

**S2 Tab. (Related to Table 2) Burden of *de novo* variants in different sub-groups of patients.**

Case group	Variant class	Number of variants	Baseline expectation	Fold enrichment	P-value
Complex (n=149)	Silent	44	44.9	0.98	0.57
	Missense	124	103.1	1.20	0.025
	D-mis	62	38.5	<b>1.61</b>	<b>3.08E-04</b>
	LGD	23	13.5	<b>1.70</b>	<b>0.012</b>
Isolated (n=208)	Silent	63	62.7	1.01	0.50
	Missense	165	144.0	1.15	0.046
	D-mis	74	53.8	<b>1.38</b>	<b>5.22E-03</b>
	LGD	31	18.9	<b>1.64</b>	<b>6.52E-03</b>
Female (n=150)	Silent	44	45.9	0.96	0.63
	Missense	118	105.6	1.12	0.12
	D-mis	64	39.3	<b>1.63</b>	<b>1.85E-04</b>
	LGD	29	13.9	<b>2.09</b>	<b>2.51E-04</b>
Male (n=212)	Silent	66	63.2	1.04	0.38
	Missense	177	145.1	1.22	5.63E-03
	D-mis	74	54.3	<b>1.36</b>	<b>6.45E-03</b>
	LGD	28	19.0	<b>1.47</b>	<b>0.032</b>

Five patients were unknown with respect to other congenital anomalies. They were not included in either complex or isolated subgroup.