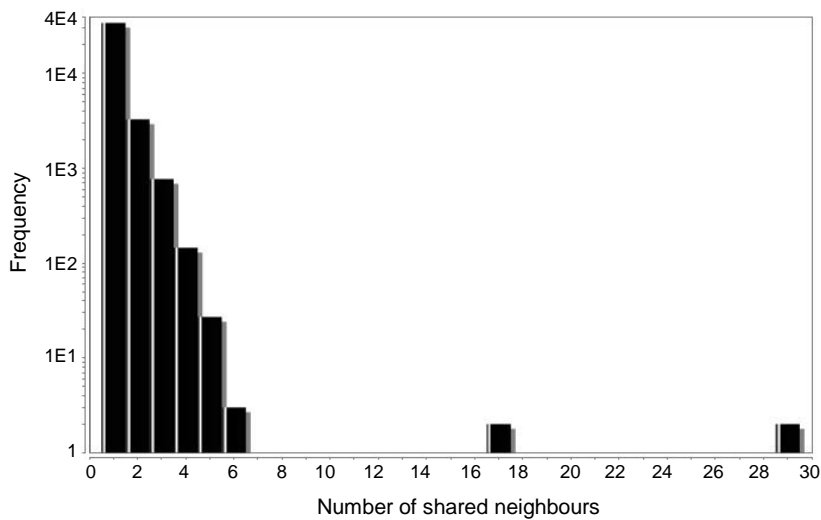
Average clustering coefficient in the network: 0.015

Supplementary Figure 4

Average clustering distribution of proteins in the three protein-protein interaction (PPI) networks.

Diagrams of the average clustering coefficients in the three PPI networks (M-NS RD, M-S RD, and AMD) are depicted. The network statistics and plots were calculated using the Cytoscape 'NetworkAnalyzer' plugin.

Related to Figure 2a.

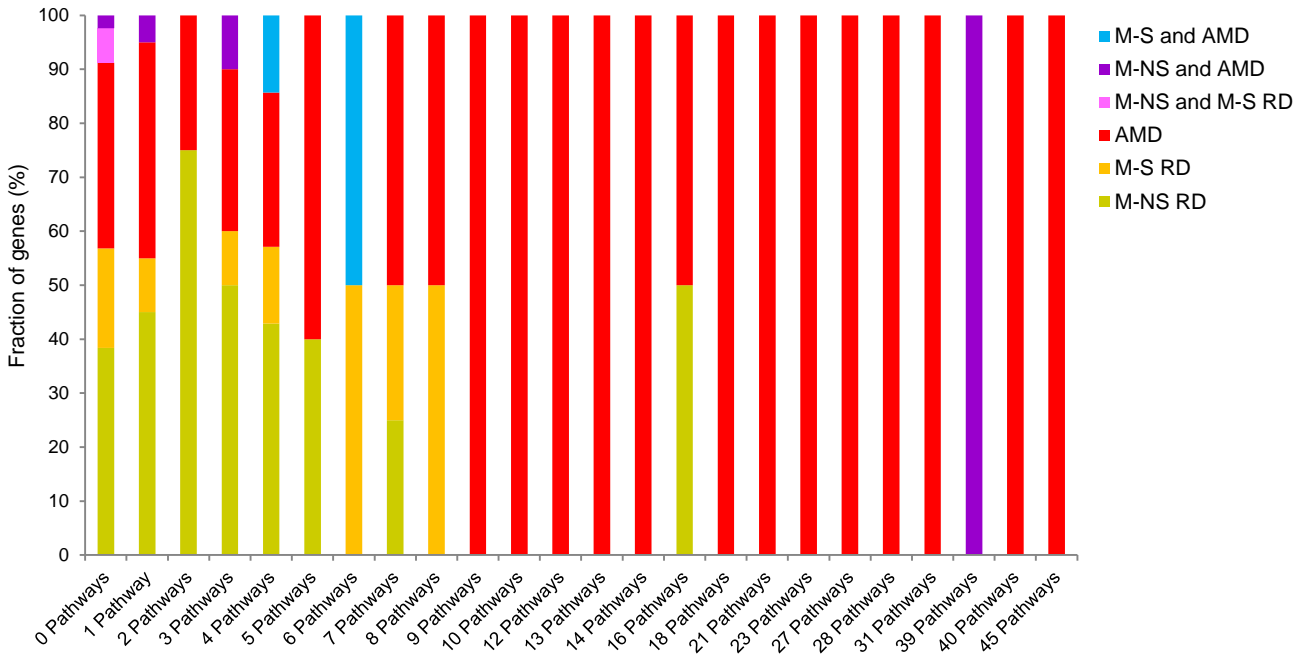


Supplementary Figure 5

Shared neighbour distribution of proteins in the three protein-protein interaction (PPI) networks.

Diagrams of the shared neighbour distribution in the three PPI networks (M-NS RD, M-S RD, and AMD) are depicted. The network statistics and plots were calculated using the Cytoscape 'NetworkAnalyzer' plugin.

Related to Figure 2a.



Supplementary Figure 6

Fraction of proteins associated to different pathways based on the HPD database.

Fraction of genes associated to a certain number of pathways coloured according to the different RD classes (see legend).

Related to Figure 2b.

source	term name (Gene Ontology (Biological process))	term ID	n. of genes	n. of genes	n. of corrected p-value	
BP	biological process	00-000001	16836	95	3.02e-02	
BP	multicellular organismal process	00-000002	1036	95	1.52e-39	
BP	neurological process	00-000003	55	64	1.21e-05	
BP	neurological system process	00-000004	1383	64	4.22e-49	
BP	sensory perception	00-000005	539	63	9.70e-56	
BP	sensory perception of light stimulus	00-000006	207	56	1.72e-95	
BP	visual perception	00-000007	207	56	1.72e-95	
BP	single-multicellular organism process	00-004707	5540	95	2.61e-02	
BP	response to stimulus	00-000008	8287	95	1.06e-05	
BP	response to abiotic stimulus	00-000009	4257	79	1.06e-05	
BP	response to biotic stimulus	00-000010	4030	79	1.06e-05	
BP	cellular response to abiotic stimulus	00-006238	1174	95	38	2.11e-18
BP	cellular response to biotic stimulus	00-007124	287	18	1.02e-09	
BP	response to light stimulus	00-000011	96	36	1.02e-09	
BP	response to light intensity	00-000012	35	36	1.02e-09	
BP	response to light stimulus	00-000013	11	36	3.92e-02	
BP	cellular response to radiation	00-007478	128	15	4.11e-12	
BP	response to external stimulus	00-000014	128	15	4.11e-12	
BP	detection of external stimulus	00-000015	2483	95	42	1.70e-10
BP	detection of external stimulus	00-000016	134	34	1.30e-41	
BP	detection of light stimulus	00-000017	18	9	1.25e-13	
BP	detection of light stimulus involved in sensory perception	00-000018	112	31	1.24e-43	
BP	photoreception of light stimulus	00-000019	113	31	1.24e-43	
BP	photoreception of light stimulus involved in visual perception	00-000020	113	31	1.24e-43	
BP	phototransduction, visible light	00-000021	97	24	1.43e-31	
BP	rhodopsin mediated signaling pathway	00-000022	30	14	4.06e-20	
BP	homeostatic process	00-000023	96	14	4.06e-20	
BP	anatomical structure morphogenesis	00-000024	341	17	2.09e-09	
BP	multicellular organismal homeostasis	00-004871	327	17	1.05e-09	
BP	multicellular organismal homeostasis	00-000025	291	17	3.48e-13	
BP	tissue homeostasis	00-000026	291	17	3.48e-13	
BP	regulation of G-protein coupled receptor protein signaling pathway	00-004544	35	15	5.52e-23	
BP	regulation of G-protein coupled receptor protein signaling pathway	00-000277	128	12	3.05e-09	
BP	cilia morphogenesis	00-000200	34	12	1.02e-16	
BP	cilia morphogenesis	00-006271	221	95	3.08e-02	
BP	single-organism developmental process	00-004707	9569	48	4.04e-02	
BP	nerve system development	00-000759	2285	39	1.52e-02	
BP	anatomical structure morphogenesis	00-000023	2894	33	8.14e-04	
BP	anatomical structure morphogenesis	00-000024	3045	36	4.43e-04	
BP	organ morphogenesis	00-000743	504	29	8.06e-20	
BP	eye development	00-000024	332	28	1.37e-23	
BP	eye morphogenesis	00-000025	143	21	7.20e-20	
BP	organ morphogenesis	00-000987	901	23	1.42e-07	
BP	sensory organ morphogenesis	00-000986	250	20	1.62e-15	
BP	eye morphogenesis	00-000026	143	21	7.20e-20	
BP	retina development, in camera-type eye	00-000941	134	23	4.11e-26	
BP	retina development, in camera-type eye	00-000942	46	11	6.24e-13	
BP	neural system development	00-000029	1506	25	4.32e-04	
BP	generation of neurons	00-000029	1506	25	4.32e-04	
BP	neural retina development	00-000407	53	11	3.52e-12	
BP	retina layer formation	00-000842	22	5	1.39e-04	
BP	neurogenesis	00-000029	1504	20	1.61e-29	
BP	neurogenesis	00-004530	45	95	20	1.61e-29
BP	eye photoreceptor cell differentiation	00-000754	45	16	4.82e-23	
BP	camera-type eye photoreceptor cell differentiation	00-000754	45	16	4.82e-23	
BP	neuron development	00-000029	8	4	1.39e-06	
BP	neuron development	00-004856	1344	56	21	1.39e-03
BP	photoreceptor cell development	00-004261	41	16	7.01e-24	
BP	photoreceptor cell development	00-004262	35	13	5.64e-29	
BP	retinal rod cell development	00-004548	11	56	3.72e-04	
BP	retinal cone cell development	00-004549	8	4	8.13e-05	
BP	retinal cone cell development	00-004550	8	4	8.13e-05	
BP	positive regulation of rhodopsin gene expression	00-004272	2	56	2	4.58e-02
BP	isoprenoid metabolic process	00-000720	126	95	8	4.54e-04
BP	terpenoid metabolic process	00-000721	100	95	8	1.10e-04
BP	terpenoid metabolic process	00-000501	94	95	8	4.58e-05
BP	vitamin K metabolic process	00-000776	9	56	3	2.09e-02
BP	retinal metabolic process	00-004272	26	95	4	1.62e-02
BP	spliceosomal tri-snRNP complex assembly	00-000244	12	95	4	5.66e-04
BP	protein localization to cilium	00-006102	27	95	4	1.58e-02
BP	protein localization to nonciliary primary cilium	00-000969	9	95	3	2.08e-02

Supplementary Figure 7

Supplementary Figure 7

Gene ontology process enrichment for M-NS RD.

Enrichment analysis for the Gene ontology (GO) 'Biological Process' for M-NS RD genes using g:Profiler.

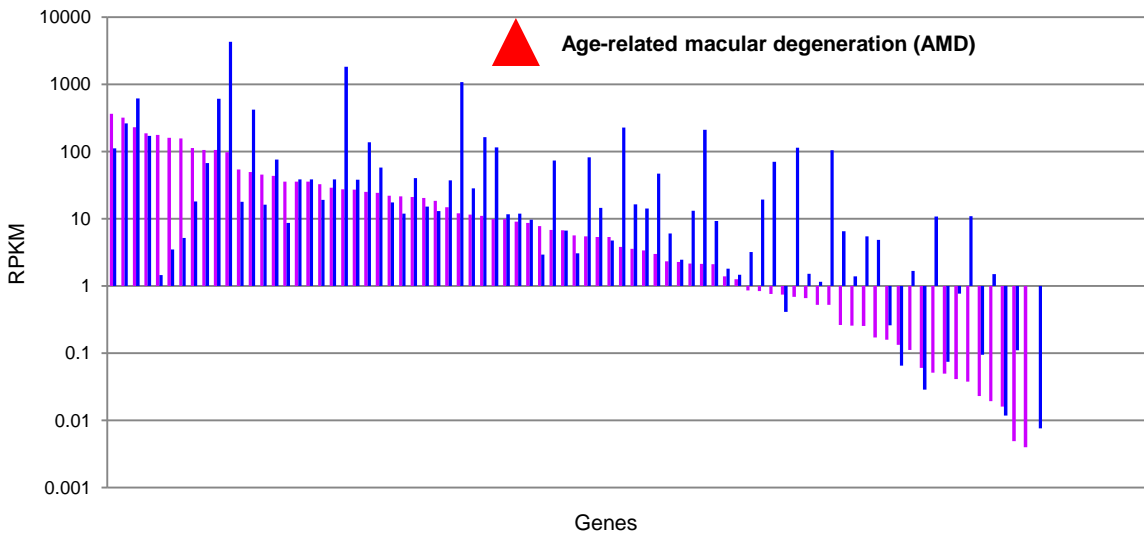
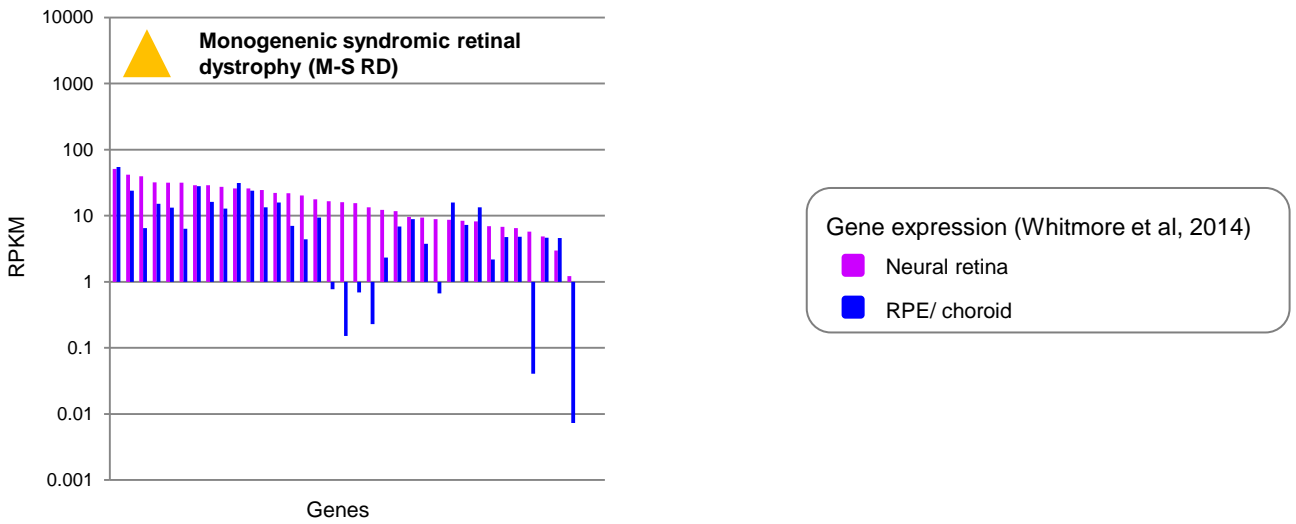
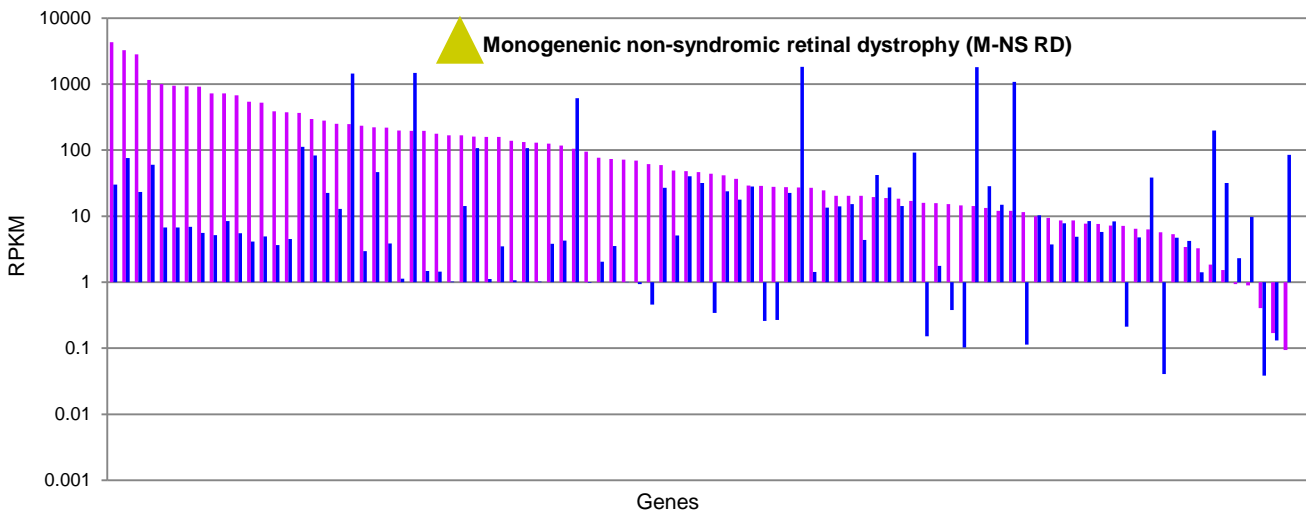
Related to Figure 3.

Supplementary Figure 8

Gene ontology process enrichment for M-S RD.

Enrichment analysis for the Gene ontology (GO) 'Biological Process' for M-S RD genes using g:Profiler.

Related to Figure 3.



Supplementary Figure 10

Gene expression levels in retinal tissues.

Average gene expression levels in neural retina and RPE/ choroid (see Whitmore et al, 2014) displayed separately for genes related to monogenic non-syndromic RD, monogenic syndromic RD, and AMD. Genes are sorted by decreasing expression levels in neural retina.

Related to Figure 4.

Supplementary Tables (online)

Supplementary Table S1

Disease associations of 208 genes related to retinal dystrophies (RD), functional classification and expression levels in retinal cell types.

Related to Figure 1b, Figure 3 and Figure 4.

Supplementary Table S2

Interaction networks reconstructed among RD genes using the HIPPIE database.

Related to Figure 2a.

Supplementary Table S3

Pathway information obtained from the HPD database.

Related to Figure 2b.

Supplementary Table S4

Processes and modulators in the physiological condition, during ageing, and in AMD pathogenesis.

Related to Figure 4.

Supplementary Table S5

Generation of a list of genes associated to AMD.

Related to Figure 1b.