

Skippy Reference: variants that create ectopic splice sites (hg18)

SNP No.	Chr	Position	Gene	Potential Coding effect	Splice site activation	Variant (DNA)	max(Ass) Reference	
1	3	15651990	BTD	Missense	3'	G->A	7.96	(1)
2	4	155708309	FGB	Missense	3'	T->A	8.37	(2)
3	6	31432182	HLA-B	Missense	3'	G->C	9.95	(3)
4	11	107511124	ACAT1	Missense	3'	C->T	2.11	(4)
5	15	41282727	EPB42	Missense	3'	G->T	13.31	(5)
6	19	17860206	SLC5A5	Missense	3'	C->G	8.06	(6)
7	X	32238252	DMD	Nonsense	3'	T->G	8.59	(7)
8	11	67567654	TCIRG1	Synonymous	3'	G->A	7.95	(8)
9	19	11084983	LDLR	Synonymous	3'	C->A	8.04	(9)
10	X	153838609	F8	Synonymous	3'	G->T	2.51	(10)
11	1	154375026	LMNA	Missense	5'	G->A	1.53	(11)
12	4	89215079	PKD2	Nonsense	5'	C->T	0	(12)
13	5	70980772	MCCB	Missense	5'	A->G	8.18	(13)
14	7	91702781	KRIT1	Missense	5'	C->G	1.81	(14)
15	7	91703738	KRIT1	Missense	5'	A->G	8.18	(14)
16	10	89682830	PTEN	Missense	5'	C->G	8.27	(15)
17	11	107708775	ATM	Missense	5'	C->T	7.75	(16)
18	16	67413594	CDH1	Missense	5'	C->T	7.75	(17)
19	17	26551666	NF1	Missense	5'	C->T	7.75	(18)
20	17	26580523	NF1	Missense	5'	G->A	3.81	(19)
21	17	26565668	NF1	Nonsense	5'	A->G	8.18	(19)
22	17	26583297	NF1	Missense	5'	T->A	5.33	(18)
23	17	38512021	BRCA1	Missense	5'	T->G	8.6	(20)
24	17	45619024	COL1A1	Missense	5'	A->G	8.18	(21)
25	X	100516810	BTK	Nonsense	5'	A->G	8.18	(22)
26	X	133436951	HPRT1	Missense	5'	G->T	7.65	(23)
27	X	135560190	CD40L	Nonsense	5'	G->T	4.23	(24)
28	X	148392770	IDS	Missense	5'	C->G	0	(25)
29	X	153235823	FLNA	Missense	5'	C->T	0	(26)
30	1	154375028	LMNA	Synonymous	5'	C->T	0.49	(27)
31	1	153474560	GBA	Synonymous	5'	A->G	8.18	(28)
32	1	156912581	SPTA1	Synonymous	5'	A->G	8.18	(29)
33	2	219382723	CYP27A1	Synonymous	5'	G->T	7.65	(30)
34	3	48593334	COL7A1	Synonymous	5'	C->T	7.75	(31)
35	3	143757971	ATR	Synonymous	5'	A->G	0	(32)
36	3	185449258	ALG3	Synonymous	5'	C->T	0.75	(33)
37	5	42747170	GHR	Synonymous	5'	C->T	7.76	(34)
38	5	42735837	GHR	Synonymous	5'	A->G	4.8	(35)
39	7	65070189	GUSB	Synonymous	5'	C->T	7.76	(36)
40	11	5204749	HBB	Synonymous	5'	G->A	2.24	(37)
41	11	5204753	HBB	Synonymous	5'	T->A	2.28	(38)
42	12	108497085	MVK	Synonymous	5'	C->T	7.75	(39)
43	12	46535733	VDR	Synonymous	5'	C->G	3.5	(40)
44	15	70428488	HEXA	Synonymous	5'	T->A	4.52	(41)
45	16	162980	HBA2	Synonymous	5'	C->T	7.76	(42)
46	16	66027759	HSD11B2	Synonymous	5'	C->G	2.51	(43)
47	17	42731797	ITGB3	Synonymous	5'	C->T	7.76	(44)
48	17	26580468	NF1	Synonymous	5'	G->A	3.51	(19)
49	17	26586877	NF1	Synonymous	5'	C->T	7.75	(19)
50	19	17808957	JAK3	Synonymous	5'	C->T	7.75	(45)
51	19	806755	ELA2	Synonymous	5'	C->A	7.03	(46)
52	X	100500293	BTK	Synonymous	5'	A->G	0	(47)
53	X	153301140	TAZ	Synonymous	5'	G->A	0	(48)
54	X	148376419	IDS	Synonymous	5'	C->T	7.75	(49)

1. Pomponio, R., Reynolds, T., Mandel, H., Admoni, O., Melone, P., Buck, G. and Wolf, B. (1997). Profound biotinidase deficiency caused by a point mutation that creates a downstream

- cryptic 3' splice acceptor site within an exon of the human biotinidase gene. *Hum Mol Genet*, *6*, 739 - 745.
2. Asselta, R., Duga, S., Spena, S., Peyvandi, F., Castaman, G., Malcovati, M., Mannucci, P. and Tenchini, M. (2004). Missense or splicing mutation? The case of a fibrinogen Bbeta-chain mutation causing severe hypofibrinogenemia. *Blood*, *103*, 3051 - 3054.
 3. Tamouza, R., El Kassar, N., Schaeffer, V., Carbonnelle, E., Tatari, Z., Marzais, F., Fortier, C., Poirier, J., Sadki, K., Bernaudin, F. *et al.* (2000). A novel HLA-B*39 allele (HLA-B*3916) due to a rare mutation causing cryptic splice site activation. *Hum Immunol*, *61*, 467 - 473.
 4. Nakamura, K., Fukao, T., Perez-Cerda, C., Luque, C., Song, X., Naiki, Y., Kohno, Y., Ugarte, M. and Kondo, N. (2001). A novel single-base substitution (380C>T) that activates a 5-base downstream cryptic splice-acceptor site within exon 5 in almost all transcripts in the human mitochondrial acetoacetyl-CoA thiolase gene. *Mol Genet Metab*, *72*, 115 - 121.
 5. Bruce, L., Ghosh, S., King, M., Layton, D., Mawby, W., Stewart, G., Oldenburg, P., Delaunay, J. and Tanner, M. (2002). Absence of CD47 in protein 4.2-deficient hereditary spherocytosis in man: an interaction between the Rh complex and the band 3 complex. *Blood*, *100*, 1878 - 1885.
 6. Pohlenz, J., Rosenthal, I., Weiss, R., Jhiang, S., Burant, C. and Refetoff, S. (1998). Congenital hypothyroidism due to mutations in the sodium/iodide symporter. Identification of a nonsense mutation producing a downstream cryptic 3' splice site. *J Clin Invest*, *101*, 1028 - 1035.
 7. Tran, V., Takeshima, Y., Zhang, Z., Habara, Y., Haginoya, K., Nishiyama, A., Yagi, M. and Matsuo, M. (2007). A nonsense mutation-created intraexonic splice site is active in the lymphocytes, but not in the skeletal muscle of a DMD patient. *Hum Genet*, *120*, 737 - 742.
 8. Frattini, A., Orchard, P., Sobacchi, C., Giliani, S., Abinun, M., Mattsson, J., Keeling, D., Andersson, A., Wallbrandt, P., Zecca, L. *et al.* (2000). Defects in TCIRG1 subunit of the vacuolar proton pump are responsible for a subset of human autosomal recessive osteopetrosis. *Nat Genet*, *25*, 343 - 346.
 9. Bourbon, M., Sun, X. and Soutar, A. (2007). A rare polymorphism in the low density lipoprotein (LDL) gene that affects mRNA splicing. *Atherosclerosis*, *195*, e17 - 20.
 10. Tavassoli, K., Eigel, A., Dworniczak, B., Valtseva, E. and Horst, J. (1998). Identification of four novel mutations in the factor VIII gene: three missense mutations (E1875G, G2088S, I2185T) and a 2-bp deletion (1780delTC). *Hum Mutat*, S260 - 262.
 11. Eriksson, M., Brown, W., Gordon, L., Glynn, M., Singer, J., Scott, L., Erdos, M., Robbins, C., Moses, T., Berglund, P. *et al.* (2003). Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature*, *423*, 293 - 298.
 12. Reynolds, D., Hayashi, T., Cai, Y., Veldhuisen, B., Watnick, T., Lens, X., Mochizuki, T., Qian, F., Maeda, Y., Li, L. *et al.* (1999). Aberrant splicing in the PKD2 gene as a cause of polycystic kidney disease. *J Am Soc Nephrol*, *10*, 2342 - 2351.
 13. Baumgartner, M., Almashanu, S., Suormala, T., Obie, C., Cole, R., Packman, S., Baumgartner, E. and Valle, D. (2001). The molecular basis of human 3-methylcrotonyl-CoA carboxylase deficiency. *J Clin Invest*, *107*, 495 - 504.
 14. Verlaan, D., Siegel, A. and Rouleau, G. (2002). Krit1 missense mutations lead to splicing errors in cerebral cavernous malformation. *Am J Hum Genet*, *70*, 1564 - 1567.
 15. Reifenberger, J., Rauch, L., Beckmann, M., Megahed, M., Ruzicka, T. and Reifenberger, G. (2003). Cowden's disease: clinical and molecular genetic findings in a patient with a novel PTEN germline mutation. *Br J Dermatol*, *148*, 1040 - 1046.
 16. Teraoka, S., Telatar, M., Becker-Catania, S., Liang, T., Onengut, S., Tolun, A., Chessa, L., Sanal, O., Bernatowska, E., Gatti, R. *et al.* (1999). Splicing defects in the ataxia-telangiectasia gene, ATM: underlying mutations and consequences. *Am J Hum Genet*, *64*, 1617 - 1631.
 17. Kaurah, P., MacMillan, A., Boyd, N., Senz, J., De Luca, A., Chun, N., Suriano, G., Zaor, S., Van Manen, L., Gilpin, C. *et al.* (2007). Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. *JAMA*, *297*, 2360 - 2372.
 18. Ars, E., Serra, E., Garcia, J., Kruyer, H., Gaona, A., Lazaro, C. and Estivill, X. (2000). Mutations affecting mRNA splicing are the most common molecular defects in patients with neurofibromatosis type 1. *Hum Mol Genet*, *9*, 237 - 247.

19. Wimmer, K., Roca, X., Beiglbock, H., Callens, T., Etzler, J., Rao, A., Krainer, A., Fonatsch, C. and Messiaen, L. (2007). Extensive in silico analysis of NF1 splicing defects uncovers determinants for splicing outcome upon 5' splice-site disruption. *Hum Mutat*, *28*, 599 - 612.
20. Yang, Y., Swaminathan, S., Martin, B. and Sharan, S. (2003). Aberrant splicing induced by missense mutations in BRCA1: clues from a humanized mouse model. *Hum Mol Genet*, *12*, 2121 - 2131.
21. Symoens, S., Nuytinck, L., Legius, E., Malfait, F., Coucke, P. and De Paepe, A. (2004). Met>Val substitution in a highly conserved region of the pro-alpha1(I) collagen C-propeptide domain causes alternative splicing and a mild EDS/OI phenotype. *J Med Genet*, *41*, e96.
22. Hashimoto, S., Tsukada, S., Matsushita, M., Miyawaki, T., Niida, Y., Yachie, A., Kobayashi, S., Iwata, T., Hayakawa, H., Matsuoka, H. *et al.* (1996). Identification of Bruton's tyrosine kinase (Btk) gene mutations and characterization of the derived proteins in 35 X-linked agammaglobulinemia families: a nationwide study of Btk deficiency in Japan. *Blood*, *88*, 561 - 573.
23. O'Neill, J., Rogan, P., Cariello, N. and Nicklas, J. (1998). Mutations that alter RNA splicing of the human HPRT gene: a review of the spectrum. *Mutat Res*, *411*, 179 - 214.
24. Ramesh, N., Fuleihan, R., Swinton, P., Rosen, F. and Geha, R. (1995). A point mutation in exon 2 of the CD40 ligand gene causes the simultaneous expression of two defective mRNA species in X-linked hyperimmunoglobulinemia M. *Hum Mol Genet*, *4*, 759 - 761.
25. Jonsson, J., Aronovich, E., Braun, S. and Whitley, C. (1995). Molecular diagnosis of mucopolysaccharidosis type II (Hunter syndrome) by automated sequencing and computer-assisted interpretation: toward mutation mapping of the iduronate-2-sulfatase gene. *Am J Hum Genet*, *56*, 597 - 607.
26. Parrini, E., Ramazzotti, A., Dobyns, W., Mei, D., Moro, F., Veggiotti, P., Marini, C., Brilstra, E., Dalla Bernardina, B., Goodwin, L. *et al.* (2006). Periventricular heterotopia: phenotypic heterogeneity and correlation with Filamin A mutations. *Brain*, *129*, 1892 - 1906.
27. Paradisi, M., McClintock, D., Boguslavsky, R., Pedicelli, C., Worman, H. and Djabali, K. (2005). Dermal fibroblasts in Hutchinson-Gilford progeria syndrome with the lamin A G608G mutation have dysmorphic nuclei and are hypersensitive to heat stress. *BMC Cell Biol*, *6*, 27.
28. Dominissini, S., Buratti, E., Bembi, B., Baralle, M. and Pittis, M. (2006). Characterization of two novel GBA mutations causing Gaucher disease that lead to aberrant RNA species by using functional splicing assays. *Hum Mutat*, *27*, 119.
29. Baklouti, F., Marechal, J., Wilmotte, R., Alloisio, N., Morle, L., Ducluzeau, M., Denoroy, L., Mrad, A., Ben Aribia, M. and Kastally, R. (1992). Elliptocytogenic alpha I/36 spectrin Sfax lacks nine amino acids in helix 3 of repeat 4. Evidence for the activation of a cryptic 5'-splice site in exon 8 of spectrin alpha-gene. *Blood*, *79*, 2464 - 2470.
30. Chen, W., Kubota, S., Teramoto, T., Nishimura, Y., Yonemoto, K. and Seyama, Y. (1998). Silent nucleotide substitution in the sterol 27-hydroxylase gene (CYP 27) leads to alternative pre-mRNA splicing by activating a cryptic 5' splice site at the mutant codon in cerebrotendinous xanthomatosis patients. *Biochemistry*, *37*, 4420 - 4428.
31. Gardella, R., Zoppi, N., Zambruno, G., Barlati, S. and Colombi, M. (2002). Different phenotypes in recessive dystrophic epidermolysis bullosa patients sharing the same mutation in compound heterozygosity with two novel mutations in the type VII collagen gene. *Br J Dermatol*, *147*, 450 - 457.
32. O'Driscoll, M., Ruiz-Perez, V., Woods, C., Jeggo, P. and Goodship, J. (2003). A splicing mutation affecting expression of ataxia-telangiectasia and Rad3-related protein (ATR) results in Seckel syndrome. *Nat Genet*, *33*, 497 - 501.
33. Denecke, J., Kranz, C., Kemming, D., Koch, H. and Marquardt, T. (2004). An activated 5' cryptic splice site in the human ALG3 gene generates a premature termination codon insensitive to nonsense-mediated mRNA decay in a new case of congenital disorder of glycosylation type Id (CDG-Id). *Hum Mutat*, *23*, 477 - 486.
34. Baumbach, L., Schiavi, A., Bartlett, R., Perera, E., Day, J., Brown, M., Stein, S., Eidson, M., Parks, J. and Cleveland, W. (1997). Clinical, biochemical, and molecular investigations of a genetic isolate of growth hormone insensitivity (Laron's syndrome). *J Clin Endocrinol Metab*, *82*, 444 - 451.

35. Berg, M., Guevara-Aguirre, J., Rosenbloom, A., Rosenfeld, R. and Francke, U. (1992). Mutation creating a new splice site in the growth hormone receptor genes of 37 Ecuadorean patients with Laron syndrome. *Hum Mutat*, *1*, 24 - 32.
36. Yamada, S., Tomatsu, S., Sly, W., Islam, R., Wenger, D., Fukuda, S., Sukegawa, K. and Orii, T. (1995). Four novel mutations in mucopolysaccharidosis type VII including a unique base substitution in exon 10 of the beta-glucuronidase gene that creates a novel 5'-splice site. *Hum Mol Genet*, *4*, 651 - 655.
37. Suwanmanee, T., Sierakowska, H., Fucharoen, S. and Kole, R. (2002). Repair of a splicing defect in erythroid cells from patients with beta-thalassemia/HbE disorder. *Mol Ther*, *6*, 718 - 726.
38. Goldsmith, M., Humphries, R., Ley, T., Cline, A., Kantor, J. and Nienhuis, A. (1983). "Silent" nucleotide substitution in a beta+-thalassemia globin gene activates splice site in coding sequence RNA. *Proc Natl Acad Sci USA*, *80*, 2318 - 2322.
39. Hospach, T., Lohse, P., Heilbronner, H. and Dannecker, G. (2005). Pseudodominant inheritance of the hyperimmunoglobulinemia D with periodic fever syndrome in a mother and her two monozygotic twins. *Arthritis Rheum*, *52*, 3606 - 3610.
40. Cockerill, F., Hawa, N., Yousaf, N., Hewison, M., O'Riordan, J. and Farrow, S. (1997). Mutations in the vitamin D receptor gene in three kindreds associated with hereditary vitamin D resistant rickets. *J Clin Endocrinol Metab*, *82*, 3156 - 3160.
41. Wicklow, B., Ivanovich, J., Plews, M., Salo, T., Noetzel, M., Lueder, G., Cartegni, L., Kaback, M., Sandhoff, K., Steiner, R. *et al.* (2004). Severe subacute GM2 gangliosidosis caused by an apparently silent HEXA mutation (V324V) that results in aberrant splicing and reduced HEXA mRNA. *Am J Med Genet A*, *127A*, 158 - 166.
42. Hartevelde, C., Wijermans, P., van Delft, P., Rasp, E., Haak, H. and Giordano, P. (2004). An alpha-thalassemia phenotype in a Dutch Hindustani, caused by a new point mutation that creates an alternative splice donor site in the first exon of the alpha2-globin gene. *Hemoglobin*, *28*, 255 - 259.
43. Lavery, G., Ronconi, V., Draper, N., Rabbitt, E., Lyons, V., Chapman, K., Walker, E., McTernan, C., Giacchetti, G., Mantero, F. *et al.* (2003). Late-onset apparent mineralocorticoid excess caused by novel compound heterozygous mutations in the HSD11B2 gene. *Hypertension*, *42*, 123 - 129.
44. Xie, J., Pabon, D., Jayo, A., Butta, N. and Gonzalez-Manchon, C. (2005). Type I Glanzmann thrombasthenia caused by an apparently silent beta3 mutation that results in aberrant splicing and reduced beta3 mRNA. *Thromb Haemost*, *93*, 897 - 903.
45. Candotti, F., Oakes, S., Johnston, J., Giliiani, S., Schumacher, R., Mella, P., Fiorini, M., Ugazio, A., Badolato, R., Notarangelo, L. *et al.* (1997). Structural and functional basis for JAK3-deficient severe combined immunodeficiency. *Blood*, *90*, 3996 - 4003.
46. Dale, D., Person, R., Bolyard, A., Aprikyan, A., Bos, C., Bonilla, M., Boxer, L., Kannourakis, G., Zeidler, C., Welte, K. *et al.* (2000). Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia. *Blood*, *96*, 2317 - 2322.
47. Yip, K., Chan, S., Ip, W. and Lau, Y. (2000). Bruton's tyrosine kinase mutations in 8 Chinese families with X-linked agammaglobulinemia. *Hum Mutat*, *15*, 385.
48. Donati, M., Malvagia, S., Pasquini, E., Morrone, A., La Marca, G., Garavaglia, B., Toniolo, D. and Zammarchi, E. (2006). Barth syndrome presenting with acute metabolic decompensation in the neonatal period. *J Inherit Metab Dis*, *29*, 684.
49. Flomen, R., Green, P., Bentley, D., Giannelli, F. and Green, E. (1992). Detection of point mutations and a gross deletion in six Hunter syndrome patients. *Genomics*, *13*, 543 - 550.