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Supplementary Materials for

Basal exon skipping and genetic pleiotropy: A predictive model of disease pathogenesis

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The PDF file includes:

Supplementary Materials:

Mild	Missense	c.1A>G*, c.2T>G*, c.2T>A*, c.21G>T, c.95T>C, c.829G>C, c.1985A>T, c.1991A>G, c.2915T>C, c.4661_4663del, c.5081T>c, c.5777G>C
	Cryptic exon	c.2991+1655A>G
Moderate	Frame Shift	c.136G>T, c.265dup, c.270_274delAGTAA, c.287del, c.381_382delinsT, c.384_387del, c.384_385del, c.437del, c.679_680del, c.2118_2122dup, c.2954del, c.4452_4455delAGAA, c.4656del, c.5256_5257del, c.5434_5435del, c.5445-8delAACT, c.5489del, c.5493del, c.5515_5518del, c.5519_5537del, c.5611_5614del, c.5649dup, c.5666del, c.6277del, c.6604del, c.7318_7321dup, c.7323_7327elAGAAG, c.7341dup, c.7366_7369del
	Splicing Event	c.2218-15_2220del, c.2218-4_2222del, c.2218-2A>C, c.5226+1G>A, c.5226+5_8delGTAA, c.5587-1G>C, c.6271-8T>G
	Early Stop	c.322C>T, c.451C>T, c.566C>G, c.613C>T, c.2213delT, c.2249T>G, c.2251C>T, c.2695C>T, c.2906dup, c.4393C>T, c.5311G>T, c.5344C>T, c.5668G>T, c.6331C>T
Severe	Early Stop	c.1078C>T, c.1236delG, c.1429C>T, c.1550del, c1593C>T, c.1645 C>T, c.1709C>G, c.1936C>T, c.1984C>T, 1985A>T, c.1987A>T, c3043G>T, c.3175del, c.3265C>T, c.3292G>T, c.3361G>T, c.3793C>T, c.3802C>T, c.3811C>T, c.3814C>T, c.3922C>T, c. 4090G>T, c.4714G>T, c.4723A>T, c.4732G>T, c.4771C>T, c.4882C>T, c.4966G>T, c.5046del, c.5182G>T, c.5218C>T, c.5722G>T, c.5776C>T, c.5824C>T, c.5866G>T, c.5932C>T, c.5941G>T, c. 6012-2A>G, c.6031C>T, c.6072C>A
	Frame Shift	c.164_167del, c.1219_1220del, c.1260_1264del, c.1361del, c.1419_1423del, c.1657_1666delA . c.1666del, c.1682_1683del, c.1830del, c.1855_1858del c. 1859_1862del, c.1860_1861del, c.1992del, c.2505_2506del, c. 3175dup, c.3176del, c.3178del, c.3185del, c.3422dup, c.4001del, c.4028del, c.4115_4116del, c.4786_4790del, c.4791_4794del, c. 4864insTdel, c.4962_4963del, c.4963_4964del, c.4965_4966del, c.5163del, c.5255-5256del, c.5734del, c.5744insT, c.5813_5817del, c.5850del, c.5865_5867delinsGG, c.6869del, c. 6870del, c.4115_4116del, c.4114_4115del
	Splicing Event	c.103-13_103-18del, c.180+1G>T, c.180+2T>A, c.1066-1G>A, c.1189+1G>A, c.1711+5A>G, c.1824G>A c.1910-2A>C, c.3104-1G>A, c.3104-2A>G, c.3310-1G>C, c.3310-1_3310delinsAA, c.4195-1G>A

** These point mutations disrupt the start codon, likely resulting in translation initiation at an in frame AUG codon at c.31-33 creating near normal levels of a protein product lacking only the first 10 amino acids*

Figure S1. Human *CEP290* mutations classified on the basis of their predicted coding effects.

Mild mutations are predicted to have little effect on protein levels, moderate to result in small amounts of near full-length protein, and severe mutations to result in no protein production, as detailed in the model described in the main text and Fig. 1.

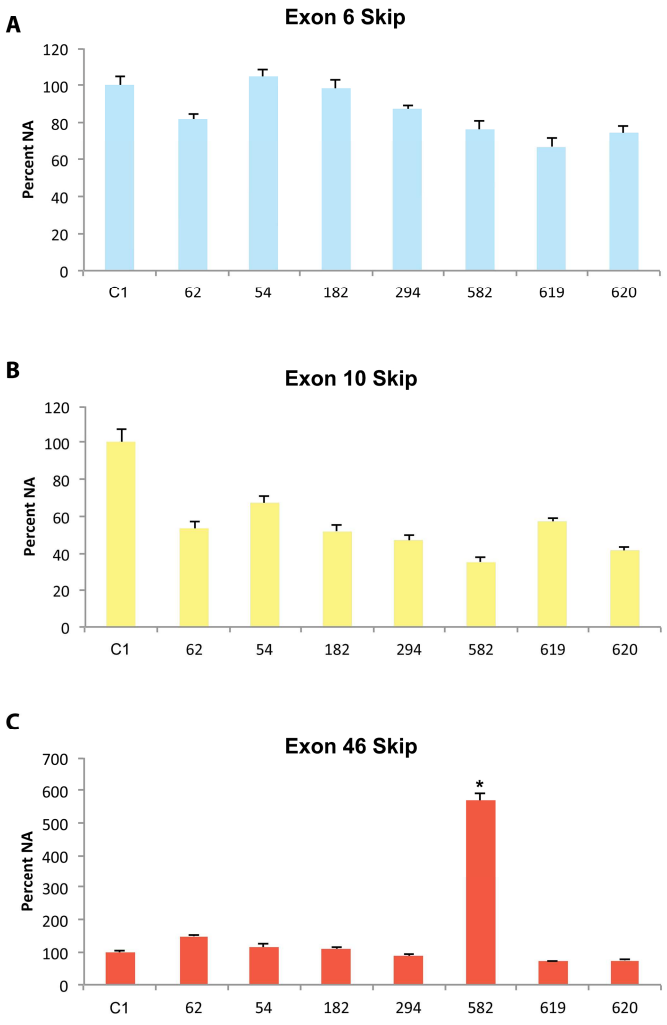

Figure S2. Levels of *CEP290* transcript lacking certain exons, normalized to total CEP290 levels

Levels of CEP290 transcript lacking exons 6 (A), 10 (B), and 46 (C) in patient (numbered) and normal control (C1) fibroblast cDNA as determined by TaqMan PCR. Data were normalized to total CEP290 transcript levels and adjusted to percent of normal C1 levels using the $\Delta\Delta C_t$ method. Data are presented as mean ± SD, n=3, means marked * are significantly different from all other means with $p < 0.0001$. Exact values are shown in Table S4.

Table S1. Phenotypes of *CEP290* disease

Disease Syndrome	Phenotype
Leber Congenital Amaurosis (LCA)	Early retinal degeneration resulting in legal blindness by the first to second decade of life. (*8*)
Senior-Løken Syndrome (SLS)	Retinal degeneration identical to LCA with additional cystic kidney disease known as nephronopthisis. (*8*)
Joubert syndrome (JS)	All patients are characterized by absence or hypoplasia of the cerebellar vermis and brain stem abnormalities. Many patients additionally manifest with intellectual disability. *(8)*
Joubert syndrome and related disorders (JSRD)	Joubert syndrome (see above) along with additional extra-CNS manifestations, such as retinal degeneration, cystic kidney disease, and/or skeletal abnormalities. (*8*)
Meckel-like syndrome (ML)	Lethal in the vast majority of cases, but with many patients surviving for many months after birth, this syndrome is characterized by cystic kidney disease, CNS malformation (typically Dandy-Walker malformation), polydactyly, and hepatic fibrosis (*8*)
Meckel-Gruber Syndrome (MKS)	Uniformly perinatal lethal disease characterized by

	renal cystic dysplasia, CNS abnormalities (commonly occipital encephalocele), polydactyly, and hepatic fibrosis. (*8*)

Table S2. Mutations harbored by reported *CEP290* patients

	Allele 1		Allele 2		
Diagnosis	Exon Effect	Coding Change	Exon Effect	Coding Change	Reference (see text for details)
JSRD	Exon 41	c.5668G>T	Exon 41	c.5668G>T	Alazami 2012
JSRD	Exon 41	c.5668G>T	Exon 41	c.5668G>T	Alazami 2012
JSRD	Exon 36	c.4714G>T	Exon 36	c.4714G>T	Alazami 2012
ML	Exon 27	c.3043G>T	Exon 28	c.3104-1G>A	Baala (2007)
ML	Exon 41	c.5649dupA	Exon 42	c.5850delT	Baala (2007)
ML	Exon 41	c.5649dupA	Exon 42	c.5850delT	Baala (2007)
ML	Exon 26	c.2906dupA	Exon 31	c.3793C>T	Baala (2007)
MKS	Exon 9	c.613C>T	Exon 9	c.613C>T	Baala (2007)
MKS	Exon 9	c.613C>T	Exon 9	c.613C>T	Baala (2007)
MKS	Exon 6	c.384_387delTAGA	Exon 6	c.384_387delTAGA	Baala (2007)
MKS	Exon 6	c.384_387delTAGA	Exon 6	c.384_387delTAGA	Baala (2007)
MKS	Exon 3	c.180+2 T>A	Exon 6	c.384_387delTAGA	Baala (2007)
MKS	Exon 3	c.180+2 T>A	Exon 6	c.384_387delTAGA	Baala (2007)
MKS	Exon 14	c.1219_1220delAT	Exon 32	c.4115_4116delTA	Baala (2007)
MKS	Exon 28	c.3175delA	Exon 28	c.3175delA	Baala (2007)
MKS	Exon 6	c.381_382delinsT	Exon 19	c.1860_1861delAA	Baala (2007)
LCA	Exon 36	c.4771C>T	Exon 36	c.4771C>T	Beryozkin 2014
JSRD	Exon 44	c.6072C>A	Exon 54	c.7321dupCTCT	Brancati (2007)
JSRD	Exon 44	c.6072C>A	Exon 54	c.7321dupCTCT	Brancati (2007)
JSRD	Exon 20	c.1985A>T	Exon 46	c.6277delG	Brancati (2007)
JSRD	Exon 17	c.1657_1666delA	Exon 44	c.6031C>T	Brancati (2007)
JSRD	Exon 37	c.4882C>T	Exon 43	c.5941G>T	Brancati (2007)
JSRD	Exon 31	c.3811C>T	Exon 42	c.5734delT	Brancati (2007)
JSRD	Exon 31	c.3811C>T	Exon 42	c.5734delT	Brancati (2007)
JSRD	Exon 42	c.5722G>T	Exon 42	c.5722G>T	Brancati (2007)
JSRD	Exon 28	c.3167_3175insA	Exon 41	c.5668G>T	Brancati (2007)
JSRD	Exon 37	c.4882C>T	Exon 41	c.5610delCAAA	Brancati (2007)
JSRD	Exon 37	c.4882C>T	Exon 41	c.5610delCAAA	Brancati (2007)
JSRD	Exon 40	c.5431_5433delGA	Exon 41	c.5668G>T	Brancati (2007)
JSRD	Exon 41	c.5668G>T	Exon 41	c.5668G>T	Brancati (2007)
JSRD	Exon 41	c.5668G>T	Exon 41	c.5668G>T	Brancati (2007)
JSRD	Exon 41	c.5668G>T	Exon 41	c.5668G>T	Brancati (2007)
JSRD	Exon 38	c.5163delT	Exon 38	c.5163delT	Brancati (2007)
JSRD	Exon 34	c.4393C>T	Exon 36	c.4723A>T	Brancati (2007)
JSRD	Exon 36	c.4786_4790delTAAA	Exon 36	c.4786_4790delTAAA	Brancati (2007)
JSRD	Exon 17	c.1682_1683delA	Exon 31	c.3814C>T	Brancati (2007)
SLS	Exon 36	c.4723A>T	Exon 34	c.4393C>T	CEP290 Mutation Database
SLS	Exon 36	c.4723A>T	Exon 34	c.4393C>T	CEP290 Mutation Database
SLS	Exon 2	c.21G>T	Exon 2	c.21G>T	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 29	c.3310-1_3310delinsAA	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 29	c.3310-1_3310delinsAA	CEP290 Mutation Database

LCA	Intron 26	c.2991+1655A>G	Exon 29	c.3310-1_3310delinsAA	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 22	c.2218-2A>C	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 14	c.1189+1G>A	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 6	c.437del	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 6	c.384_385del	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 6	c.322C>T	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 43	c.5865_5867delinsGG	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 40	c.5519_5537del	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 40	c.5493del	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 39	c.5344C>T	CEP290 Mutation Database
LCA	Exon 18	c.1824G>A	Exon 38	c.5081T>C	CEP290 Mutation Database
LCA	Exon 36	c.4723A>T	Exon 36	c.4723A>T	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 36	c.4723A>T	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 36	c.4723A>T	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 36	c.4723A>T	CEP290 Mutation Database
LCA	Exon 36	c.4723A>T	Exon 35	c.4696G>C	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 34	c.4393C>T	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 31	c.4001del	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 29	c.3422dup	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 25	c.2695C>T	CEP290 Mutation Database
LCA	Intron 26	c.2991+1655A>G	Exon 19	c.1859_1862del	CEP290 Mutation Database
JSRD	Exon 54	c.7366_7369del	Exon 54	c.7366_7369del	CEP290 Mutation Database
JSRD	Exon 54	c.7366_7369del	Exon 54	c.7366_7369del	CEP290 Mutation Database
JSRD	Exon 41	c.5587-1G>C	Exon 31	c.3793C>T	CEP290 Mutation Database
LCA	Exon 26	c.2954delT	Exon 52	c.7028_7034 +3 dup	Chen 2013
LCA	Exon 29	c.3361G>T	Minimal effect	c.2817+2T>C	Chen 2013
LCA	Exon 28	c.3265C>T	Exon 32	c.4090G>T	Chen 2013
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Cideciyan (2007)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Cideciyan (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 41	c.5668G>T	Cideciyan (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 41	c.5668G>T	Cideciyan (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 37	c.4882C>T	Cideciyan (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 14	c.1260_1264delTAAAG	Cideciyan (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 3	c.180+1G>T	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Exon 54	c.7341dupA	den Hollander (2006)

LCA	Intron 26	c.2991+1655A>G	Exon 5	c.265dupA	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Exon 43	c.5866G>T	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Exon 42	c.5813_5817delCTTTA	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Exon 37	c.4966G>T	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Exon 32	c.4115_4116delTA	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Exon 31	c.3814C>T	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Exon 22	c.2249T>G	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Exon 21	c.2118_2122dupTCAGC	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Exon 16	c.1550delT	den Hollander (2006)
LCA	Intron 26	c.2991+1655A>G	Exon 10	c.679_680delGA	den Hollander (2006)
MKS	Exon 40	c.5489delA	Exon 40	c.5489delA	Frank (2008)
MKS	Exon 40	c.5489delA	Exon 40	c.5489delA	Frank (2008)
MKS	Exon 40	c.5489delA	Exon 40	c.5489delA	Frank (2008)
MKS	Exon 40	c.5489delA	Exon 40	c.5489delA	Frank (2008)
JSRD	Exon 41	c.5666delA	Exon 41	c.5666delA	Ghaffari 2013
JS	Exon 41	c.5666delA	Exon 41	c.5666delA	Ghaffari 2013
JSRD	Exon 41	c.5666delA	Exon 41	c.5666delA	Ghaffari 2013
SLS	Exon 2	c.95T>C	Minimal effect on 39	c.5226+5_8delGTAA	Halbritter 2014
SLS	Exon 5	c.270_274delAGTAA	Exon 45	c.6277delG	Halbritter 2014
SLS	Exon 20	c.1984C>T	Exon 36	c.4723A>T	Halbritter 2014
SLS	Exon 20	c.1987A>T	Exon 36	c.4723A>T	Halbritter 2014
SLS	Exon 31	c.3802C>T	Exon 36	c.4723A>T	Halbritter 2014
SLS	Exon 35	c.4452_4455delAGAA	Exon 36	c.4723A>T	Halbritter 2014
SLS	Exon 14	c.1189+1A>G	Exon 36	c.4723A>T	Halbritter 2014
SLS	Exon 2 - CDS	c.A1>G	Exon 15	c.1419-1423del AATAA	Helou (2007)
JSRD	Exon 38	c.4882C>T	Exon 44	c.5941G>T	Helou (2007)
JSRD	Exon 32	c.3811C>T	Exon 43	c.5734delT	Helou (2007)
JSRD	Exon 32	c.3811C>T	Exon 43	c.5734delT	Helou (2007)
JSRD	Exon 13	c.1066-1G>A	Exon 39	c.5163delT	Helou (2007)
LCA	Exon 7	c.451C>T	Intron 26	c.2991+1655A>G	Littink Karin (2010)
MKKS	Exon 41	c.5668G>T	NULL	NULL	Molin 2013
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Moloney 2014
SLS	Exon 41	c.5649-50insA	Exon 42	c.5850delT	Otto 2014
SLS	Exon 26	c.2915T>C	Exon 26	c.2915T>C	Otto 2014
JSRD	Exon 41	c.5668G>T	Exon 41	c.5668G>T	Otto 2014
JSRD	Exon 41	c.5668G>T	Exon 41	c.5668G>T	Otto 2014
JSRD	Exon 40	c.5445-8delAACT	Exon 39	c.5311G>T	Otto 2014
JSRD	Exon 45	c.6277delG	Exon 38	c.5182G>T	Otto 2014
JSRD	Exon 41	c.5649-50insA	Exon 3	c.136G>T	Otto 2014
JSRD	Exon 41	c.5668G>T	Exon 13	c.1189G>A	Otto 2014
LCA	Intron 26	c.2991+1655A>G	Exon 41	c.5587-1G>C	Papon 2014
LCA	Intron 26	c.2991+1655A>G	Exon 41	c.5587-1G>C	Papon 2014
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Papon 2014
LCA	Exon 36	c.4723A>T	Exon 36	c.4723A>T	Papon 2014

LCA	Exon 36	c.4723A>T	Exon 36	c.4723A>T	Papon 2014
LCA	Intron 26	c.2991+1655A>G	Exon 31	c.4028delA	Papon 2014
LCA	Intron 26	c.2991+1655A>G	Exon 31	c.3922C>T	Papon 2014
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Pasadhika 2010
LCA	Intron 26	c.2991+1655A>G	Exon 42		Pasadhika 2010
LCA	Intron 26	c.2991+1655A>G	Exon 37	c.4962_4963delAA	Pasadhika 2010
LCA	Exon 42	c.5850delT	Exon 41	c.5587-1G>C	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 41	c.5587-1G>C	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 41	c.5587-1G>C	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 39	c.5226+1G>A	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 20	c.1910-2A>G	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 6	c.384-387delTAGA	Perrault (2007)
LCA	Exon 20	c.1936C>T	Exon 48	c.6604delA	Perrault (2007)
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LCA	Intron 26	c.2991+1655A>G	Exon 48	c.6604del	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 48	c.6604del	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 48	c.6604del	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 48	c.6604del	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 48	c.6604del	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 42	c.5850delT	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 38	c.5163delT	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 38	c.5163delT	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 38	c.5163delT	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 37	c.4962_4963delAA	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 37	c.4882C>T	Perrault (2007)
LCA	Exon 36	c.4723A>T	Exon 36	c.4723A>T	Perrault (2007)
LCA	Exon 36	c.4723A>T	Exon 36	c.4723A>T	Perrault (2007)
LCA	Exon 36	c.4723A>T	Exon 36	c.4723A>T	Perrault (2007)
LCA	Exon 36	c.4723A>T	Exon 36	c.4723A>T	Perrault (2007)
LCA	Exon 36	c.4723A>T	Exon 36	c.4723A>T	Perrault (2007)
LCA	Exon 42	c.5850delT	Exon 35	c.4661_4663delAAG	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 32	c.5255-5256delGG	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 32	c.5255-5256delGG	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 31	c.4028delA	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 31	c.3922C>T	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 28	c.3175insA	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 28	c.3292G>T	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 20	c.1992delT	Perrault (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 19	c.1855-1858delAAAG	Perrault (2007)
LCA	Exon 36	c.4723A>T	Exon 17	c.1709C>G	Perrault (2007)

LCA	Intron 26	c.2991+1655A>G	Exon 14	c.1219_1220delAT	Perrault (2007)
LCA	Exon 16	c.1593C>A	Exon 1	c.2T>A	Perrault (2007)
JSRD	Exon 17	c.1711+5G>A	Exon 41	c.5587-1G>C	Perrault (2007)
JSRD	Exon 36	c.4723A>T	Exon 36	c.4723A>T	Perrault (2007)
SLS	Exon 22	c.2218-2222delccagATAGA	Exon 22	c.2218-2222delccagATAGA	Sayer (2006)
SLS	Exon 22	c.2218-2222delccagATAGA	Exon 22	c.2218-2222delccagATAGA	Sayer (2006)
JSRD	Exon 41	c.5515-5518delGAGA	Exon 42	c.5649insA	Sayer (2006)
JSRD	Exon 42	c.5668G>T	Exon 42	c.5668G>T	Sayer (2006)
JSRD	Exon 42	c.5668G>T	Exon 42	c.5668G>T	Sayer (2006)
JSRD	Exon 42	c.5668G>T	Exon 42	c.5668G>T	Sayer (2006)
JSRD	Exon 42	c.5668G>T	Exon 42	c.5668G>T	Sayer (2006)
JSRD	Exon 36	c.4656delA	Exon 41	c.5668G>T	Sayer (2006)
JSRD	Exon 54	c.7341-7342insA	Exon 29	c.3175-3176insA	Sayer (2006)
LCA	Intron 26	c.2991+1655A>G	Exon 9	c.566C>G	Simonelli (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 38	c.5041–5046delA	Simonelli (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 28	c.3292G>T	Simonelli (2007)
LCA	Intron 26	c.2991+1655A>G	Exon 14	c.1219–1220delAT	Simonelli (2007)
ML	Exon 42	c.5744insT	Exon 42	c.5744insT	Szymanska 2012
ML	Exon 22	c.2251C>T	Exon 36	c.4864insTdelCG	Szymanska 2012
ML	Exon 22	c.2251C>T	Exon 36	c.4864insTdelCG	Szymanska 2012
ML	Exon 10	c.679_680delGA	Exon 20	c.1984C>T	Szymanska 2012
ML	Exon 10	c.679_680delGA	Exon 20	c.1984C>T	Szymanska 2012
ML	Exon 15	c.1429C>T	Exon 15	c.1429C>T	Szymanska 2012
ML	Exon 12	c.954delT	Exon 12	c.954delT	Szymanska 2012
SLS	Exon 41	c.5649 ins A	Exon 33	c.4195-1 G>A	Tory (2007)
JSRD	Exon 29	c.3310-1 G>C	Minimal Effect on 46	c.6271-8 T>G	Tory (2007)
JSRD	Exon 37	c.4963–4964 del AG	Minimal effect on 3	c.103-13 to -18 delGCTTTT	Tory (2007)
JSRD	Exon 15	c.1361 del G	Exon 50	c.6869 del A	Tory (2007)
JSRD	Exon 22	c.2251 C>T	Exon 50	c.6869 del A	Tory (2007)
JSRD	Exon 41	c.5649 ins A	Exon 42	c.5850 del T	Tory (2007)
JSRD	Exon 41	c.5649 ins A	Exon 42	c.5850 del T	Tory (2007)
JSRD	Exon 41	c.5649 ins A	Exon 17	c.1645 C>T	Tory (2007)
JS	Exon 42	c.5824C>T	Exon 42	c.5824C>T	Valente (2006)
JSRD	Exon 42	c.5824C>T	Exon 42	c.5824C>T	Valente (2006)
JSRD	Exon 41	c.5668G>T	Exon 41	c.5668G>T	Valente (2006)
JSRD	Exon 41	c.5668G>T	Exon 41	c.5668G>T	Valente (2006)
JSRD	Exon 36	c.4732G>T	Exon 36	c.4732G>T	Valente (2006)
JSRD	Exon 36	c.4732G>T	Exon 36	c.4732G>T	Valente (2006)
JSRD	Exon 36	c.4732G>T	Exon 36	c.4732G>T	Valente (2006)
JSRD	Exon 28	c.3176delT	Exon 28	c.3176delT	Valente (2006)
JSRD	Exon 2	c.21G>T	Exon 2	c.21G>T	Valente (2006)

LCA	Intron 26	c.2991_1655A>G	Intron 26	c.2991_1655A>G	Vallespin (2007)
LCA	Intron 26	c.2991_1655A>G	Intron 26	c.2991_1655A>G	Vallespin (2007)
LCA	Exon 17	c.1709C>G	Intron 26	c.2991+1655A>G	Walia 2010
LCA	Exon 37	c.4966G>T	Intron 26	c.2991+1655A>G	Walia 2010
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Walia 2010
LCA	Intron 26	c.2991+1655A>G	Exon 42	c.5813_5817delCTTTA	Walia 2010
LCA	Intron 26	c.2991+1655A>G	Exon 41	c.5668G>T	Walia 2010
LCA	Intron 26	c.2991+1655A>G	Exon 41	c.4882C>T	Walia 2010
LCA	Intron 26	c.2991+1655A>G	Exon 37	c.4962_4963delAA	Walia 2010
LCA	Intron 26	c.2991+1655A>G	Exon 37	c.4882C>T	Walia 2010
LCA	Intron 26	c.2991+1655A>G	Exon 37	c.4966G>T	Walia 2010
LCA	Intron 26	c.2991+1655A>G	Exon 37	c.4966G>T	Walia 2010
LCA	Intron 26	c.2991+1655A>G	Exon 36	c.4723A>T	Walia 2010
LCA	Intron 26	c.2991+1655A>G	Exon 16	c.1550delT	Walia 2010
LCA	Intron 26	c.2991+1655A>G	Exon 14	c.1260_1264delTAAAG	Walia 2010
LCA	Intron 26	c.2991+1655A>G	Exon 14	c.1260_1264delTAAAG	Walia 2010
JSRD	Exon 54	c.7323_7327delAGAAG	Exon 44	c.6012-2A>G	Wang 2014
LCA	Intron 26	c.2991+1655A>G	Exon 41	c.5587-1G>C	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Exon 3	c.180+1G>T	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Intron 26	c.2991+1655A>G	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Exon 5	c.265dupA	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Exon 41	c.5668G>T	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Exon 31	c.3814C>T	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Exon 28	c.3175dup	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Exon 17	c.1645C>T	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Exon 13	c.1078C>T	Yzer 2012
LCA	Intron 26	c.2991+1655A>G	Exon 10	c.679_680delGA	Yzer 2012

Table S3. Mutations harbored by reported *CC2D2A* patients

	Allele 1		Allele 2		
Diagnosis	Exon Effect	Coding Change	Exon Effect	Coding Change	Reference (see text for details)
JS	POINT	c.3341 C>T (Thr111rMet)	POINT	c.4667A>T (Asp1556V)	Mougou-Zerelli (2009)
JS	Exon 11	c.(1263_4InsGGCATGTTTTGGC) (S423GFS)	POINT	c.1268G>A (V1151A)	Bachmann-Gagescu (2011)
JS	Exon 11	c.(1263_4InsGGCATGTTTTGGC) (S423GFS)	POINT	c.1268G>A (V1151A)	Bachmann-Gagescu (2011)
JS	POINT	c.1676T>C (L559P)	Exon 29	c.3892_3del(GT) (V1298FS)	Bachmann-Gagescu (2011)
JS	Exon 23	c.3055C>T (R1019X)	POINT	c.3288G>C (Q1096H)	Bachmann-Gagescu (2011)
JS	Exon 23	c.3055C>T (R1019X)	POINT	c.4667A>T (Asp1556V)	Bachmann-Gagescu (2011)
JS	POINT	c.3134T>C (V1045A)	POINT	c.3850C>T (R1284C)	Bachmann-Gagescu (2011)
JS	Exon 25	c.3289delG (V1097 FS)	POINT	c.4289T>C (V1430A)	Bachmann-Gagescu (2011)
JS	Exon 25	c.3289delG (V1097 FS)	POINT	c.4289T>C (V1430A)	Bachmann-Gagescu (2011)
JS	Exon 25	c.3289delG (V1097 FS)	POINT	c.3851G>A (R1284H)	Bachmann-Gagescu (2011)
JS	POINT	c.3364C>T (p1122S)	POINT	c.3364C>T (p1122S)	Bachmann-Gagescu (2011)
JS	Exon 29	c.3772-1G>T (Intron 29)	POINT	c.4582C>T (R1528C)	Bachmann-Gagescu (2011)
JS	Exon 30	c.3976-3C>A (Intron 30)	Exon 36	c.4844_4847delCTCT (S1615FS)	Bachmann-Gagescu (2011)
JS	Exon 31	c.4179+1delG (E1393FS)	POINT	c.4667A>T (Asp1556V)	Bachmann-Gagescu (2011)
JS	POINT	c.4582C>T (R1528C)	POINT	c.4582C>T (R1528C)	Bachmann-Gagescu (2011)
JS	POINT	c.4582C>T (R1528C)	POINT	c.4582C>T (R1528C)	Bachmann-Gagescu (2011)
JS	Exon 8	c.517C>T	POINT	c.1676T>C (L559P)	Bachmann-Gagescu (2011)
JSRD	Exon 19	IVS 19 +1 G>C	Exon 19	IVS 19 +1 G>C	Noor (2008)
JSRD	Exon 19	IVS 19 +1 G>C	Exon 19	IVS 19 +1 G>C	Noor (2008)
JSRD	Exon 19	IVS 19 +1 G>C	Exon 19	IVS 19 +1 G>C	Noor (2008)
JSRD	Exon 19	IVS 19 +1 G>C	Exon 19	IVS 19 +1 G>C	Noor (2008)
JSRD	Exon 19	IVS 19 +1 G>C	Exon 19	IVS 19 +1 G>C	Noor (2008)
JSRD	Exon 23	c.3145C>T (R1049X)	POINT	c.3347C>T (T1116M)	Bachmann-Gagescu (2011)
JSRD	Exon 25	c.3289delG (V1097 FS)	POINT	c.3347C>T (T1116M)	Bachmann-Gagescu (2011)
JSRD	Exon 25	c.3289delG (V1097 FS)	POINT	c.3347C>T (T1116M)	Gorden (2008)
JSRD	Exon 25	c.3289delG (V1097 FS)	POINT	c.4582C>T (R1528C)	Bachmann-Gagescu (2011)
JSRD	Exon 21	c.2848C>T (R950X)	Exon 21	c.2848C>T (R950X)	Gorden (2008)
JSRD	Exon 21	c.2848C>T (R950X)	Exon 21	c.2848C>T (R950X)	Bachmann-Gagescu (2011)
JSRD	POINT	L1551P	POINT	L1551P	Gorden (2008)
JSRD	POINT	c.3364C>T (p1122S)	POINT	c.3364C>T (p1122S)	Bachmann-Gagescu (2011)
MKS	Exon 27	c.3540delA (R1180FS)	Exon 27	c.3540delA (R1180FS)	Szymanska (2012)
MKS	Exon 27	c.3540delA (R1180FS)	Exon 27	c.3540delA (R1180FS)	Szymanska (2012)
MKS	Exon 15	c.1538T>A	Exon 32	c.4179+1delG	Mougou-Zerelli (2009)
MKS	Exon 16	c.1762C>T	Exon 16	c.1762C>T	Tallila (2008)
MKS	Exon 16	c.1762C>T	Exon 16	c.1762C>T	Tallila (2008)

MKS	Exon 16	c.1762C>T	Exon 16	c.1762C>T	Tallila (2008)
MKS	Exon 16	c.1762C>T	Exon 16	c.1762C>T	Tallila (2008)
MKS	Exon 16	c.1762C>T	Exon 16	c.1762C>T	Tallila (2008)
MKS	Exon 16	c.1762C>T	Exon 16	c.1762C>T	Tallila (2008)
MKS	Exon 16	c.1762C>T	Exon 16	c.1762C>T	Tallila (2008)
MKS	Exon 16	c.1762C>T	Exon 16	c.1762C>T	Tallila (2008)
MKS	Exon 16	c.1762C>T	Exon 16	c.1762C>T	Tallila (2008)
MKS	Exon 16	c.1762C>T	Exon 16	c.1762C>T	Tallila (2008)
MKS	Exon 16	c.1762C>T	Exon 16	c.1762C>T	Tallila (2008)
MKS	Exon 22	c.2673C>T	Exon 19	c.2486+1G>C	Mougou-Zerelli (2009)
MKS	Exon 25	c.3084delG	Exon 25	c.3084delG	Mougou-Zerelli (2009)
MKS	Exon 25	c.3145C>G	Exon 25	c.3145C>G	Mougou-Zerelli (2009)
MKS	Exon 28	c.3399_3975 del	Exon 28	c.3399_3975 del	Mougou-Zerelli (2009)
MKS	Exon 26	c.3399-3C>A	Exon 36	c.3399-3C>A	Mougou-Zerelli (2009)
MKS	Exon 29	c.3522_3523insTG	Exon 35	c.4496+1 T>A	Mougou-Zerelli (2009)
MKS	POINT	c.3544T>C (W1192R)	Exon 29	c.3774_5insT (E1259fsX1)	Szymanska (2012)
MKS	Exon 29	c.3584delT	Exon 29	c.3584delT	Mougou-Zerelli (2009)

Table S4. Tabular presentation of data

Figure	Sample	Value 1	Value 2	Value 3
3C	C1	102.1774152	108.7317317	94.65392308
	C2	100.0053446	100.7555035	109.3339885
	C3	110.8963528	102.2962199	96.01194298
	54	59.80431573	57.03941778	49.58938901
	62	43.56808934	43.4187774	24.1010986
	182	48.43480804	49.75827661	17.85550174
	294	31.91719632	49.44754819	13.86263798
	582	15.20222189	7.871449466	3.558466723
	619	44.98910897	44.07026932	12.47522255
	620	37.67048643	44.15744785	17.54395383
Figure 4D	C1 Total CEP290	100	100	100
	C1 Exon 6 Skip	100	100	100
	C1 Exon 10 Skip	100	100	100
	C1 Exon 41 Skip	100	100	100
	C1 Exon 46 Skip	100	100	100
	54 Total CEP290	41.40299391	54.68173788	37.39955476
	54 Exon 6 Skip	39.30288169	47.1005235	45.78224137
	54 Exon 10 Skip	25.49096686	32.23846593	28.28893952
	54 Exon 41 Skip	50.2282181	45.47233521	46.21265877
	54 Exon 46 Skip	54.78986675	52.92366948	46.19219474
	62 Total CEP290	26.41034403	32.84070493	30.55056571
	62 Exon 6 Skip	29.92690521	32.51672803	36.35304205
	62 Exon 10 Skip	19.27985358	23.03615756	21.2352353
	62 Exon 41 Skip	24.1518231	26.98109865	30.37766741

	62 Exon 46 Skip	23.56595415	29.15513686	30.00962092
	182 Total CEP290	13.27515858	14.08070037	16.96093961
	182 Exon 6 Skip	17.88149172	15.32556322	19.17367781
	182 Exon 10 Skip	8.76836096	9.611070897	9.385237083
	182 Exon 41 Skip	12.05797042	12.70354455	14.88801171
	182 Exon 46 Skip	12.74013968	13.44436014	15.33923033
	294 Total CEP290	29.30130856	35.23211529	33.77054661
	294 Exon 6 Skip	31.94973787	31.92027531	37.71833768
	294 Exon 10 Skip	17.03339596	19.08843856	18.63825888
	294 Exon 41 Skip	14.70103873	18.62706142	17.46713623
	294 Exon 46 Skip	17.96414279	19.46836995	21.7686976
	582 Total CEP290	3.853010693	3.880848702	3.408319755
	582 Exon 6 Skip	11.37472049	12.17992369	13.6815776
	582 Exon 10 Skip	5.489768031	6.787946479	5.098234345
	582 Exon 41 Skip	64.09270214	57.33563577	52.06365496
	582 Exon 46 Skip	51.12886835	53.79339694	54.54483517
	619 Total CEP290	17.3117143	23.46837736	31.20287784
	619 Exon 6 Skip	17.94525713	15.87937461	18.40407314
	619 Exon 10 Skip	9.561405393	11.4951564	9.866956782
	619 Exon 41 Skip	8.840433956	10.21924133	9.133116207
	619 Exon 46 Skip	10.97930775	11.76703706	11.7589814
	620 Total CEP290	20.8243591	22.46300744	26.45107021
	620 Exon 6 Skip	15.93156612	19.85273943	19.87224816
	620 Exon 10 Skip	10.78066442	11.44365647	8.96347524
	620 Exon 41 Skip	9.876899223	9.56181299	9.396986589
	620 Exon 46 Skip	9.572502884	12.32498674	13.10583338
Figure 4E	C1	100	100	100

	54	137.8405153	144.6934886	131.3121125
	62	114.1554707	121.9685475	106.842885
	182	105.7018041	110.0732314	101.5039827
	294	75.57599642	79.40965172	71.92741828
	582	616.0297394	643.5550043	589.6817479
	619	57.51459467	60.27375182	54.88174371
	620	62.33005971	65.54010925	59.27723326
Figure S2 A	C1	100	100	100
	54	82.18801873	86.32214038	78.25188756
	62	104.6810282	107.1120648	102.3051669
	182	98.14590639	103.3926202	93.16543986
	294	87.35728959	89.38507667	85.37550483
	582	76.68413298	80.85561628	72.72786384
	619	66.85002477	71.86469831	62.185272
	620	74.38068812	78.41582819	70.55318924
Figure S2 B	C1	100	100	100
	54	53.4032704	56.8199972	50.19199983
	62	67.36167884	71.40785165	63.54477374
	182	52.19559637	55.82085819	48.80577563
	294	47.17191254	49.86954401	44.62020612
	582	35.60125489	37.78266237	33.54579245
	619	39.50206559	40.86213419	38.18726596
	620	41.69655219	43.23748642	40.21053509
Figure S2 C	C1	100	100	100
	54	149.2778383	158.3468524	140.7282348
	62	115.7490217	118.1495542	113.3972626
	182	110.8800644	114.2355453	107.6231452

	294	88.27029963	92.18385087	84.52289336
	582	568.4368173	591.6415929	546.1421561
	619	70.51489802	73.33697781	67.80141467
	620	75.05395488	76.64334504	73.49752466