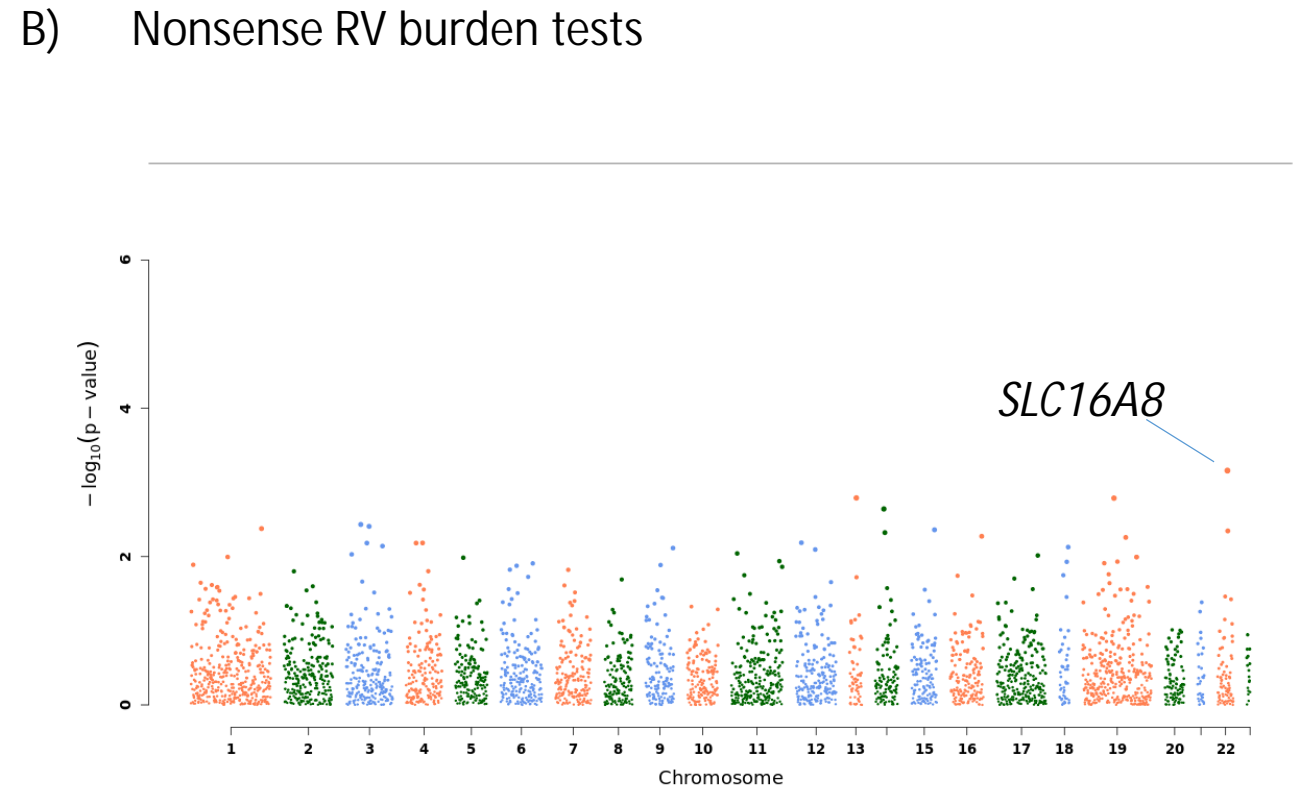
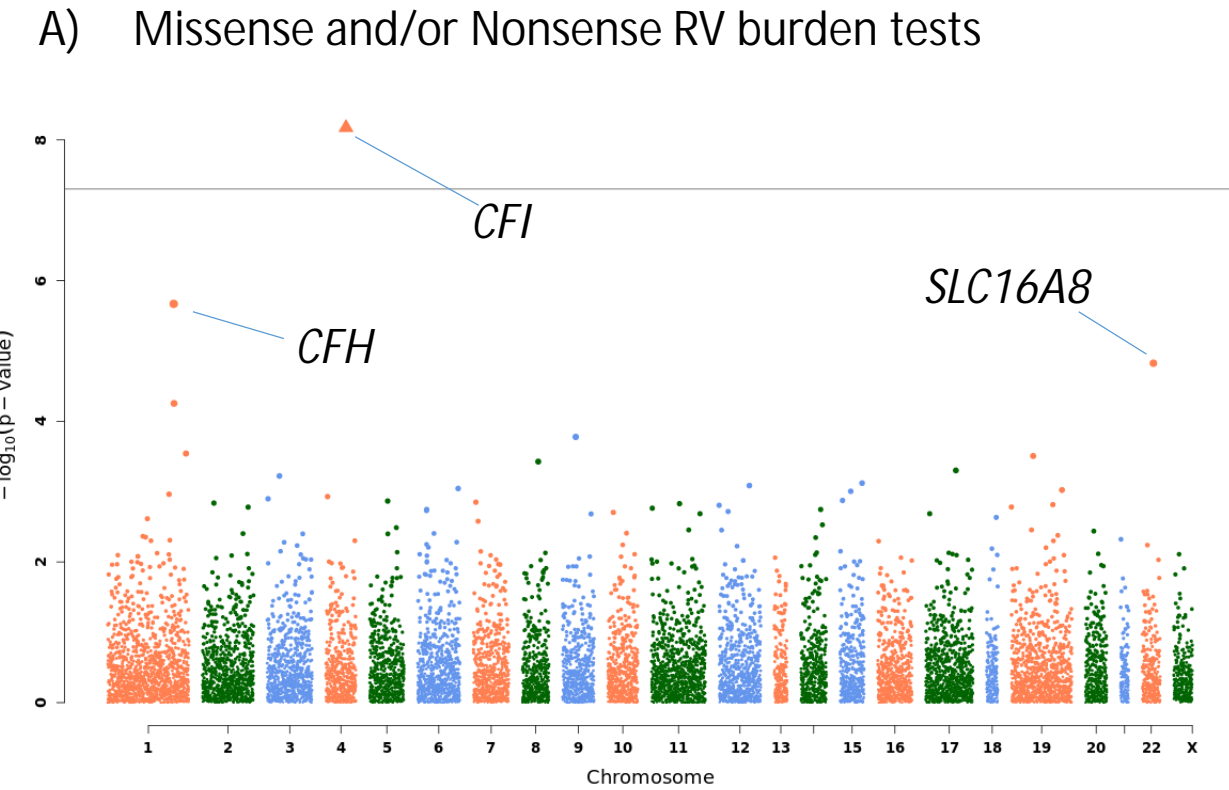


Supplementary Figure 1. Manhattan plots of WGS advanced AMD cases and controls using two different protein altering rare variant burden tests.



Supplementary Table 1. List of WGS cohorts for rare variant burden testing. All WGS cohorts were primarily of European ancestry and non-AMD diseased cohorts from multiple different proprietary internal clinical trials were used as controls.

Study Cohorts for RV Burden Analyses

Study Name	Disease Phenotype	N	Reference	WGS Year
ARCHWAY	AMD	195	https://clinicaltrials.gov/ct2/show/NCT03677934	2020
AREDS	AMD	1590	https://clinicaltrials.gov/ct2/show/NCT00000145	2020
CHROMA	AMD	741	https://clinicaltrials.gov/ct2/show/NCT02247479	2016, 2017
Dawn	AMD	346	https://clinicaltrials.gov/ct2/show/NCT03034772	2015
Dr. FU AMD	AMD	35	https://clinicaltrials.gov/ct2/show/NCT02960828	2015
HARBOR	AMD	930	https://clinicaltrials.gov/ct2/show/NCT00891735	2014, 2015
LADDER	AMD	157	https://clinicaltrials.gov/ct2/show/NCT02510794	2019
LAMPA	AMD	87	https://clinicaltrials.gov/ct2/show/NCT01229215	2016
LUCERNE	AMD	369	https://clinicaltrials.gov/ct2/show/NCT03823300	2020
MAHALO	AMD	90	https://clinicaltrials.gov/ct2/show/NCT01229215	2015
PALMER	AMD	18	https://clinicaltrials.gov/ct2/show/NCT02960828	2015
PROXIMA_A	AMD	208	https://clinicaltrials.gov/ct2/show/NCT02479386	2016, 2017
PROXIMA_B	AMD	154	https://clinicaltrials.gov/ct2/show/NCT02399072	2016, 2017
SAVE	AMD	29	https://clinicaltrials.gov/ct2/show/NCT02960828	2015
SPECTRI	AMD	755	https://clinicaltrials.gov/ct2/show/NCT02247531	2016
TENAYA	AMD	351	https://clinicaltrials.gov/ct2/show/NCT03823287	2020

Supplementary Table 2. Subset of human genes from protein altering rare variant burden tests associated with AMD (P < 0.05) and corresponding ranked orthologs identified for RNAi screenings. BL (Bloomington Drosophila Stock Center) and VDRC (Vienna Drosophila RNAi Center). See methods.

Negative Controls				
Target Gene	RNAi Stock (BL or VDRC)	%DPP+ (Day 1)	%DPP+ (Day 7)	%DPP+ (Day 14)
<i>UAS-mCherry RNAi</i>	BL35785	100	70	100
<i>UAS-luciferase RNAi</i>	BL31603	100	100	100
<i>UAS-LacZ RNAi</i>	Jasper Lab	90	80	100
<i>UAS-tdTomato</i>	Jasper Lab	100	80	100

AMD associated human genes and orthologs screened								
Human Gene	Fly Gene	Ortho Rank	Fly Gene ID	Fly Base ID	RNAi Stock (BL/VDRC)	%DPP+ (Day 1)	%DPP+ (Day 7)	%DPP+ (Day 14)
<i>CFH</i>	Hasp	high	35238	FBgn0032797	BL-65101	70	n/a	70
<i>CFH</i>	Hasp	high	35238	FBgn0032797	BL-101250	100	n/a	80
<i>RGS7</i>	RSG7	high	32674	FBgn0024941	BL-28574	100	n/a	100
<i>RGS7</i>	RSG7	high	32674	FBgn0024941	VDRC-101733	100	n/a	100
<i>SLC16A8</i>	Sln	moderate	36263	FBgn0033657	VDRC-109464	100	100	10
<i>SLC16A8</i>	Sln	moderate	36263	FBgn0033657	VDRC-4607	100	100	100
<i>SLC16A8</i>	Sln	moderate	36263	FBgn0033657	VDRC-4609	100	100	80
<i>SLC16A8</i>	Sln	moderate	36263	FBgn0033657	VDRC-109464	100	90	0
<i>SLC16A8</i>	Sln	moderate	36263	FBgn0033657	VDRC-4607	90	100	100

Supplementary Data 1: List of human genes associated with advanced AMD by protein altering RV burden testing.

Supplementary Data 2: Distribution of high impact SLC16A8 nonsense and/or missense mediated loss of function rare variants predicted by burden tests to disrupt corresponding MCT3 protein function. Protein domains location in cellular compartments were identified using UNIPROT.