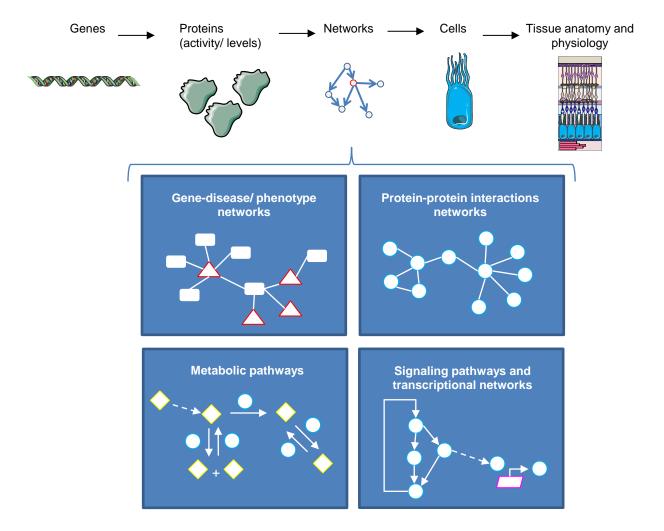
Supplementary information for:

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

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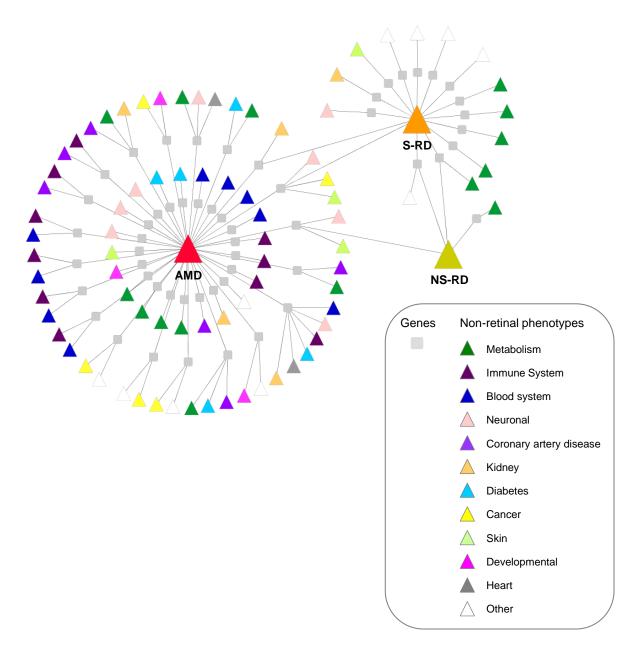
¹EMBL/CRG Systems Biology Research Unit, Centre for Genomic Regulation (CRG), Barcelona Institute of Science and Technology, Dr. Aiguader 88, 08003 Barcelona, Spain ²Universitat Pompeu Fabra (UPF), 08003 Barcelona, Spain ³Department of Ocular Biology and Therapeutics, UCL Institute of Ophthalmology, and NIHR Biomedical Research Centre, University College London, 11-43 Bath Street, London EC1V 9EL, UK ⁴Institució Catalana de Recerca i Estudis Avançats (ICREA), Pg. Lluís Companys 23, 08010 Barcelona, Spain *christina.kiel@crg.eu



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-imagebank), which is licensed under a Creative Commons Attribution 3.0 Unported License.

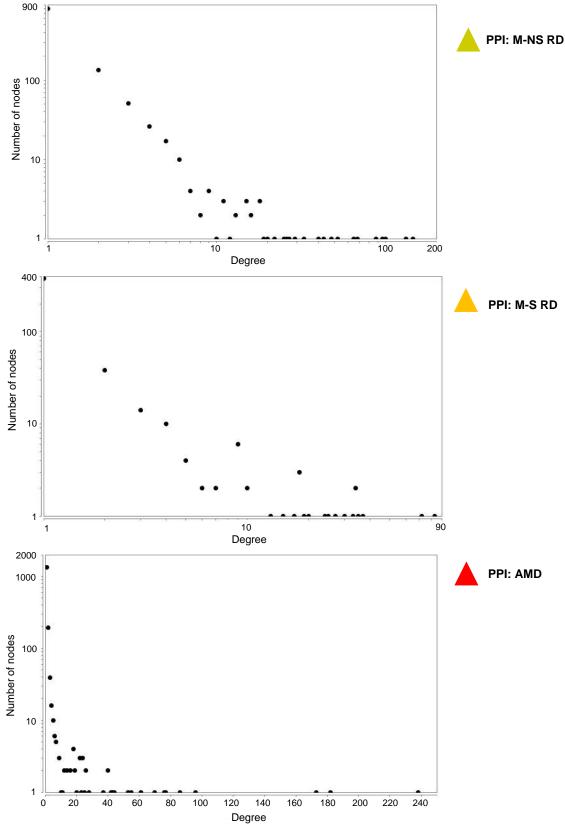
Related to Figure 1b.



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).

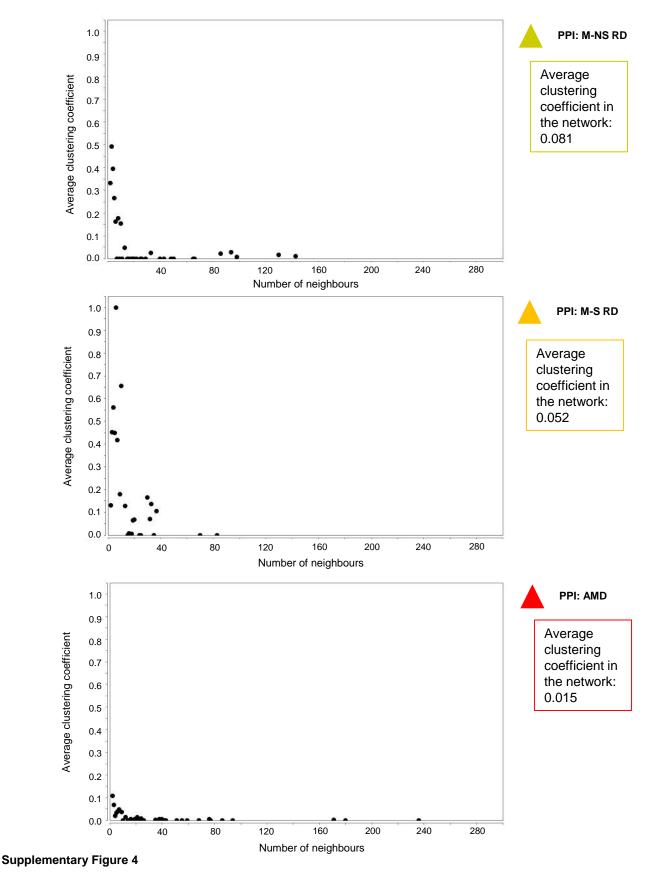
Related to Figure 1b.



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.

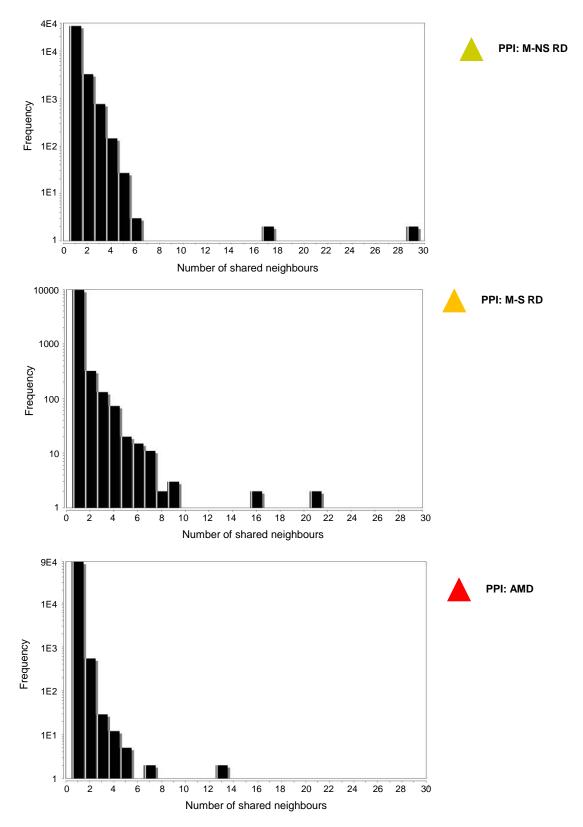
Related to Figure 2a.



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.

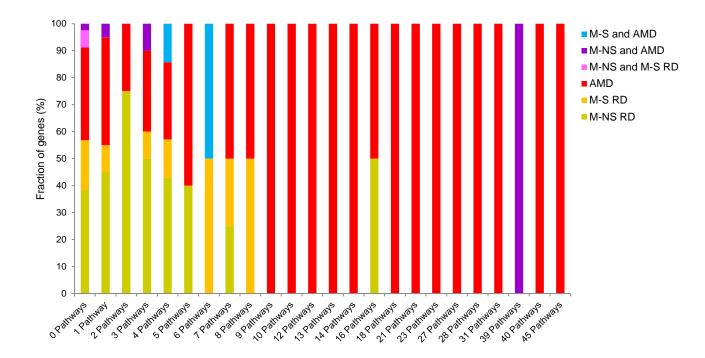
Related to Figure 2a.



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.



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.



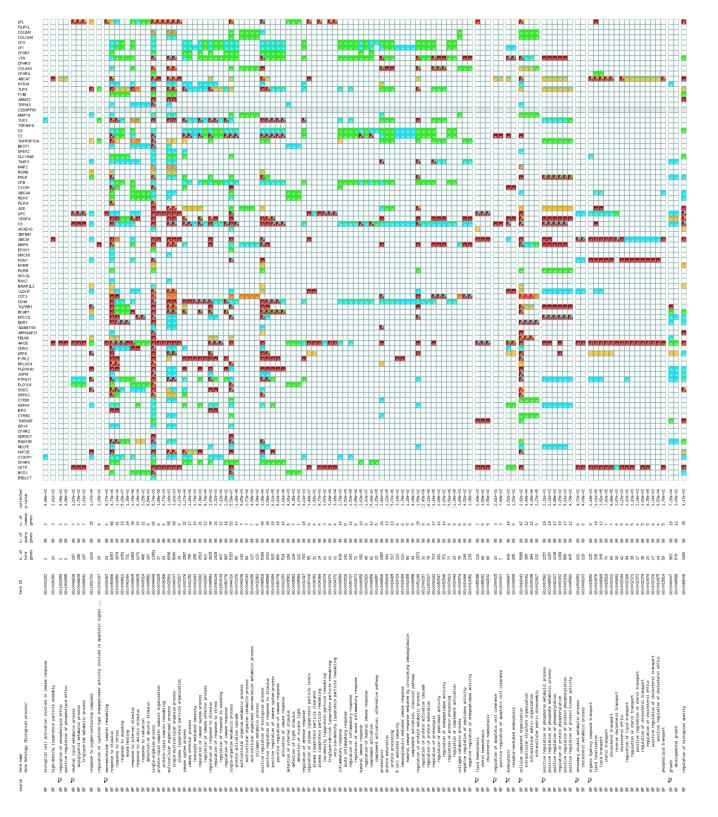
Gene ontology process enrichment for M-NS RD.

Enrichment analysis for the Gene ontology (GO) 'Biological Process' for M-NS RD genes using g:Profiler. Related to Figure 3.

source	terw name Gene Ontology (Biological process)	term ID	n. of term genes	n. of query genes	n. of common genes	corrected p-value	CLRN1 CLRN1 USH06 USH06 USH06 USH16 CH28 CH28 PH78 PH78 PH78 PH78 PH78 PH78 PH78 PH7
BP	protein localization to cilium	G0:0061512	27	35	4	3.96e-04	
BP 🔁	protein localization	GD:0008104	2414	35	15	2.06e-02	
BP	establishment of protein localization	GD:0045184	2011	35	14	1.28e-02	
BP 🔁	single-organism process	GD:0044699	13451	35	35	1.01e-02	
BP	single-organism cellular process	GD:0044763	12256	35	35	3.87e-04	5
BP	pigmentation	GD:0043473	93	35	7	7.55e-07	
BP	cellular pignentation	GD:0033059	49	35	7	7.25e-09	
BP	developmental process	GD:0032502	5755	35	27	2.88e-05	
BP	anatomical structure development	GD:0048856	5404	35	26	4.99e-05	
BP	tissue development	GD:0009888	1707	35	13	1.20e-02	S S S C C S S S C C C C C C C C C C C C
BP	epithelium development	GD:0060429	1051	35	11	3.93e-03	
BP	single-organism developmental process	GD:0044767	5669	35	27	2.01e-05	SI TRIS SIST THE ST. ST. S. TRIS TRIC C. M. TRIM TRIS SIT. M. M. M. C. C. A.
BP	head development	GD:0060322	717	35	10	9.87e-04	
BP BP	cellular developmental process	GD:0048869	4021 3731	35 35	26 21	5.08e-08	
BP	cell differentiation fat cell differentiation	GD:0030154 GD:0045444	198	35	8	3.77e-04 5.20e-06	
BP	cell development	GD:0048468	2149	35	15	4.78e-03	San
BP	anatomical structure morphogenesis	GD:0009653	2694	35	22	9.48e-08	
BP	tissue worphogenesis	GD:0048729	575	35	10	1.27e-04	
BP	worphogenesis of an epithelium	GD:0002009	442	35	8	2.55e-03	
BP	epithelial tube morphogenesis	GD:0060562	308	35	6	4.48e-02	
BP	anatomical structure formation involved in morphogenesis	GD:0048646	1120	35	15	7.70e-07	
BP	multicellular organismal process	GD:0032501	6936	35	31	4.60e-07	STATES AND
BP	system process	GD:0003008	1928	35	21	1.46e-09	
BP	neurological system process	GD:0050877	1263	35	21	3.16e-13	
BP	neuromuscular process	GD:0050905	103	35	6	7.42e-05	
BP	neuromuscular process controlling balance	GD:0050885	55	35	6	1.60e-06	
BP	sensory perception	GD:0007600	939	35	21	7.49e-16	
BP	sensory perception of light stimulus	GD:0050953	210	35	20	1.72e-27	
BP	visual perception	GD:0007601	207	35	17	1.80e-21	
BP	sensory perception of mechanical stimulus	GD:0050954	155	35	11	5.94e-12	
BP	sensory perception of sound	GD:0007605	139	35	11	1.75e-12	
BP	equilibrioception	GD:0050957	7	35	6	4.11e-13	
BP	single-multicellular organism process	GD:0044707	5940	35	29	8.06e-07	
BP BP	multicellular organism development	GD:0007275 GD:0048731	4865 4327	35 35	23 22	1.45e-03 9.20e-04	SISSISTERS STATES TO THE STATE OF THE STATES
BP	system development nervous system development	GD:0007399	2355	35	21	7.14e-08	
BP	neurogenesis	GD:0022008	1684	35	15	2.00e-04	
BP	generation of neurons	GD:0048699	1606	35	15	1.06e-04	
BP	neuron differentiation	GD:0030182	1494	35	14	3.48e-04	
BP	photoreceptor cell differentiation	GD:0046530	56	35	5	1.34e-04	
BP BP	mechanoreceptor differentiation	GD:0042490 GD:0048666	61 1244	35 35	6 13	3.04e-06 3.26e-04	
BP	neuron development photoreceptor cell development	GD:0042461	41	35	4	2.24e-03	
BP	animal organ development	GD:0048513	3045	35	19	4.75e-04	S Sa
BP	sensory organ development	GD:0007423	504	35	13	5.34e-09	
BP	ear development	GD:0043583	202	35	8	6.09e-06	
BP	inner ear development	GD:0048839	176	35	8	2.05e-06	
BP	inner ear receptor cell differentiation	GD:0060113	57	35	6	2.00e-06	
BP	inner ear receptor cell development	G0:0060119	41	35	5	2.69e-05	
BP	eye development	G0:0001654	332	35	8	2.91e-04	
BP	organ πorphogenesis	GD:0009887	901	35	14	5.34e-07	
BP	sensory organ πorphogenesis	GD:0090596	250	35	8	3.24e-05	
BP	eye morphogenesis	GD:0048592	143	35	6	5.26e-04	
BP	eye photoreceptor cell differentiation	GD:0001754	45	35	4	3.29e-03	
BP	brain development	GD:0007420	678	35	9	6.34e-03	
BP	embryo development	GD:0009790	947	35	10	1.22e-02	SSS C
BP	embryonic morphogenesis	GD:0048598	568	35	10	1.13e-04	
BP	embryonic organ development	GD:0048568	413	35	10	5.47e-06	
BP	embryonic organ morphogenesis	GD:0048562	286	35	9	4.05e-06	
BP BP	embryonic heart tube development embryonic heart tube morphogenesis	GD:0035050 GD:0003143	75 65	35 35	5	5.92e-04 2.87e-04	
BP	pattern specification process	GD:0007389	438	35	9	1.63e-04	
BP	specification of symmetry	GD:0009799	123	35	8	1.16e-07	S S S E S S S S S S S S S S S S S S S S
BP	determination of bilateral symmetry	GD:0009855	122	35	8	1.09e-07	
BP	determination of left/right symmetry	GD:0007368	114	35	8	6.27e-08	
BP	determination of heart left/right asymmetry	GD:0061371	63	35	5	2.45e-04	
BP	heart looping	GD:0001947	60	35	5	1.91e-04	
BP	cellular component organization or biogenesis	GD:0071840	6111	35	29	1.71e-06	
BP	cellular component biogenesis	GD:0044085	2545	35	18	1.83e-04	
BP	homeostatic process	GD:0042592	1513	35	16	5.01e-06	
BP	anatomical structure homeostasis	GD:0060249	341	35	16	5.27e-16	
BP	multicellular organismal homeostasis	GD:0048871	327	35	16	2.69e-16	
BP	tissue homeostasis	GD:0001894	201	35	16	9.89e-20	
BP	retina homeostasis	GD:0001895	68	35	14	6.53e-23	
BP	photoreceptor cell maintenance	GD:0045494	35	35	13	7.03e-25	
BP	organelle localization	GD:0051640	444	35	8	2.64e-03	
BP	vesicle localization	GD:0051648	230	35	7	4.12e-04	
BP	pignent granule localization	GD:0051875	26	35	7	5.72e-11	
BP	melanosome localization	GD:0032400	25	35	6	1.02e-08	SSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSSS
BP	cellular component organization	GD:0016043	5985	35	29	9.85e-07	
BP	cellular component morphogenesis	GD:0032989	1517	35	18	4.12e-08	
BP	cell part morphogenesis	GD:0032990	1109	35	17	3.39e-09	
BP	cell morphogenesis	GD:0000902	1444	35	18	1.80e-08	
BP	organelle organization	GD:0006996	3556	35	24	3.16e-07	A LESSUR CLINA A PLA STANS AN CLIPPE A MOSTAN A LESSUA DE LESSUA DE LESSUA DE LESSUA DE LESSUA DE LESSUA DE LES
BP	single-organism organelle organization	GD:1902589	2543	35	20	2.90e-06	
BP	cellular component assembly	GD:0022607	2353	35	18	5.33e-05	D the System of the second sec
BP	cellular component assembly involved in morphogenesis	GD:0010927	273	35	14	4.47e-14	
BP	organelle assembly	GD:0070925	546	35	15	2.61e-11	
BP	cell projection organization	GD:0030030	1488	35	24	8.65e-16	
BP	cilium organization	GD:0044782	204	35	15	1.01e-17	
BP	cell projection assembly	GD:0030031	359	35	15	5.27e-14	
BP	cell projection morphogenesis	GD:0048858	1090	35	17	2.57e-09	
BP	cilium morphogenesis	GD:0060271	221	35	15	3.45e-17	
BP	cilium assembly	GD:0042384	187	35	14	2.09e-16	
BP	nonmotile primary cilium assembly	GD:0035058	24	35	8	9.38e-14	
BP	inner ear receptor stereocilium organization	GD:0060122	26	35	5	2.41e-06	
BP BP	establishment of organelle localization	GD:0051656 GD:0050893	385	35 35	7	1.29e-02 2.42e-02	
BP	sensory processing establishment of vesicle localization	60:0051650	219	35	7	2.95e-04	
BP	establishment of pigment granule localization	GD:0051905	24	35	7	3.01e-11	
BP	pigment granule aggregation in cell center	GD:0051877	2	35	2	8.09e-03	
BP	establishment of melanosome localization	GD:0032401	23	35	6	5.81e-09	
BP	multicellular organism growth	GD:0035264	145	35	5	1.56e-02	
BP	subpallium development	GD:0021544	22	35	3	2.09e-02	
BP	striatum development	GD:0021756	16	35	3	7.67e-03	
BP	pigment granule transport	GD:0051904	23	35	7	2.14e-11	
BP	melanosome transport	60:0032402	22	35	6	4.30e-09	
BP [™] ⊂ BP	cilium movement cilium or flagellum-dependent cell motility	GD:0003341 GD:0001539	43 21	35 35	4	2.73e-03 1.81e-02	
BP	cilium-dependent cell motility	GD:0060285	15	35	3	6.24e-03	
BP	regulation of microtubule-based movement	GD:0060632	19	35	3	1.32e-02	
BP BP	regulation of cilium movement regulation of cilium-dependent cell motility	GD:0003352 GD:1902019	12	35 35	3	3.03e-03 2.78e-04	
BP	regulation of cilium beat frequency	GD:0003356	11	35	3	2.28e-03	
BP BP	cilium movement involved in cell motility regulation of cilium movement involved in cell motility	GD:0060294 GD:0060295	11 6	35 35	3	2.28e-03 2.78e-04	
BP	regulation of cilium beat frequency involved in ciliary motility	GD:0060296	6	35	3	2.78e-04	
BP 🔁	chaperone-mediated protein complex assembly response to leptin	GD:0051131 GD:0044321	15 20	35 35	3	6.24e-03 1.55e-02	
BP	cellular response to leptin stimulus	G0:0044320	16	35	3	7.67e-03	
BP BP	regulation of appetite regulation of response to food	GD:0032098 GD:0032095	24 20	35 35	3	2.75e-02 1.55e-02	
BP	negative regulation of response to food	GD:0032096	13	35	3	3.93e-03	
BP	negative regulation of appetite	GD:0032099	13	35	3	3.93e-03	
BP	leptin-mediated signaling pathway	GD:0033210	9	35	3	1.16e-03	
BP	negative regulation of appetite by leptin-wediated signaling pathway	GD:0038108	4	35	3	5.56e-05	

Gene ontology process enrichment for M-S RD.

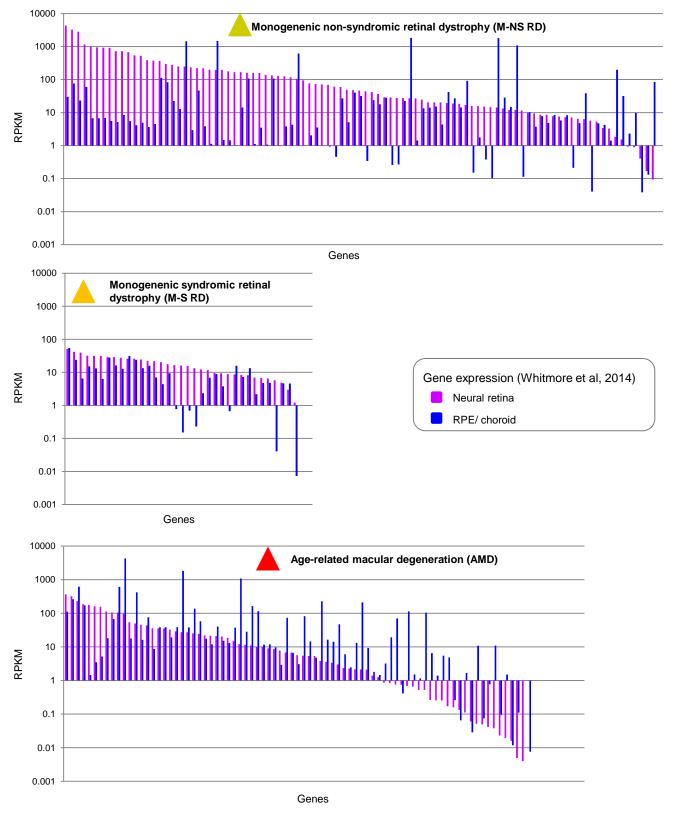
Enrichment analysis for the Gene ontology (GO) 'Biological Process' for M-S RD genes using g:Profiler. Related to Figure 3.



Gene ontology process enrichment for AMD.

Enrichment analysis for the Gene ontology (GO) 'Biological Process' for AMD genes using g:Profiler.

Related to Figure 3.



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 Figure1b, 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.