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Supplemental Data

Heterozygous Loss-of-Function Mutations in *YAP1* Cause Both Isolated and Syndromic Optic Fissure Closure Defects

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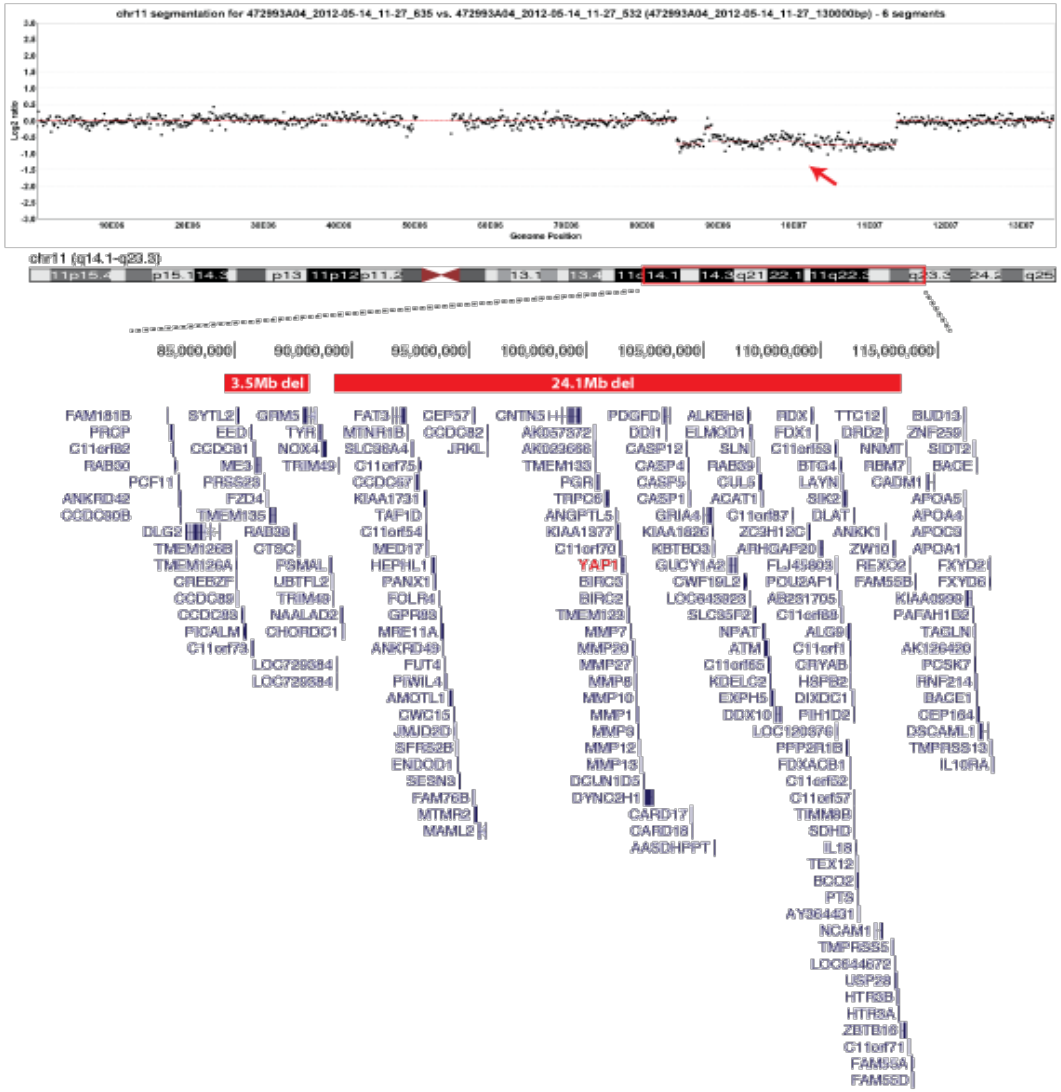

Figure S1: Schematic diagram showing two heterozygous deletions on chromosome 11q identified by array comparative genomic hybridization (array CGH). A 3.5 Mb deletion (hg19 chr11:84886352-88434352) and a 24.1 Mb deletion (hg19 chr11:89604352-113918790) were identified in F432. The 24.1 Mb deletion resulted in a loss of a single copy of *YAP1*, shown in red. Deletions are marked by red bars and are displayed using hg18 genomic coordinates in this figure. These genomic variants have been entered into the DECIPHER database as case number 282360.

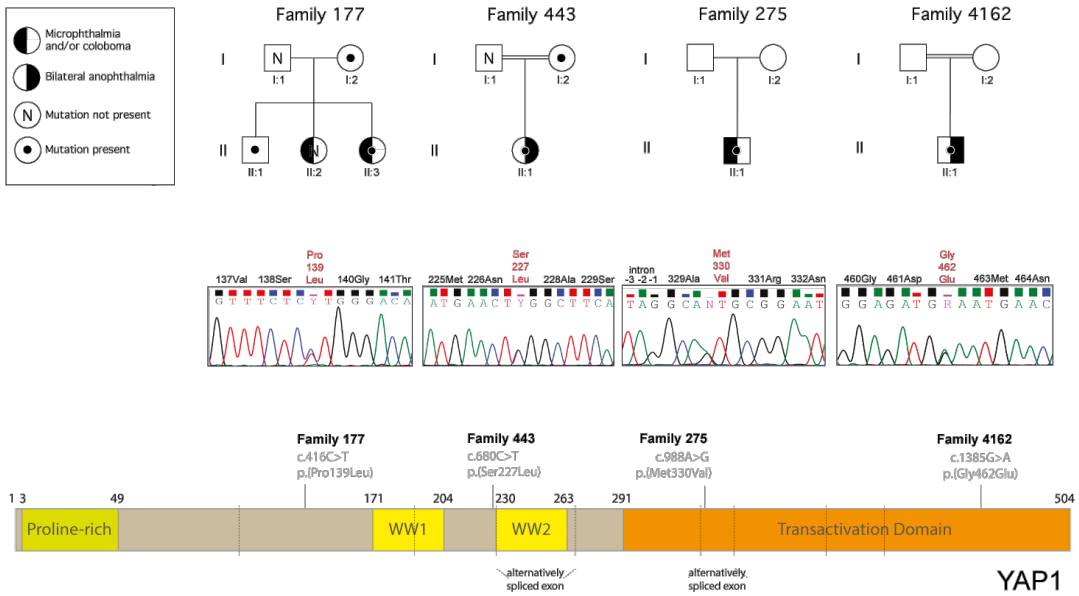

Figure S2: *YAP1* missense mutations. Pedigrees of the four families with rare missense mutations in *YAP1*. Representative chromatograms from Sanger sequencing of the heterozygous mutation are below each pedigree and the position of each mutation is indicated on the cartoon of the protein structure in the bottom panel. As can be seen in Family 177 the mutation does not segregate with the phenotype. In Family 443 the mother carries the mutation but is unaffected. In Families 275 and 4162 there is a single heterozygous proband but the parents are not available for testing.

Figure S3: Alignment of human YAP1 with mouse, chick and zebrafish orthologs. Multiple protein alignment of human YAP1 (P46937 YAP1_HUMAN) with zebrafish (A1L1U5 A1L1U5_DANRE), mouse (P46938 YAP1_MOUSE) and chick (P46936 YAP1_CHICK) orthologs. The position of the nonsense mutations is given in red and the missense mutation in yellow. The positions of the WW domains are given in blue shading. The exon boundary between exon 1 and 2 is indicated by the purple shading and all methionine residues upstream of Met179 in the human protein are indicated in bold.

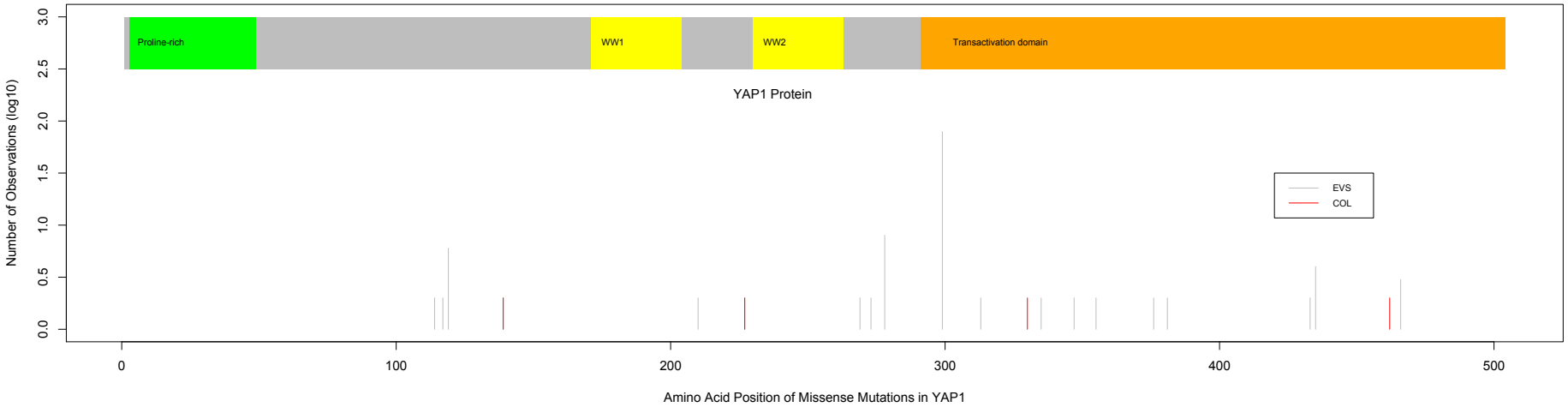

Figure S4: Distribution of YAP1 substitutions encoded by single nucleotide variants (SNV)

Graphical representation of the position and log(10) frequency of missense variants derived from EVS data (gray lines). The missense variants identified in the UK10K coloboma exome data and resequencing data are shown in red. No clustering of the missense variants present in either group is apparent.

Table S1: Oligonucleotides used to amplify *YAP1* from gDNA and *Yap1* & *YAP1* from cDNA.

	forward oligonucleotide 5'→3'	reverse oligonucleotide 5'→3'	amplicon length, bp / species
gDNA template			
YAP1 exon 1	**GTAGCGCGACGGCCAGT**CCCTGAGAGCGAGGACAG	**CAGGGCGCAGCGATGAC**CCTGACCAGAGCTGGCG	580
YAP1 exon 2	**GTAGCGCGACGGCCAGT**AACCTGTGTTCTCCAGTGTCG	**CAGGGCGCAGCGATGAC**CCCATACTAACAAAGGTATTTAGGTC	499
YAP1 exon 3	**GTAGCGCGACGGCCAGT**GCACCCTTTGATTATGAGCC	**CAGGGCGCAGCGATGAC**CACATCAACTTTTACCAATGCG	301
YAP1 exon 4	**GTAGCGCGACGGCCAGT**CCTTTCTTCTCTGAACACAGCC	**CAGGGCGCAGCGATGAC**GTAAACATTGGGTGGGCAG	434
YAP1 exon 5	**GTAGCGCGACGGCCAGT**CATCGAATATCCCAAATTGC	**CAGGGCGCAGCGATGAC**CCAACTTTAAGAAAACAAACCCC	373
YAP1 exon 6	**GTAGCGCGACGGCCAGT**AAGTCAGCCTACACAGCCAG	**CAGGGCGCAGCGATGAC**AGGACAGGACCCTGGAATG	241
YAP1 exon 7	**GTAGCGCGACGGCCAGT**GGTTACTCTGATGAACGTTTTATTTC	**CAGGGCGCAGCGATGAC**GGCCCACACAGATGTTCC	357
YAP1 exon 8	**GTAGCGCGACGGCCAGT**TCTTTGAGAATTATGTTGCTGCTC	**CAGGGCGCAGCGATGAC**CCTGGTGATAACATATCCCACTG	306
YAP1 exon 9	**GTAGCGCGACGGCCAGT**TGATACAGCCCTGATGTTAGC	**CAGGGCGCAGCGATGAC**GCCTGAAAACTGCAACTGGC	426
cDNA template			
Met1	GTCATGAACCCCAAGACG	GAGAAACAGCTCCCAACTGC	Human
Met179	CGGGTTAAGGAGGAGGAAAG	GGTCAGTGTCCCAGGAGAAA	Human
YAP1	CGGGATGTCTCAGGAATTGA	CCAGGAATGGCTTCAAGGTA	Human
ß-ACTIN	GGCATGGGTCAGAAGGATT	GGGGTGTTGAAGGTCTCAAA	Human
m1	TTCAATGCCGTCATGAACC	TGTGAGTGTCCCAGGAGAAA	Mouse
m2	GCGTTGCAGGTTGACTCATA	TGTGAGTGTCCCAGGAGAAA	Mouse
m3	GCGGGATCCTTTCACACTC	TGTGAGTGTCCCAGGAGAAA	Mouse
Yap1	ATGCTTTCGCAACTGAACG	GAGTGATCCTCTGGTTCATGG	Mouse
ß-Actin	TTCTTTGCAGCTCCTTCGTT	CTCGTCACCCACATAGGAGTC	Mouse

Table S2: *In silico* prediction of the pathogenicity of YAP1 non-synonymous variants.

Gene	Nucleotide change	Protein change	MAF% (from EVS)	Align-GVGD class	PolyPhen-2		SIFT		Mutation Taster	
					prediction	score	prediction	score	prediction	*p-value*
NM_001130145.2 *YAP1*	c.416C>T	p.(Pro139Leu)	0	C0	probably damaging	0.97	Tolerated	0.41	Disease causing	1.0
NM_001130145.2 *YAP1*	c.680C>T	p.(Ser227Leu)	0.0077	C0	benign	0.013	Tolerated	0.33	Disease causing	0.998
NM_001130145.2 *YAP1*	c.988A>G	p.(Met330Val)	0	C0	benign	0.001	Tolerated	1.00	Disease causing	1.0
NM_001130145.2 *YAP1*	c.1385G>A	p.(Gly462Glu)	0	C0	possibly damaging	0.526	Deleterious	0.03	Disease causing	0.835