

# SI GUIDE

File Name: Supplementary Information

Description: Supplementary Figures and Supplementary Tables.

Supplementary Data

File Name: Supplementary Data 1

Description: Gene set enrichment analysis (GSEA) input

File Name: Supplementary Data 2

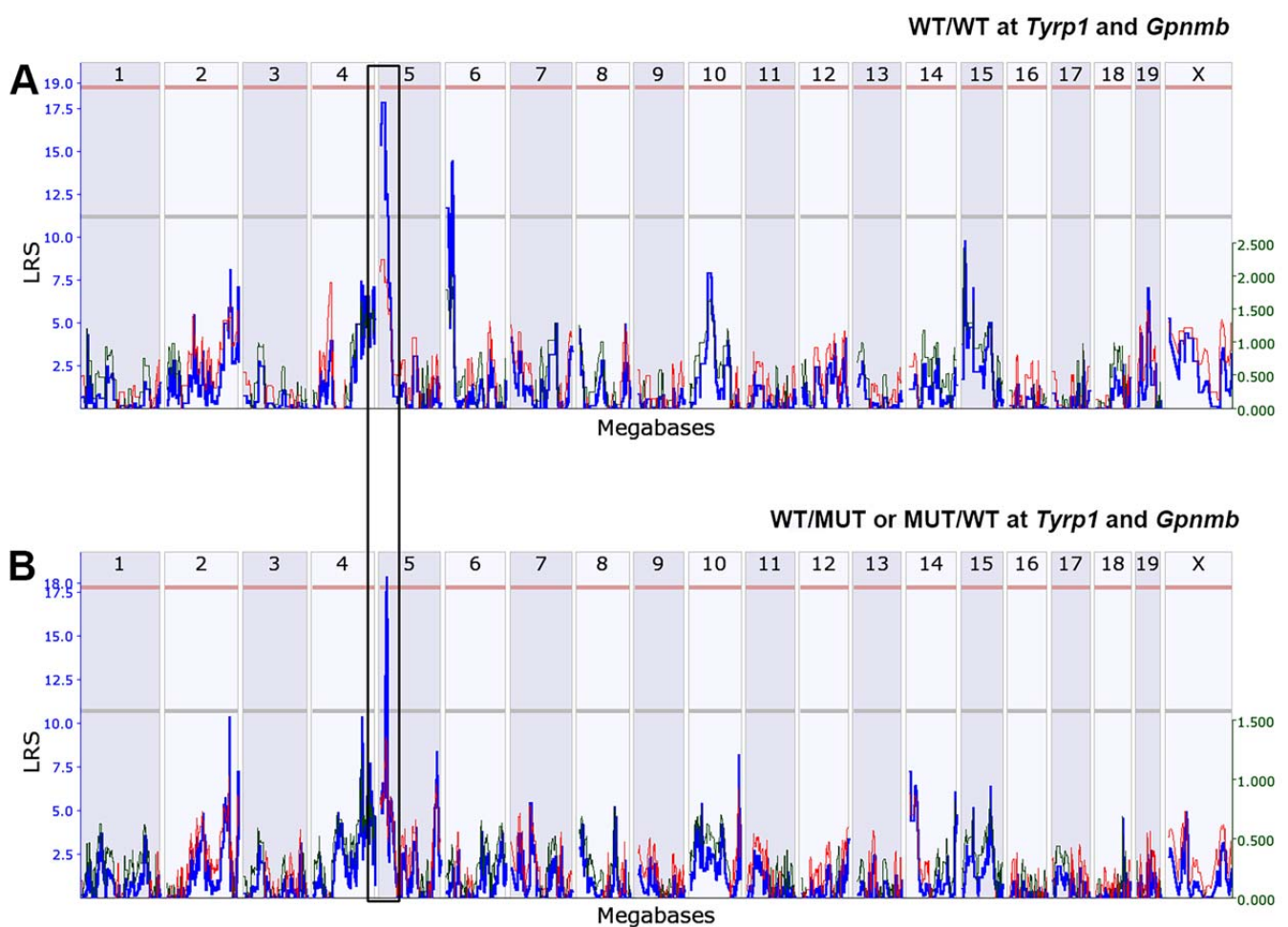
Description: All sequence polymorphisms and structural variants (insertions/deletions) between the reference sequence (B6) and parental strain D2 according to the Sanger Institute's Mouse Genomes Project and the CITG.

File Name: Peer Review File

1 **Supplementary Figure 1:** Genetic interval mapping of IOP revealed a single significant eQTL on  
2 proximal Chr 5 (enclosed in black box) in BXD strains that are WT/WT and WT/MUT or MUT/WT at  
3 *Tyrp1* and *Gpnmb*. The presence of either or both mutations does not influence the location to which  
4 IOP maps.

5 A. Genetic interval mapping using revealed a single significant eQTL on proximal Chr 5 for IOP in  
6 BXD strains that are WT/WT at *Tyrp1* and *Gpnmb*.

7 B. Genetic interval mapping using revealed a single significant eQTL on proximal Chr 5 for IOP in  
8 BXD strains that are lacking both mutations in *Tyrp1* and *Gpnmb* (i.e., WT/MUT or MUT/WT).  
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**Supplementary Table 1:** *Cis*-regulated positional candidates in the chromosome 5 locus arranged by location

<b>Gene Symbol</b>	<b>Description</b>	<b>SNP count</b>	<b>Trait ID in GeneNetwork</b>	<b>Location</b>	<b>Max LRS</b>
<i>Sema3e</i>	Sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3E	67	1427673_a_at	Chr5: 14.2	15.0
<i>Pclo</i>	Presynaptic cytomatrix protein	503	1455373_at	Chr5: 14.8	28.2
<i>Cacna2d1</i>	Calcium channel voltage dependent alpha2/delta subunit 1	1056	1446324_at, 1449999_a_at	Chr5: 15.8	143.0
<i>Gnai1</i>	Guanine nucleotide binding protein, alpha inhibiting 1	14	1454959_s_at	Chr5: 17.7	19.4
<i>Ptpn12</i>	Protein tyrosine phosphatase, non-receptor type 12	19	1455105_at 1422045_a_at 1450479_x_at	Chr5: 20.5	14.8
<i>Gsap</i>	Gamma-secretase activating protein	6	1435596_at	Chr5: 20.8	23.0
<i>Dnajc2</i>	DnaJ (Hsp40) homolog subfamily C member 2	180	1417657_s_at	Chr5: 21.3	28.6
<i>Psmc2</i>	Proteasome 26S subunit ATPase 2	80	1426611_at 1435859_x_at 1443307_at	Chr5: 21.3	31.8
<i>Lhfp13</i>	Lipoma HMGIC fusion partner-like 3	5633	1429592_at	Chr5: 22.6	16.1
<i>Kmt2e</i>	Lysine (K)-specific methyltransferase 2E	230	1432602_at	Chr5: 22.9	43.3
<i>Srpk2</i>	Serine/arginine-rich protein specific kinase 2	1024	1417134_at 1435746_at 1442241_at 1431372_at	Chr5: 23.0	142.6
<i>Tomm7</i>	Translocase of outer mitochondrial membrane 7 homolog	21	1428216_s_at	Chr5:23.3	106.1
<i>Drctnmb1a</i>	Down-regulated by catenin beta 1 activated	748	1450724_at	Chr5: 23.4	15.9
<i>Klhl7</i>	Kelch-like 7	343	1428091_at 1452660_s_at	Chr5: 23.6	31.4
<i>Nupl2</i>	Nucleoporin like 2	123	1456773_at	Chr5: 23.6	28.2
<i>Nos3</i>	Nitric oxide synthase 3	149	1422622_at	Chr5: 23.8	162.2
<i>Abcb8</i>	ATP-binding cassette, sub-family B (MDR/TAP), member 8	133	1423713_at	Chr5: 23.9	31.9

<i>Accn3</i>	Amiloride-sensitive cation channel 3	13	1439983_a_at	Chr5: 23.9	15.7
<i>Slc4a2</i>	Solute carrier family 4 (anion exchanger), member 2	77	1416637_at	Chr5: 23.9	31.3
<i>Faslk</i>	Fas-activated serine/threonine kinase	11	1460635_at	Chr5: 23.9	13.5
<i>Smarca3</i>	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 3	29	1418467_at	Chr5: 24.0	34.9
<i>Crygn</i>	Crystallin, gamma N	67	1425286_at	Chr5: 24.3	15.8
<i>Abcf2</i>	ATP-binding cassette, sub-family F (GCN20), member 2	52	1423863_at	Chr5: 24.6	14.4
<i>Nub1</i>	Nedd8 ultimate buster 1	180	1452777_a_at 1452776_a_at 1420535_a_at 1428439_at	Chr5: 24.7	110.0
<i>Galnt11</i>	UDP-N-acetyl-alpha-D galactosamine:polypeptide N-acetylgalactosaminyltransferase 11	9	1424748_at	Chr5: 24.7	55.5

Note: Whole eye transcript data from BXD strains were used to perform eQTL mapping for genes under the Chr 5 QTL locus. Those genes that had a peak LRS at the location of the gene (*cis* or locally regulated genes) were considered to be *cis*-regulated. Only the probes that hybridized to SNP-free regions of the genome were evaluated.

Key: LRS, likelihood ratio statistic

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**Supplementary Table 2:** Positional candidates in the chromosome 5 locus and scoring

<b>Gene Symbol</b>	<b>Criterion 1</b>	<b>Criterion 2</b>	<b>Criterion 3</b>		<b>Criterion 4</b>	<b>Criterion 5</b>	<b>Criterion 6</b>	<b>Criterion 7</b>	<b>Criterion 8</b>	<b>Score</b>
	Located in Chr 5 QTL peak	<i>Cis</i> -eQTL	Linear correlation with IOP	Partial correlation with IOP	Functional network	Sequence variants in gene	Expression in eye structures associated with IOP	Human GWAS	Biological association with glaucoma or treatment	
<i>Cacna2d1</i>	YES	YES	YES	YES	YES	YES	YES	YES	YES	8
<i>Ptpn12</i>	YES	YES	YES	NO	-	-	-	-	-	3
<i>Sema3e</i>	YES	YES	YES	NO	-	-	-	-	-	3
<i>Abcb8</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Abcf2</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Accn3</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Crygn</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Dnajc2</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Drctnmb1a</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Fastk</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Galnt11</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Gnai1</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Gsap</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Klhl7</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Kmt2e</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Lhfpl3</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Nos3</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Nub1</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Nupl2</i>	YES	YES	NO	-	-	-	-	-	-	2
<i>Pclo</i>	YES	YES	NO	-	-	-	-	-	-	2



<i>Rheb</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Rint1</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Rsbn1l</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Sema3a</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Sema3c</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Sema3d</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Slc26a5</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Speer3</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Speer4c</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Speer4d</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Speer4e</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Speer4f</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Speer7-ps1</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Speer8-ps1</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Tmem60</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Tmub1</i>	YES	NO	-	-	-	-	-	-	-	-	1
<i>Wd486</i>	YES	NO	-	-	-	-	-	-	-	-	1

**Note:** Genes located under the Chr 5 QTL peak were scored sequentially based upon our 8 step selection criteria. If a gene did not fulfill a criterion (indicated by a dash), it was eliminated as a gene candidate for modulating IOP.

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**Supplementary Table 3: Effect of SNPs in *Cacna2d1* gene locus in NEIGHBORHOOD POAG case/control GWAS and multi-ethnic meta-analysis IOP GWAS**

<b>NEIGHBORHOOD POAG case/control GWAS (Bailey et al., Nature Genetics, 2016 Feb;48(2):189-94.</b>											
CHR	BP	SNP	Allele 1	Allele 2	Freq1	Effect (beta)	StdErr	OR	p-value	n-studies	Direction
7	82011270	7:82011270:AATAC	d	r	0.2127	-0.1426	0.0432	0.86710084	0.0009616	8	-----
7	82011353	rs2299184	a	g	0.7798	0.1359	0.0413	1.145567331	0.001009	8	+++++++
7	82011262	7:82011262:TATAA	d	r	0.2226	-0.1328	0.042	0.875640203	0.001581	8	-----
7	82011505	rs2299185	a	g	0.2284	-0.1296	0.0412	0.878446739	0.001651	8	-----
7	82011839	rs6955149	a	g	0.2264	-0.1273	0.0413	0.880469492	0.002054	8	-----
7	82013761	rs11971283	c	g	0.1468	-0.1344	0.049	0.874240299	0.006075	8	----+--
7	82011004	7:82011004:G_GA	i	r	0.1462	-0.132	0.0488	0.876340995	0.006847	6	+---+---
7	82013521	rs11982475	t	c	0.8531	0.1301	0.0486	1.138942272	0.007447	8	+++++++
7	82010067	rs62465968	c	g	0.1395	-0.1293	0.0495	0.878710313	0.009054	6	+---+---
7	82013917	7:82013917:TGAA_	d	r	0.1425	-0.1253	0.0503	0.882232193	0.01285	8	----+---
7	81976258	rs117054034	t	c	0.9456	0.2484	0.1032	1.281972619	0.01606	3	?+++????
7	81971354	rs149421676	t	c	0.0543	-0.2476	0.1033	0.78067215	0.01653	3	?---????
7	82013962	7:82013962:G_GA	i	r	0.1515	-0.1202	0.0504	0.88674307	0.01699	8	+---+---
7	81799213	rs38541	a	c	0.722	0.0905	0.0398	1.094721508	0.02298	7	?+-----
7	81668864	rs73151509	t	c	0.0623	0.1694	0.0767	1.184593882	0.02712	7	?+++++++
7	81799650	rs38542	t	g	0.7164	0.0841	0.0392	1.087737662	0.03175	7	?+-----
7	82013724	rs10274659	t	c	0.7589	0.086	0.0403	1.089806328	0.03297	8	-+-----
7	81713810	rs73151543	t	c	0.9045	-0.1835	0.0862	0.832351876	0.03337	3	?--?????
7	81849719	rs146555498	t	c	0.9482	-0.2183	0.1063	0.80388424	0.04008	2	?-+?????
7	81806942	rs3919483	t	g	0.7259	0.0817	0.0399	1.085130222	0.04049	7	?+-----
7	81737230	rs59891073	c	g	0.086	-0.1259	0.062	0.881703013	0.04219	8	-----+-
7	82009164	rs10954678	c	g	0.5887	0.0696	0.0343	1.072079264	0.04267	6	+++++---
7	82009771	rs10808299	a	c	0.4139	-0.0689	0.0341	0.933420017	0.04328	6	-----++
7	81739755	rs78203609	t	c	0.9141	0.124	0.0614	1.132015871	0.04338	8	++++-++
7	81736414	rs6950805	a	t	0.9133	0.125	0.0621	1.133148453	0.04409	8	++++-++
7	81741120	rs77007284	a	g	0.9141	0.1229	0.0613	1.130771338	0.04482	8	++++-++
7	81736679	rs78489742	a	c	0.0868	-0.1242	0.062	0.883203183	0.04515	8	-----+-
7	81736674	rs77787735	a	g	0.9132	0.1242	0.062	1.132242297	0.04518	8	++++-++
7	81736521	rs74521466	c	g	0.0868	-0.1242	0.062	0.883203183	0.04523	8	-----+-
7	81736895	7:81736895:AAAT_	d	r	0.0868	-0.124	0.0619	0.883379841	0.04526	8	-----+-
7	81736865	rs77450603	a	t	0.9132	0.124	0.0619	1.132015871	0.04531	8	++++-++
7	81737600	rs60993894	a	g	0.0867	-0.1236	0.0617	0.883733263	0.04532	8	-----+-
7	81736729	rs74484242	a	c	0.0868	-0.124	0.062	0.883379841	0.04535	8	-----+-
7	81738857	rs2097913	t	c	0.9137	0.1225	0.0612	1.13031912	0.04535	8	++++-++
7	81738190	rs79083404	a	g	0.9133	0.1231	0.0615	1.130997515	0.04537	8	++++-++
7	81738147	rs75530395	c	g	0.0867	-0.1231	0.0615	0.884175241	0.04546	8	-----+-
7	81738919	7:81738919:TA_T	d	r	0.0863	-0.1224	0.0612	0.88479438	0.04546	8	-----+-
7	81738984	rs75681972	a	g	0.0868	-0.1223	0.0612	0.884882864	0.04565	8	-----+-
7	81737040	rs147041350	t	c	0.0868	-0.1237	0.0619	0.883644895	0.04573	8	-----+-
7	81739027	rs78816329	t	c	0.9132	0.1223	0.0612	1.130093079	0.04577	8	++++-++
7	81739258	rs77959549	a	g	0.9132	0.1221	0.0612	1.129867083	0.04611	8	++++-++
7	81738903	rs2097914	t	c	0.0869	-0.1214	0.0612	0.885679617	0.04712	8	-----+-
7	82008631	7:82008631:T_TG	i	r	0.4448	-0.0669	0.0338	0.935288726	0.04759	6	-----++
7	81745621	7:81745621:TA_T	d	r	0.0859	-0.1203	0.0612	0.8866544	0.04927	8	-----+-



**Multi-ethnic meta-analysis IOP (Hysi et al., Nature Genetics, 2014 Oct;46(10):1126-30.**

CHR	BP	SNP	Allele 1	Allele 2	Freq1	Effect (beta)	StdErr	p-value	q_p-value	i2	n-studies	Direction
7	82011353	rs2299184	a	g	0.2024	0.0188	0.0312	0.546435	0.354773	0.08504	17	++++?+++++----
7	82011505	rs2299185	a	g	0.7913	-0.0108	0.0305	0.723717	0.268008	0.15845	17	----?+-----+----
7	82011839	rs6955149	a	g	0.7958	-0.0121	0.0310	0.695687	0.324138	0.11091	17	----?+-----+----
7	82013761	rs11971283	c	g	0.8698	-0.0224	0.0377	0.552393	0.520873	0	17	----?+-----+----
7	82013521	rs11982475	t	c	0.8744	-0.0213	0.0384	0.579035	0.367274	0.07444	17	---?+-----+----
7	82013724	rs10274659	t	c	0.7754	0.0026	0.0296	0.93056	0.225233	0.19556	17	---?+-----+----
7	82009164	rs10954678	c	g	0.4292	0.0091	0.0245	0.709253	0.295265	0.13260	18	+++++-----+----
7	82009771	rs10808299	a	c	0.5741	-0.0147	0.0244	0.548053	0.265419	0.15734	18	-----+-----+----