

**Table S2A**

<b>Genes modulating phenotypes of 16p12.1 homologs<sup>#</sup></b>	<b>Total</b>	<b>16p12.1 homologs</b>	<b>Patient-specific "second-hit" genes</b>	<b>Neurodevel/ functionally related genes</b>	<b>Transcriptome targets</b>
Total number of crosses	521	39	227	119	136
RNAi/mutant/overexp lines	134	10	46	24	54
Genes (fly homologs)	80	4	24	13	39
Tested pairwise combinations of RNAi lines	388	30	181	95	82
Tested pairwise combinations of genes	224	12	96	55	61
Pairwise combinations enhancing phenotypes due to knockdown of 16p12.1 homologs	54	3	26	6	19
Pairwise combinations suppressing phenotypes due to knockdown of 16p12.1 homologs	29	1	6	12	10
Pairwise combinations that do not affect the phenotype of 16p12.1 homologs	76	3	32	17	24
Pairwise combinations whose effects on 16p12.1 homologs were not validated	65	5	32	20	8

**Table S2B**

<b>Interactions*</b>	<b>Total</b>	<b>16p12.1 homologs</b>	<b>Patient-specific "second-hit" genes</b>	<b>Neurodevel/ functionally related genes</b>	<b>Transcriptome targets</b>
Negative interactions (confirmed and potential)	41	0	6	10	25
Positive interactions (confirmed and potential)	63	3	31	12	17
No interaction (confirmed and potential)	61	2	30	18	11
Not validated interaction	55	7	29	12	7

<sup>#</sup>Genes modulating phenotypes of 16p12.1 homologs were confirmed using Mann-Whitney tests.

\*Genetic interactions identified using the multiplicative model. Genes with no single knockdown *Flynotyper* phenotypes were excluded from multiplicative model testing.