<u>Supporting Information for Deslauriers et al., 2023</u>

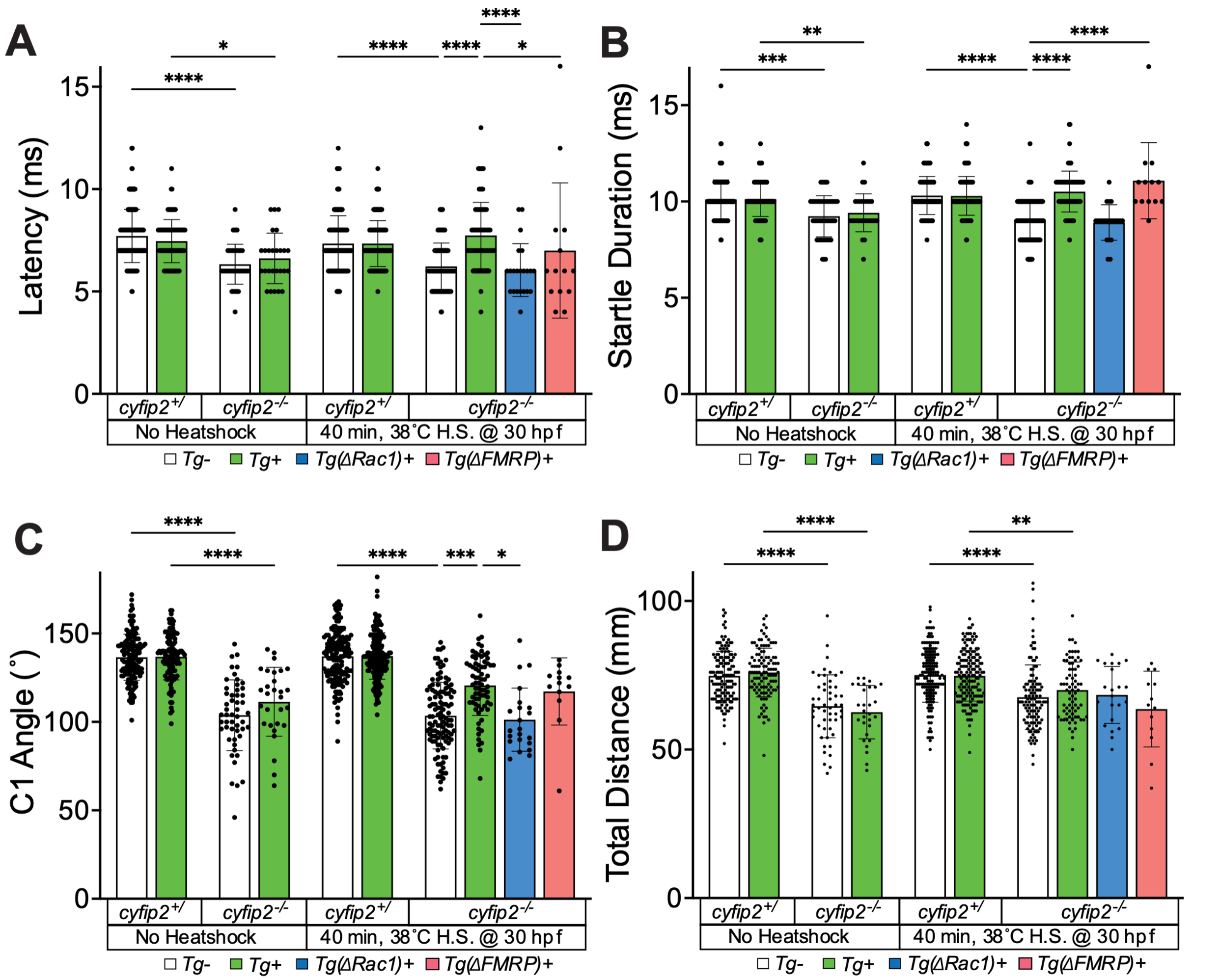

Figure S1. Restoring Cyfip2 at 30 hpf rescues startle latency and duration phenotypes in *cyfip2* mutants. (A) Average startle latency (milliseconds; ms) of larvae shown in Figure 1 at 53.6 dB for *cyfip2* sibling (+/) and mutant (+/+) larvae expressing either normal (*Tg*+; green), Rac1- (Δ*Rac1*+; blue) or FMRP/eIF4E- (Δ*FMRP*+; pink) binding deficient versions of Cyfip2-EGFP. Comparisons were made to both non-transgenic (*Tg*-) and non-heatshocked controls. All indices (mean ± SD) compared using a Kruskal-Wallis test with Dunn's multiple comparisons correction; p* < 0.05; p**** < 0.0001. (B) Average startle duration (ms) of larvae shown in Figure 1 at 53.6 dB. Comparisons made as previously. p** < 0.01; p*** < 0.001; p**** < 0.0001. (C) Average initial turn (C1) angle (degrees) of larvae shown in Figure 1 at 53.6 dB. Comparisons made as previously. p* < 0.05; p*** < 0.001; p**** < 0.0001. (D) Total distance traveled (mm) of larvae shown in Figure 1 at 53.6 dB. Comparisons made as previously. p** < 0.01; p**** < 0.0001.

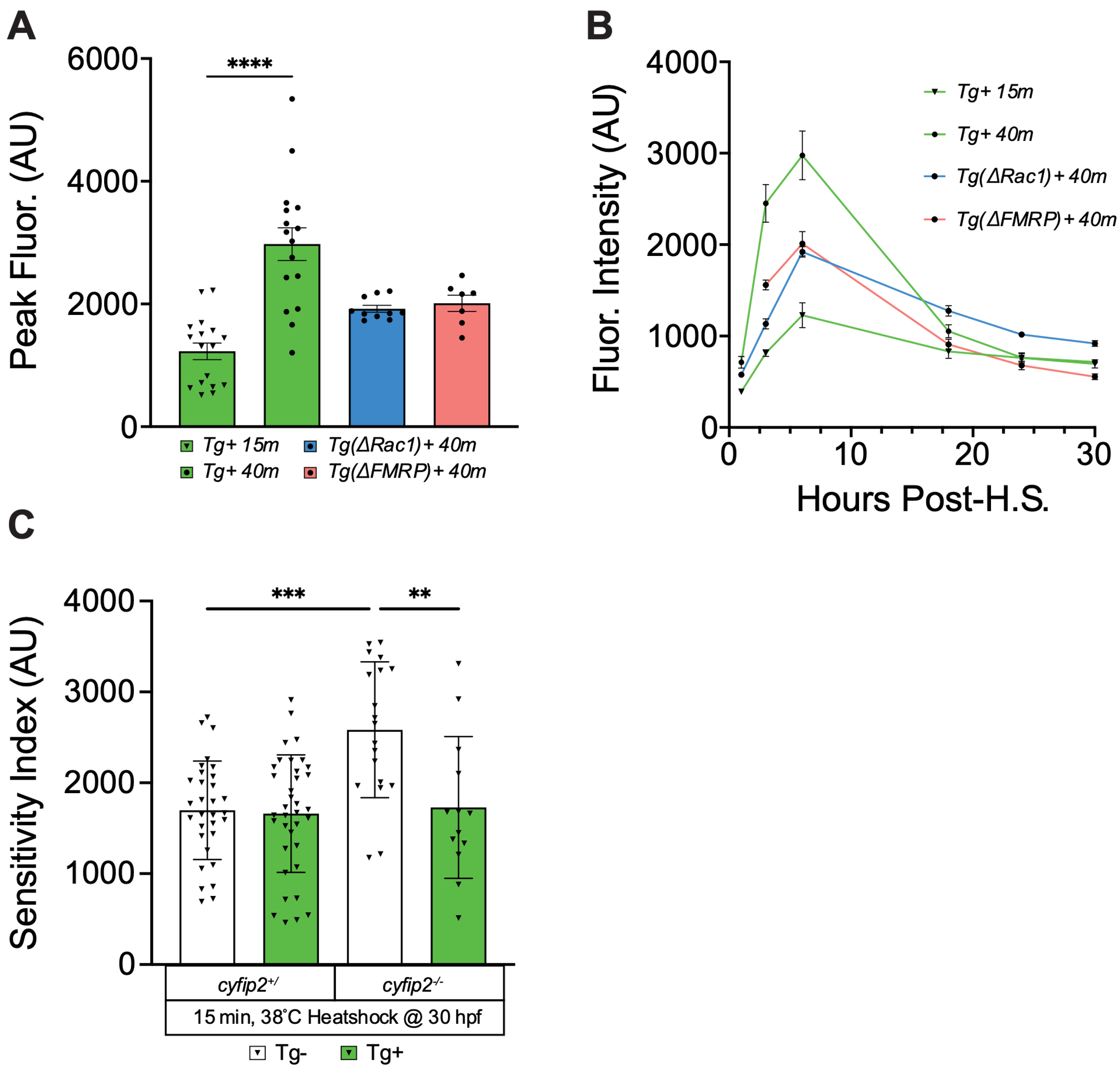

Figure S2. Rac1 and FMRP/eIF4E interactions are critical to establishing the innate acoustic startle threshold. (A) Peak fluorescence, at approximately 6 hours post-heatshock of *Tg(hsp70:cyfip2-EGFP)*+, *Tg(hsp70:cyfip2-(ΔRac1)-EGFP)*+, and *Tg(hsp70:cyfip2-(ΔFMRP)-EGFP)*+ larvae following either a 15- or 40-minute, 38˚C heatshock at 30 hpf. Measurements taken correspond to body specific expression, excluding saturating transgenic expression in the eye and auto fluorescence in the yolk sac, using FIJI image analysis software on lateral view images at the 6-hour post heatshock time point. *Tg*+ 15 min heatshock (green bar, filled triangles), *Tg*+ 40 min heatshock (green bar, filled circles), *Tg*(*ΔRac1*)+ 40 min heatshock (blue bar, filled circles), and Tg(*ΔFMRP*)+ 40 min heatshock (pink bar, filled circles). Peak fluorescence values (mean ± SEM) were compared using a Kruskal-Wallis test with Dunn's multiple comparisons correction; p**** < 0.0001. (B) Fluorescence intensity (mean ± SEM) of *Tg(hsp70:cyfip2-EGFP)*+, *Tg(hsp70:cyfip2-(C179R)-EGFP)*+, and *Tg(hsp70:cyfip2-(K723E)-EGFP)*+ larvae following either a 15- or 40-minute, 38˚C heatshock at 30 hpf. Measurements taken as in S2A at 1, 3, 6-, 18-, 24-, and 30-hours post heatshock. Colors as in S2A. (C) Sensitivity indices for 5 dpf *cyfip2* sibling (+/) and mutant (-/-) larvae, following a 15-minute heatshock at 30 hpf to express normal (*Tg*+) Cyfip2-EGFP. Comparisons were made both between transgene conditions and between genotypes. All indices (mean ± SD) compared using a Kruskal-Wallis test with Dunn's multiple comparisons correction; p** < 0.01; p*** < 0.001.

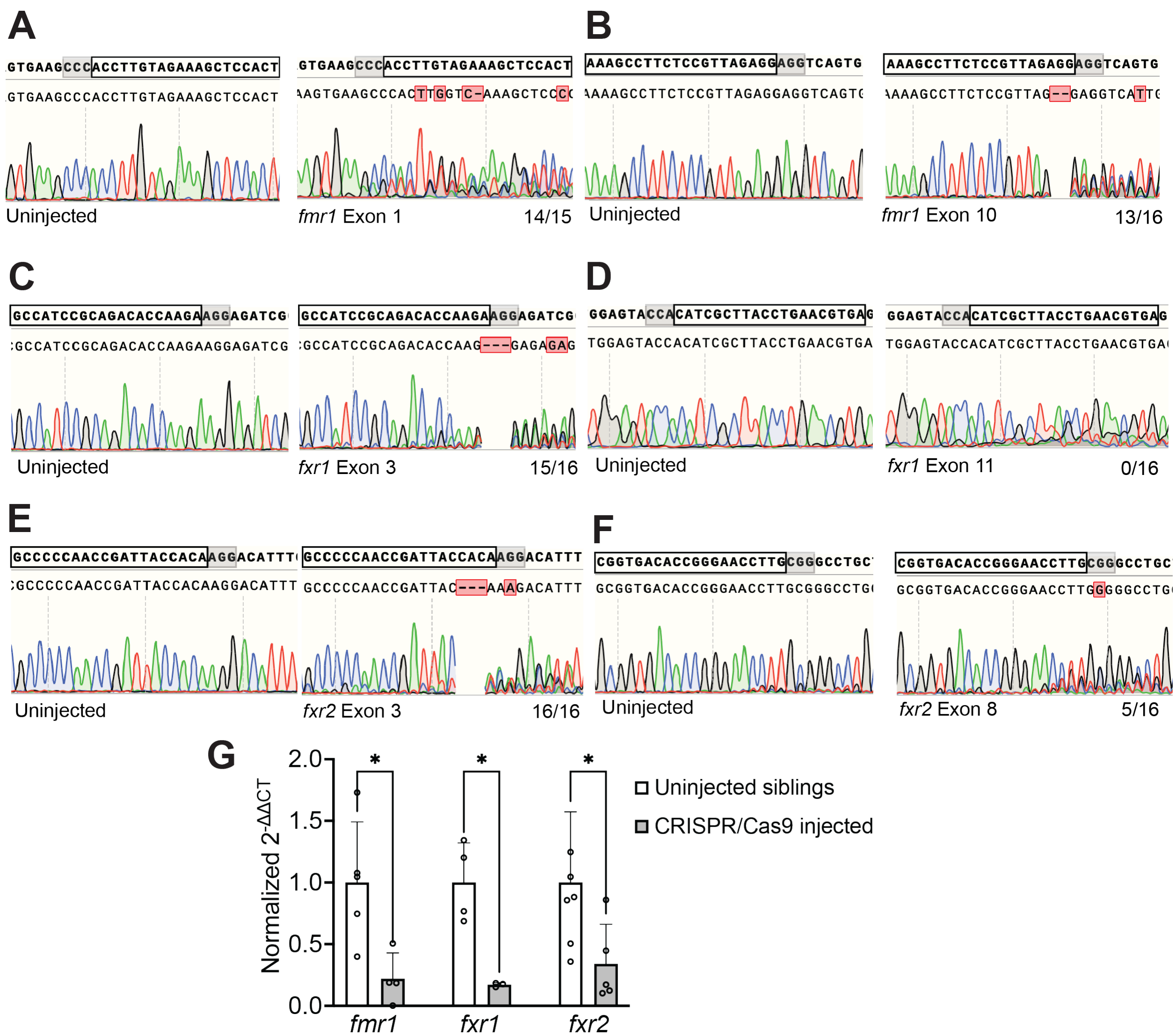

Figure S3. FMR1, FXR1 and FXR2 CRISPR gRNAs induce mutations at their target sites. Sanger sequencing chromatogram results for uninjected and CRISPR/Cas9-injected sibling larvae. Target site outlined above each chromatogram by black box, PAM site highlighted in gray, and fractions indicated editing efficiency (# of individuals with edits / total # analyzed). (A) *fmr1* exon 1 target site, (B) *fmr1* exon 10 target site, (C) *fxr1* exon 3 target site, (D) *fxr1* exon 11 target site, (E) *fxr2* exon 3 target site, (F) *fxr2* exon 8 target site. (G) qPCR results showing knockdown of *fmr1, fxr1,* and *fxr2* in CRISPR/Cas9-injected larvae compared to uninjected siblings.

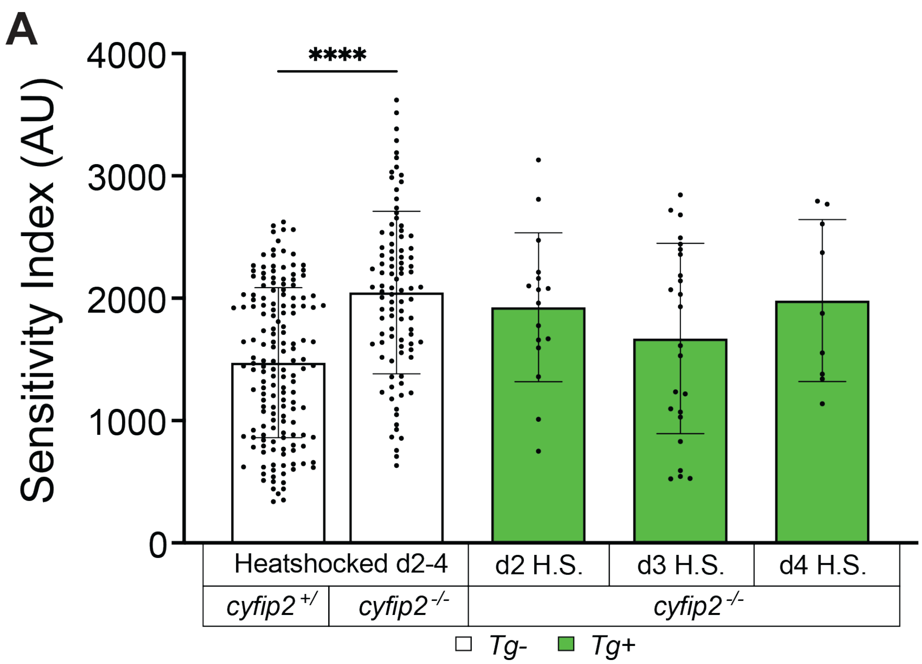

Figure S4. Cyfip2 fails to rescue mutant hypersensitivity when expressed after 30 hpf. (A) Sensitivity indices for 5 dpf *cyfip2* sibling (+/) and mutant (-/-) larvae, following a 40-minute, 38°C heatshock at 2, 3 or 4 dpf to express normal (*Tg*+) Cyfip2-EGFP. Comparisons were made both between genotypes, and within genotype by condition. All indices (mean ± SD) compared using a Kruskal-Wallis test with Dunn's multiple comparisons correction; p**** < 0.0001.

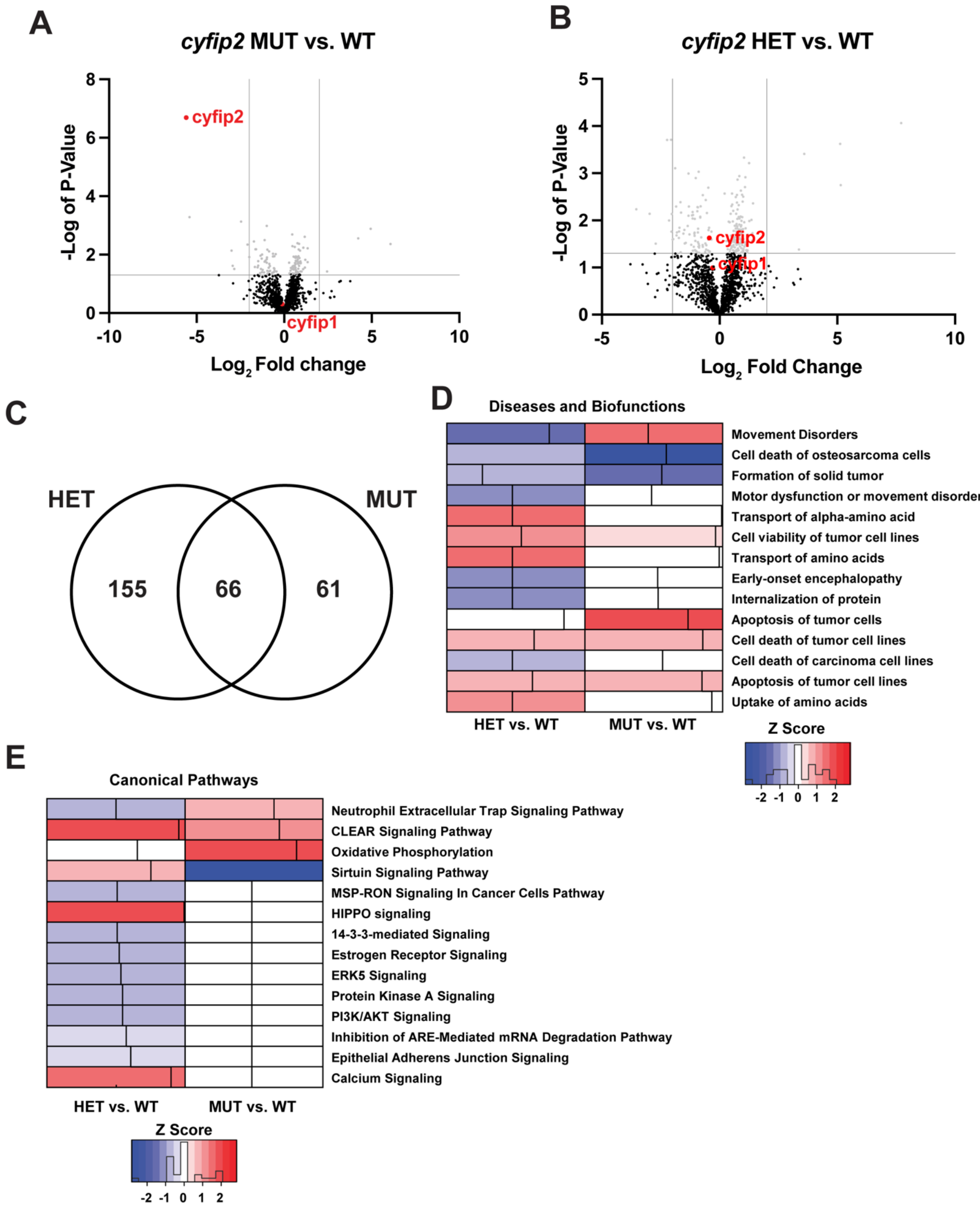

Figure S5. Loss of Cyfip2 causes substantial changes to the proteome. (A-B) Volcano plot highlighting the differentially expressed proteins (DEPs) in *cyfip2* mutants (A) and heterozygotes (B) compared to wildtypes. Gray dots indicate the significantly dysregulated proteins ($p \leq 0.05$) while the black dots represent non-significantly ($p \geq 0.05$) regulated proteins compared to the control group (*cyfip2* wildtype). Red dots highlight Cyfip1 and Cyfip2 proteins. (C) Venn diagram shows the overlap of DEPs between both genotype groups. (D-E) Heat map displaying the impacted diseases and biological functions (D) and canonical pathways (E) identified using IPA to compare *cyfip2* heterozygotes (HET) and mutants (MUT) to wildtypes (WT). The red- or blue-colored rectangles indicate the z-score activities, where red shading indicates predicted activation and blue shading indicates predicted inhibition.

Table S1. Non-branched actin regulation does not influence acoustic startle regulation.

<table>
<tr><th rowspan="2">Compound</th><th rowspan="2">Concentration (μM)</th><th colspan="5">Incubation Period</th></tr>
<tr><th>30 min.</th><th>1 hr.</th><th colspan="3">16 hr.</th></tr>
<tr><td rowspan="2">SMIFH2</td><td>1</td><td>79% of Control, p > 0.99</td><td>110.13% of Control, p > 0.99</td><td colspan="3">97.53% of Control, p > 0.99</td></tr>
<tr><td>5</td><td>69.45% of Control, p = 0.1598</td><td>109.36% of Control, p > 0.99</td><td colspan="3">Lethal</td></tr>
<tr><td rowspan="2">IPA-3</td><td>20</td><td>75.64% of Control, p = 0.5816</td><td>134.28% of Control, p = 0.3003</td><td colspan="3">Lethal</td></tr>
<tr><td>50</td><td>82.92% of Control, p > 0.99</td><td>147.04% of Control, p = 0.2631</td><td colspan="3">Lethal</td></tr>
<tr><td rowspan="3">GSK429286</td><td rowspan="3">100</td><td rowspan="3">93.11% of Control, p > 0.99</td><td rowspan="3">-</td><td colspan="3">62.37% of Control, p*** = 0.0003</td></tr>
<tr><td>cyfip2(+/+)</td><td>cyfip2(+/-)</td><td>cyfip2(-/-)</td></tr>
<tr><td>62.23% of Control, p = 0.6254</td><td>78.17% of Control, p > 0.99</td><td>76.31% of Control, p > 0.99</td></tr>
</table>

Startle indices comparisons for all tested concentrations and incubation periods of non-branched actin nucleation (SMIFH2) and actin severing pathway antagonists (IPA-3; GSK429286). Significant differences ($p < 0.05$) between treatment groups and controls are listed (**bold**), using a Kruskal-Wallis test with Dunn's multiple comparisons correction.

Table S2. Cyfip2-dependent branched actin polymerization regulates the acoustic startle threshold.

Compound	Concentration (μM)	Incubation Period (30 minutes)	
		cyfip2$^{+/+}$	*cyfip2*$^{+/p400}$
CK-666	5	58.42% of DMSO control, p > 0.99	110.49% of DMSO control, p > 0.99
	10	78.97% of DMSO control, p > 0.99	120.27% of DMSO control, p > 0.99
	20	128.33% of DMSO control, p > 0.99	154.19% of DMSO control, p = 0.3823
	35	165.57% of DMSO control, p = 0.7021	203.72% of DMSO control, p = 0.1073
	50	**341.10% of DMSO control, p*** = 0.0002**	**421.21% of DMSO control, p**** < 0.0001**
CK-869	5	110.31% of DMSO control, p > 0.99	115.61% of DMSO control, p > 0.99
	7.5	93.81% of DMSO control, p > 0.99	84.02% of DMSO control, p > 0.99
	10	180.76% of DMSO control, p = 0.6087	**266.15% of DMSO control p*** = 0.0005**
	20	153.06% of DMSO control, p = 0.7128	**289.66% of DMSO control, p**** < 0.0001**
	35	**251.53% of DMSO control, p*** = 0.0006**	**367.73% of DMSO control, p**** < 0.0001**
	50	**244.93% of DMSO control, p* = 0.0338**	**339.15% of DMSO control, p**** < 0.0001**

Startle indices comparisons for all tested concentrations of Arp2/3 inhibitors (CK-666 & CK-869) used in this work. Significant differences ($p < 0.05$) between treatment groups and controls are listed (**bold**), using a Kruskal-Wallis test with Dunn's multiple comparisons correction.

Table S3. Research animals/strains used in this work.

Experimental Models	Origin	ZFIN ID
Zebrafish: *cyfip2*^{p400}	Marsden et al., 2018	ZDB-ALT-180305-9
Zebrafish: *Tg(hsp70:cyfip2-EGFP)* line 14	Marsden et al., 2018	ZDB-ALT-180309-1
Zebrafish: *Tg(hsp70:cyfip2-(C179R)-EGFP)*	This Paper	ZDB-ALT-220719-3
Zebrafish: *Tg(hsp70:cyfip2-(K723E)-EGFP)*	This Paper	ZDB-ALT-220719-4

Table S4. Oligonucleotide Primers used in this work.

Primers	Sequence (5' -> 3')	Ref #
rhAmp *cyfip2*^{p400} Allele Specific #1	ACCATCTGCTACACAGGTTArUACTG	192743289; This Paper
rhAmp *cyfip2*^{p400} Allele Specific #2	CCATCTGCTCACACAGGTTTrUACTG	192743288; This Paper
rhAmp *cyfip2*^{p400} Locus Specific	GCTGCATTTTCATTCCTCTTCTCTCTTTrC TCTC	192743287; This Paper
cyfip2^{p400} dCAPS Forward	CAAAGTCTTGCTGCGGATAAAAG	Marsden et al., 2018
cyfip2^{p400} dCAPS Reverse	CTGCACCATCTGCTCACACAAATT	Marsden et al., 2018
cyfip2^{p400} Reverse	CTCTGAGCGCCAGGTCAAAC	This Paper
GFP Forward	GACGTAAACGGCCACAAGTT	Marsden et al., 2018
GFP Reverse	GAACTCCAGCAGGACCATGT	Marsden et al., 2018
cyfip2 Seq1F	TGGAGGTGATCCCAGGTTAT	This Paper
cyfip2 Seq2F	GGTCTGGACAGTCAGAAGTCTGAT	This Paper
cyfip2 Seq3F	CCCCCTAATGACCCTTGTCTG	This Paper
cyfip2 Seq4F	GCCCTCACAAAATTCAAGAAGCAG	This Paper
cyfip2 Seq5F	GCCAACCACAACGTCTCTGC	This Paper
cyfip2 Seq6F	AGAGACTCGGGACTCCACAG	This Paper
cyfip2-C179R Fwd	GAACATGAAGcgcAGTGTAAAAAATG	This Paper
cyfip2-C179R Rev	TTCAGTTCGTCCAGCACA	This Paper
cyfip2-K723E Fwd	CCTCCTAGACgAACGCTTCCG	This Paper
cyfip2-K723E Rev	ACACTTCCAGCCATTGCTTT	This Paper

Table S5. List of all CRISPR-Cas9 guide RNAs used in this work.

CRISPR gRNA	Sequence (5’ -> 3’)	Target Exon	Ref #
fmr1 gRNA1	AGTGGAGCTTTCTACAAGGTGGG	Exon 1	This Paper
fmr1 gRNA2	AAAGCCTTCTCCGTTAGAGGAGG	Exon 10	This Paper
fxr1 gRNA1	GCCATCCGCAGACACCAAGAAGG	Exon 3	This Paper
fxr1 gRNA2	TCACGTTCAGGTAAGCGATGTGG	Exon 11	This Paper
fxr2 gRNA1	GCCCCCAACCGATTACCACAAGG	Exon 3	This Paper
fxr2 gRNA2	CGGTGACACCGGGAACCTTGCGG	Exon 8	This Paper

Table S6. List of all pharmacologic compounds used in this work.

Compound	Molecular Target	CAS #	Manufacturer
CK-869	Arp2/3 antagonist	388592-44-7	Sigma-Aldrich
CK-666	Arp2/3 antagonist	442633-00-3	Sigma-Aldrich
MK-801	NMDA receptor antagonist	77086-22-7	Sigma-Aldrich
SMIFH2	Formin antagonist	340316-62-3	Fisher/Tocris
IPA-3	p21-associated kinase 1 (Pak1) antagonist	42521-82-4	Fisher/Tocris
GSK429286	Rho associated coiled coil containing kinase (ROCK) antagonist	37-261-R	Fisher/Tocris
N-phenylanthranilic acid (NPAA)	Chloride (Cl^-) channel antagonist	91-40-7	Sigma-Aldrich
Meclofenamic Acid (MA)	Potassium (K^+) channel antagonist	6385-02-0	Sigma-Aldrich
Phenoxybenzamine (POBA)	Alpha-adrenergic receptor/calmodulin antagonist	62-92-3	Sigma-Aldrich
Etazolate (ETAZ)	Phosphodiesterase 4 (PDE-4) inhibitor	35838-58-5	Sigma-Aldrich
NSC23766	Rac1 antagonist	1177865-17-6	Fisher/Tocris
BMS204352	K^+ channel agonist/GABA-A receptor inhibitor	187523-35-9	Sigma-Aldrich
Muscimol	GABA-A receptor agonist	2763-96-4	Sigma-Aldrich
Baclofen	GABA-B receptor agonist	1134-47-0	Sigma-Aldrich

Table S7. All differentially expressed proteins for the *cyfip2* heterozygous group (HET).

HET vs WT		
Uniprot IDs	**P value**	**Fold change**
A0A2R8RZ61	8.66E-05	7.71476
Q7ZUM0	0.000196	-2.05927
E7F354	0.000197	-2.2296
B8A4S4	0.000238	5.11688
E9QFS3	0.000389	3.59577
B0R1C4	0.000465	1.03931
F1QT45	0.000613	1.25343
B7ZD02	0.000781	-1.88612
Q6DGY7	0.000926	-0.88896
A0A0R4IUZ8	0.001019	-1.31951
B8JLV7	0.001154	0.83548
Q6NUT5	0.00122	1.09879
Q7ZTS3	0.001266	-1.0092
Q6PD99	0.001361	0.762697
Q7ZVN9	0.001786	5.1448
Q6DRC1	0.001975	1.0806
Q804G7	0.002031	-0.479638
Q7ZUU5	0.002345	0.905212
Q7ZYX4	0.00269	0.210278
Q1JPZ7	0.002694	0.527177
X1WD74	0.002859	0.957053
Q5TZI1	0.002897	0.740421
F8W4Q9	0.002915	-0.715132
B0S5S9	0.003161	1.00585
Q6DBT9	0.003202	0.686377
Q6PC82	0.003687	-0.591262
Q7SYE1	0.003993	0.981394
Q7SZC9	0.004124	-1.66381
Q6PBQ4	0.004184	0.73479
E9QCA9	0.004355	1.42082
Q804C3	0.004622	0.54113
F1QUW4	0.004741	0.814594
A0A2R8QJJ5	0.005004	0.500837
A8WG05	0.005058	-0.800756
B3DJH0	0.005072	-1.30422
Q6IQQ0	0.005082	-1.84776
Q6DGY4	0.005253	-0.93853
Q6AXJ2	0.005264	-0.920406
Q7SXQ3	0.00584	-3.53452
Q90ZM2	0.005852	0.760472
B8JL35	0.006264	0.576817
Q6P027	0.006418	-0.948851
Q7ZV04	0.006652	-1.14902
Q6DG71	0.006826	-1.63392
B0S754	0.006975	-0.540343
Q90ZM2	0.007239	-2.96893
Q803J3	0.007245	0.474805
E9QE47	0.007272	0.700467
Q801M0	0.0073	-2.03043
B2GSH6	0.007691	-1.12915
Q6P2T0	0.007844	-1.1738
Q6IQ97	0.007976	-1.31667
F1QMZ6	0.00826	0.892981
Q6PBX8	0.008349	-0.822399
A5WV37	0.008488	0.811984
Q1LYP4	0.008545	0.962926
Q6P959	0.008691	-0.820321
Q6PC34	0.009116	0.845695
Q90WX5	0.009118	-1.14349
Q6TGY8	0.009261	0.751429
Q9I9E5	0.009283	-1.0516
F1RAV6	0.009806	1.35714
P17561	0.010064	-2.14753
A0A8M9P7D1	0.010204	0.927811
Q6PYX3	0.010331	1.26646
Q567V5	0.010536	0.564191
Q7SZD2	0.010652	0.391492
Q4G5V7	0.010925	1.0493
D7RVS0	0.010925	0.429207
B0S553	0.011947	0.717731
Q6P0H1	0.012309	0.834073
Q5XJT7	0.012654	0.921172
F6NK19	0.012961	0.682257
G4XPM3	0.013015	0.648204
Q5U3R4	0.013168	-1.35827
Q6NWC6	0.01337	0.753258
Q6DBW5	0.013479	0.904397
Q7SY50	0.014323	-1.70132

A0A8M1P182	0.01433	-0.44557
Q5SNP7	0.014698	1.10813
Q6NWH2	0.01483	0.689758
F1Q9I7	0.014938	0.752187
B8A518	0.015037	-0.91227
Q5U369	0.015386	0.996881
Q6PHE5	0.01539	0.997368
Q503N6	0.015597	0.834698
F1QCR7	0.015701	0.913886
E7FC95	0.015893	-1.49379
Q502L5	0.015932	0.819911
Q6DGN1	0.016077	-0.470161
A0A2R8RKK2	0.016391	0.913101
F1QDE7	0.016648	0.596429
Q803G7	0.016773	0.605661
Q5XJP7	0.01719	0.709815
F1Q5B8	0.017246	-1.72005
Q8JHH3	0.017291	-2.04476
O42248	0.017431	-0.343451
F8W4X0	0.01804	-1.81403
A0A8M1NE64	0.018124	-0.923081
Q66L49	0.018135	0.948545
Q6NWK7	0.018146	-1.06605
Q7ZUD6	0.018215	0.835702
Q6RKB0	0.018704	1.39215
Q5U3E5	0.019095	0.912415
Q8JH72	0.019139	-1.06957
Q4VBK0	0.0192	-1.53365
Q7T341	0.019305	0.711135
F1R3D3	0.019784	-1.28123
B2GS26	0.019955	0.786676
A4FUK1	0.020276	1.20295
Q6PFU0	0.020812	-1.82557
Q1LVM0	0.021127	0.479118
F8W4E2	0.021296	1.22339
Q6DGT8	0.021298	-1.0666
Q7T296	0.021559	0.559891
Q8UVZ4	0.021686	0.706464
CON__P35527	0.021755	0.819402
Q6DGS3	0.02185	0.552607
Q9I8U8	0.022048	1.22729
Q803L1	0.02245	0.679484
Q5D018	0.022475	0.341981
F1QII8	0.022878	0.595292
Q566S4	0.022946	-0.781161
A7E2L8	0.023575	-1.72753
A5A5E1	0.023603	-0.437627
E7F5G8	0.02374	0.85531
E7FGW2	0.023919	0.839511
X1WET9	0.024128	0.60789
E7FBU7	0.024738	0.809415
Q6IQK3	0.024859	-0.379822
F6PBX0	0.024882	1.01335
Q66IB3	0.024931	-1.97329
Q08B95	0.025284	0.607609
Q803H5	0.025368	-0.478846
Q6P3J5	0.02548	-0.342405
Q6NWI7	0.025516	-1.99737
F1QKW3	0.025541	0.888355
B0R193	0.025913	0.675828
Q6AXJ2	0.026561	0.483077
E7FFL3	0.026751	0.683697
Q6PBM9	0.026821	0.365942
F5HSE3	0.026872	1.37693
Q6PHJ1	0.027168	-1.02579
A5HLY6	0.027238	0.537177
Q6P0H6	0.027449	0.285213
Q0P408	0.028206	0.632262
A4FVL3	0.028395	0.572223
Q32LR2	0.02873	0.911809
Q6TNV0	0.028779	0.63668
A7MBY4	0.028987	-0.920881
U3JAA1	0.029106	0.78484
F1QPP6	0.029141	1.07232
Q5TZ35	0.029741	0.74973
E7EZE6	0.030136	-1.43541
A0A0R4IP12	0.030347	0.479474
A2CEA9	0.030526	0.936813
Q6PBJ9	0.030622	0.893379
F1QTW8	0.030716	0.701908

Q6Q420	0.030796	0.848694
Q9DGR5	0.030806	-1.48242
Q7T356	0.03086	-0.602564
Q7ZWJ4	0.031077	-2.71144
Q7SX97	0.031287	0.821599
Q08BY9	0.031438	0.713483
Q6DC80	0.031539	-0.88979
A4QN66	0.031829	0.81361
Q568L3	0.03283	1.09307
E7F8M1	0.032937	-1.20617
Q7ZUT3	0.032972	0.722386
Q0R680	0.033196	-0.724326
Q5U3G0	0.033329	0.96201
Q6DBW7	0.033451	0.598706
Q802X5	0.03365	-0.566586
Q5RHR9	0.034789	-0.861663
F6P9B5	0.035034	0.506165
A5A4L9	0.035657	0.528285
Q503D5	0.03579	0.861811
Q7T2P3	0.035996	-0.899419
Q1LVE8	0.036044	1.05433
A2RUZ3	0.036188	0.565196
F8W2Z3	0.036363	-0.709115
A7E2K5	0.036366	-1.0977
F1Q8W8	0.037522	0.642242
C5IG48	0.037925	-0.867814
Q6DGE9	0.038805	0.494877
Q8UUX9	0.038886	0.923285
O42271	0.03978	0.776283
Q1LVQ8	0.040416	0.993941
Q6IQI2	0.040487	1.01537
Q6P6E0	0.040686	0.347212

Q5XIZ4	0.04114	0.773116
Q6NWJ2	0.041379	-0.573219
A8E7T1	0.041641	3.37243
Q6PBW7	0.042433	0.446904
X1WCE0	0.042587	1.13429
F1QKX8	0.042624	0.709089
E9QG51	0.042638	-1.04685
Q5U3U1	0.042803	1.00916
A0A8M9PPE1	0.043044	0.56731
B2GPU7	0.043045	-1.04725
Q5U396	0.043053	1.18915
E9QFU8	0.043186	0.804141
Q1LWH1	0.043812	-0.489061
Q4G5T8	0.043931	1.14432
Q9IAB6	0.043991	0.986611
Q9MIY5	0.044195	-1.13639
B5DDZ4	0.044323	0.736048
D5LHQ7	0.044385	0.609837
Q68EH2	0.044392	-1.00263
O57521	0.045903	-0.411109
CON__P00761	0.046359	-0.968283
B2GSX0	0.046508	0.669394
Q7T3G2	0.046605	-0.609184
Q5RLN6	0.047349	0.425562
Q6DH38	0.047581	-1.6536
Q567D7	0.047841	1.00903
Q6TLF6	0.047968	1.17672
Q4G5K8	0.048197	0.927052
I3ITF4	0.048443	-0.886983
D2X2I2	0.048705	-0.864377
Q6IQ59	0.048911	-0.431266

Table S8. All differentially expressed proteins for the homozygous *cyfip2* mutant group (MUT).

MUT vs. WT		
Uniprot IDs	**P value**	**Fold change**
A5A5E1	2.03911E-07	-5.59564
F1QMR9	0.00052236	-5.40953
Q90ZM2	0.000742062	-2.45573
Q7ZTS3	0.001033618	-0.989005
Q7ZVN9	0.001309001	4.94043
Q15I86	0.00205608	0.460352
F8W4E2	0.002459291	1.17022
B8A4S4	0.002777218	4.23144
Q6IQQ0	0.003172488	-1.1173
Q7ZWJ4	0.003522735	-1.72366
Q6PBQ4	0.004052005	0.758154
D7RVS0	0.004280456	0.851676
A0A2R8RZ61	0.004334111	6.07489
Q8JGR4	0.00456983	-2.09505
A2BE76	0.00513949	0.47299
Q804C3	0.005435131	0.606574
F1QT45	0.005818754	1.08996
Q9MIY1	0.006076171	1.33827
Q6PFU0	0.006509086	-1.64371
Q6NUW5	0.006565231	-1.61033
Q4G5V7	0.006652732	0.824453
Q08C47	0.006788597	-0.963854
A5WV37	0.0072716	0.904072
Q5RKM3	0.007343617	-3.00481
Q6NWK7	0.007706373	-0.855665
Q7ZUP6	0.009266378	-0.639457
B3DJH0	0.009579658	-0.482817
Q6DG71	0.009897374	-1.26208
B0UYS0	0.010827046	-1.35404
Q1L8Q3	0.011347495	0.816093
B2GRG9	0.011405649	-0.558996
A0N0A7	0.01157071	0.669225
Q804G9	0.011589908	-0.64098
Q9YH92	0.011746812	0.542367
Q6PBW7	0.011936033	0.576003
Q5RZ65	0.01204814	-1.99309
Q66HZ3	0.012094001	0.78498
F1QMZ6	0.012444286	0.741557
P87360	0.012459482	-0.987051
Q502L5	0.012858491	0.655478
E7FC33	0.013080972	0.876769
B7ZD02	0.013674139	-1.28274
Q7ZUI4	0.014325177	-0.989663
A7E2K4	0.014937228	0.768817
E9QBF1	0.015047349	1.20558
Q7SXX4	0.016119442	0.659585
B2GSH6	0.016226319	-1.07757
Q9DEU1	0.016772199	-1.48524
Q8UUX9	0.016879128	0.927227
B8JL35	0.017280647	0.691652
A7MCQ5	0.017463448	-1.11373
F5HSE3	0.017940725	1.34055
A0A0K0F5S9	0.017980013	0.809795
E9QCD1	0.018926487	0.28596
Q6NX91	0.018962692	-0.991968
B0R1C4	0.019269924	0.955031
B2GS26	0.019459425	0.84403
Q7ZUY9	0.019565908	0.621363
F1QJU0	0.01992783	0.94014
U3JAA1	0.020536196	0.78544
Q8JHG2	0.020872766	-0.845503
Q567V5	0.020991332	0.653493
A7E2L8	0.023647215	-1.48568
Q803G7	0.023807292	0.605124
Q45QT2	0.024222	-2.9438
Q803G1	0.024300209	0.534508
A4QN66	0.024331563	0.850256
Q7T1R2	0.024443872	-0.816371
Q6NSN5	0.025136222	0.485523
Q6TGT0	0.026478904	-1.66869
Q6PC34	0.026535666	0.61495
Q6DRD6	0.027525169	0.55623
Q6P271	0.027539116	-1.51148
A5A4L9	0.027549264	0.453133
Q6RKB0	0.027945379	1.17807
Q6IMF9	0.027991747	-0.880959
Q7SX97	0.028174745	0.651189
Q7ZSY3	0.028547626	0.383965

F1QXB0	0.02909913	-0.58536
A0A8M1NUM0	0.030134223	0.536331
E7FGU0	0.030396949	-0.564946
E7FBD3	0.030633033	0.810468
Q6PHJ4	0.030688807	-1.32292
F6NK19	0.030819103	0.465742
B1WB89	0.030951379	-2.85524
Q5RGQ4	0.031226981	0.564689
Q7SYI7	0.031303291	1.08607
Q6P6E0	0.032237399	0.543235
F1R922	0.033585359	-1.23018
Q7T160	0.033845427	0.674531
B8JLR6	0.035505039	0.360222
Q05AP7	0.035874842	-0.8066
Q803G3	0.036131833	-0.96478
Q7ZUP2	0.03625434	-0.551839
A0A0R4ID71	0.037442083	-0.859924
Q08BX5	0.037567301	0.932148
Q5XJT7	0.037568166	0.993062
A8E5J3	0.037577683	0.673695
Q803M8	0.037853845	-0.437536
F1Q6K1	0.037923639	2.44782
E7F1G8	0.039049008	0.775294
Q49HM7	0.039433924	-0.583182
Q4VBK0	0.039829972	-1.27735
E9QF63	0.041049701	-1.15528
Q6Q420	0.041214497	0.796659
B0S5T1	0.04128003	-0.647926
Q08B95	0.042082352	0.793835
Q6PC82	0.042264915	-0.66847
B8JLV7	0.042667775	0.69309
Q6TNV0	0.043011046	0.662924
D2K290	0.043024913	-1.38382
Q1JPZ7	0.043664652	0.308879
Q6DBW7	0.044002768	0.492137
Q7ZVF9	0.044286361	-0.697097
Q6DGE9	0.044472342	0.485659
Q6NYB0	0.044772361	-0.948409
X1WET9	0.04550614	0.586884
R4GDP5	0.045929318	0.658113
E7FBU7	0.046439764	0.566435
Q4V9H6	0.046743368	0.831491
Q6DGN1	0.046922377	0.371283
A2VD35	0.047314036	0.849927
Q7ZVQ3	0.047615681	-0.848595
Q7SXN2	0.049150733	-0.857413
Q9DDE1	0.049492569	0.910999
F1QUY7	0.049811544	-0.336958
Q6YBS2	0.049935569	-0.368233

Table S9. List of canonical pathways activation/inhibition for each genotype and their respective z scores.

Canonical Pathways	HET vs WT	MUT vs WT
Neutrophil Extracellular Trap Signaling Pathway	-2.333	0.816
CLEAR Signaling Pathway	1.89	1
Oxidative Phosphorylation	-0.905	1.633
Sirtuin Signaling Pathway	0	-2.449
MSP-RON Signaling In Cancer Cells Pathway	-2.236	N/A
HIPPO signaling	2.236	N/A
14-3-3-mediated Signaling	-2.236	N/A
Estrogen Receptor Signaling	-2.121	N/A
ERK5 Signaling	-2	N/A
Protein Kinase A Signaling	-1.89	0
PI3K/AKT Signaling	-1.89	N/A
Inhibition of ARE-Mediated mRNA Degradation Pathway	-1.633	N/A
Epithelial Adherens Junction Signaling	-1.342	N/A
Calcium Signaling	1.342	N/A
AMPK Signaling	1.342	N/A
Endocannabinoid Neuronal Synapse Pathway	-1	N/A
SNARE Signaling Pathway	1	N/A
Insulin Secretion Signaling Pathway	0	1
Cardiac Hypertrophy Signaling	-1	N/A
Xenobiotic Metabolism CAR Signaling Pathway	-1	N/A
EIF2 Signaling	N/A	-1
G Beta Gamma Signaling	-1	N/A
Spliceosomal Cycle	0.816	N/A
Coronavirus Pathogenesis Pathway	-0.447	N/A