N

Human Ortholog Candidates

Drosophila melanogaster - Homo sapiens

Exclude low score

Human Ortholg Candidate(s)	DIOPT Score	Best score from Human gene to Fly?	MARRVEL Link
NOTCH1	10/12	Yes	MARRVEL it
NOTCH2	8/12	Yes	MARRVEL it
NOTCH3	8/12	Yes	MARRVEL it
NOTCH4	5/12	Yes	MARRVEL it

INPUT
Variant
Gene
NOTCH4

DATABASES
OMIM
ExAC / Geno2MP
ClinVar
DGV

MODEL ORGANISMS
Predicted Orthologs
Protein Domain
Protein Alignment

New search

Human Gene Description (OMIM)

NOTCH, DROSOPHILA, HOMOLOG OF, 4; NOTCH4

MIM number: 164951

Description: Notch proteins are single-pass transmembrane receptors that regulate cell fate decisions during development. The Notch family includes 4 receptors, NOTCH1 (190198), NOTCH2 (600275), NOTCH3 (600276), and NOTCH4, whose ligands include JAG1 (601920), JAG2 (602570), DLL1 (606582), DLL3 (602768), and DLL4 (605185). All of the receptors have an extracellular domain containing multiple epidermal growth factor (EGF; 131530)-like repeats and an intracellular region containing the RAM domain, ankyrin repeats, and a C-terminal PEST domain (Das et al., 2004).

Gene-Phenotype Relationships

OMIM

No OMIM gene-phenotype relationships found

Reported Alleles From OMIM

NOTCH4

No OMIM allelic variants found

Control Population Gene Summary

NOTCH4 (ExAC Gene Table)

Constraint from ExAC	Expected no. variants	Observed no. variants	ConstraintMetric
Synonymous	333.3	246	z=2.96
Missense	737.1	601	z=2.45
LoF	59.2	27	pLI=0.00
CNV	7.5	10	z=-0.28

Geno2MP Total Heterozygote Count — NOTCH4: 258

Geno2MP Total Homozygote Count — NOTCH4: 67

Disease Population (Geno2MP Database)

NOTCH4

Variant	rsID	HPO Profiles	# het	# hom
6:32163664 C>T	rs8192581	1	0	1
6:32165065 T>G	NA	1	1	0
6:32165200 C>G	NA	3	2	0
6:32165201 G>A	rs148746475	3	3	0
6:32165237 C>T	NA	1	1	0
6:32165201 G>A	rs148746475	3	3	0
6:32165237 C>T	NA	1	1	0
6:32165258 C>T	NA	1	1	0
6:32165300 A>G	rs8192576	40	79	1
6:32169952 C>A	rs151325272	1	0	1
6:32170009 C>T	rs61729677	1	0	1

Benign (ClinVar): 4 | Likely Benign (ClinVar): 2 | Pathogenic (ClinVar): 2 | Likely Pathogenic (ClinVar): 0 | Risk Factor (ClinVar): 0 | Uncertain Significance (ClinVar): 6 | Conflicting Interpretations (ClinVar): 0

Reported Alleles From ClinVar

NOTCH4

Variation	Location	Condition(s)	Frequency	Clinical Significance	Review Status
Single allele	Chr6:32188383-32629802	Ductal breast carcinoma		Uncertain significance	no assertion criteria provided
NM_004557.3(NOTCH4):c.4927C>T (p.Arg1643Ter)	Chr6:32165201	not specified	GO-ESP:0.00021(A)	Uncertain significance	criteria provided, single submitter
NM_004557.3(NOTCH4):c.2443T>G (p.Cys815Gly)	Chr6:32180684	Anophthalmia - microphthalmia	GMAF:0.00340(C)GO-ESP:0.00468(C)	Likely benign	criteria provided, single submitter
NM_004557.3(NOTCH4):c.45_47delGCT (p.Leu16del)	Chr6:32191659-32191661	not specified	GMAF:0.48520(AGC)	Benign	criteria provided, single submitter
NM_004557.3(NOTCH4):c.36_47delGCTGCTGCTGCT (p.Leu13_Leu16del)	Chr6:32191659-32191670	not specified	GO-ESP:0.01625(-)	Benign	criteria provided, single submitter
NC_000006.11:g.(?_32052479)_(32184403_?)dup	Chr6:32052479-	See cases		Uncertain	criteria provided, single

Copy Number Variation In Control Population (DGV Database)

NOTCH4

Show 10 entries — Search:

Position	Size	Type	Subtype	Frequency	Gain	Loss	Sample Size	References	Genes
6 31423100 33448200	2025100	CNV	deletion	0.50000000	0	1	2	24896259	ABHD16A AGER AGPAT1 AIF1 APOM ATF6B ATP6V1G2 ATP6V1G2-DDX39B B3GALT4 BAG6 BRD2 BTNL2 C2 C4A C4B C4B_2 C6orf10 C6orf25 C6orf47 C6orf48 CFB SAPCD1 MSH5 SAPCD1 VWA7 VARS LSM2 HSPA1L HSPA1A HSPA1B SNORD52 SNORD48 SLC44 DPA1 HLA-DPB1 HLA-DPB2 RXRB SLC39A7 HSD17B8 RING1 HCG25 VPS52 RPS18 WDR46 RGL2
6 31424199 33448300	2024101	CNV	deletion	1.00000000	0	1	1	25765185	ABHD16A AGER AGPAT1 AIF1 APOM ATF6B ATP6V1G2 ATP6V1G2-DDX39B B3GALT4 BAG6 BRD2 BTNL2 C2 C4A C4B C4B_2 C6orf10 C6orf25 C6orf47 C6orf48 CFB SAPCD1 MSH5 SAPCD1 VWA7 VARS LSM2 HSPA1L HSPA1A HSPA1B SNORD52 SNORD48 SLC44 DPA1 HLA-DPB1 HLA-DPB2 RXRB SLC39A7 HSD17B8 RING1 HCG25 VPS52 RPS18 WDR46 RGL2
6 31280327 32484368	1204041	CNV	loss	0.00028701	0	5	17421	21841781	ABHD16A AGER AGPAT1 AIF1 APOM ATF6B ATP6V1G2 ATP6V1G2-DDX39B BAG6 BTNL2 C2 C4A B HCP5 MICA MICB MCCD1 SNORD117 SNORD84 NFKBIL1 LTA TNF LTB LST1 NCR3 PRRC2A SN EGFL8 RNF5 PBX2 GPSM3 **NOTCH4** HCG23 HLA-DRA RNF5P1 MIR6891 HCG26 LOC102060414 M
6 31425100 32562200	1137100	CNV	deletion	0.50000000	0	1	2	24896259	ABHD16A AGER AGPAT1 AIF1 APOM ATF6B ATP6V1G2 ATP6V1G2-DDX39B BAG6 BTNL2 C2 C4A C4B C4B_2 C6orf10 C6orf25 C6orf47 C6orf48 CFB CLIC1 CSNK2B SAPCD1 MSH5 SAPCD1 VWA7 VARS LSM2 HSPA1L HSPA1A HSPA1B SNORD52 SNORD48 SLC44
6 31785438 32651056	865618	CNV	loss	0.00309971	0	54	17421	21841781	AGER AGPAT1 ATF6B BTNL2 C2 C4A C4B C4B_2 C6orf10 C6orf48 CFB CYP21A1P CYP21A2 DXO DQB1 RNF5P1 LOC102060414 MIR1236 LOC100507547 MIR6721 MIR6833 HLA-DRB6
6 31953467 32779803	826336	CNV	loss	0.00011480	0	2	17421	21841781	AGER AGPAT1 ATF6B BTNL2 C4A C4B C4B_2 C6orf10 CYP21A1P CYP21A2 EGFL8 FKBPL STK19
6 31871512 32209113	337601	CNV	gain+loss	0.12962963	4	31	270	17122850	AGER AGPAT1 ATF6B C2 C4A C4B C4B_2 CFB CYP21A1P CYP21A2 DXO EGFL8 FKBPL NELFE SI
6 32043978 32189787	145809	CNV	loss	0.01052632	0	1	95	17160897	AGER AGPAT1 ATF6B EGFL8 FKBPL TNXB PPT2 PRRT1 PPT2-EGFL8 RNF5 PBX2 GPSM3 **NOTCH**
6 32064726 32171683	106957	CNV	loss	0.00005740	0	1	17421	21841781	AGER AGPAT1 ATF6B EGFL8 FKBPL TNXB PPT2 PRRT1 PPT2-EGFL8 RNF5 PBX2 GPSM3 **NOTCH**
6 32151443 32177900	26457	CNV	loss	0.00064226	0	1	1557	19166990	AGER PBX2 GPSM3 **NOTCH4**

Showing 1 to 10 of 14 entries — Previous 1 2 Next

Gene Function Table

NOTCH4

Show only best DIOPT v6 score gene

	Homolog	DIOPT Score	Expression	Molecular function	Cellular component	Biological process
Human	NOTCH4 PubMed Monarch	NA	No data available Show all / GTEx	• protein binding	• cell surface	• mammary gland development
Mouse	Notch4 PubMed IMPC	11/13	• embryo ectoderm • cardiovascular system • alimentary system • limbs • nervous system Show 12 more Open on MGI	• Notch binding • protein binding	• endoplasmic reticulum • cytoplasmic vesicle	• patterning of blood vessels • morphogenesis of a branching structure • regulation of Notch signaling pathway • embryo development • regulation of protein localization Show 6 more
Zebrafish	notch1a PubMed	2/12	• brain • central nervous system • dorsal aorta • ectoderm • hindbrain Show 32 more Open on ZFIN	No term based on experiment	No term based on experiment	• somitogenesis • neural plate development • hematopoietic progenitor cell differentiation • Notch signaling pathway • determination of left/right symmetry Show 15 more
	notch3 PubMed	2/12	• artery • brain • caudal artery • central nervous system • dorsal aorta Show 35 more Open on ZFIN	No term based on experiment	No term based on experiment	• neural plate development • liver development • hematopoietic progenitor cell differentiation • Notch signaling pathway • oligodendrocyte development Show 17 more
	notch2 PubMed	2/12	• brain • ectoderm • otic vesicle • presumptive segmental plate • pharyngeal arch 3-7 skeleton Show 21 more Open on ZFIN	No term based on experiment	No term based on experiment	• liver development • vasculature development • lymphangiogenesis • tissue regeneration • face morphogenesis Show 1 more
	notch1b PubMed	2/12	• artery • brain • cardiac ventricle • central nervous system • dorsal aorta Show 36 more Open on ZFIN	No term based on experiment	No term based on experiment	• blood vessel development • lymphangiogenesis • hematopoietic progenitor cell differentiation • ventral spinal cord interneuron differentiation • rhombomere boundary formation Show 5 more
Drosophila	N PubMed	3/12	• Thoracic-Abdominal Ganglion • Ovary Show all (25)	• chromatin binding • protein binding	• intracellular • nucleus • cytoplasm • lysosome • endosome Show 8 more	• compound eye morphogenesis • actin filament organization • heterophilic cell-cell adhesion via plasma membrane cell adhesion molecules • I-kappaB phosphorylation • germarium-derived egg chamber formation Show 71 more
C Elegans	lin-12 PubMed	3/12	Open on WormBase	• transmembrane signaling receptor activity • protein binding	• nematode larval development • nucleus • plasma membrane • apical plasma membrane • vulval development Show 2 more	• cell fate specification • Notch signaling pathway • mechanosensory behavior • response to mechanical stimulus • oviposition Show 3 more
	glp-1 PubMed	3/12	Open on WormBase	• transmembrane signaling receptor activity	• cytoplasm • plasma membrane • endomembrane system • lateral plasma membrane • maintenance of dauer Show 1 more	• cell fate specification • Notch signaling pathway • gamete generation • germ cell development • mechanosensory behavior Show 10 more

Human Gene Protein Domains DIOPT V6

NOTCH4

Index	Domain name	Domain start	Domain stop	Domain description	Protein ID	External ID
hs1	Ank_2	1638	1731	Ankyrin repeats (3 copies); pfam12796	NP_004548.3	CDD:205076
hs1	EGF_CA	<364	>384	Calcium-binding EGF-like domain, present in a large number of membrane-bound and extracellular (mostly animal) proteins. Many of these proteins require calcium for their biological function and calcium-binding sites have been found to be located at the...; cl09941	NP_004548.3	CDD:209104
hs1	LNR 1	1170	1213	propagated from UniProtKB/Swiss-Prot (Q99466.2)	NP_004548.3	
hs1	ANK 5	1766	1798	propagated from UniProtKB/Swiss-Prot (Q99466.2)	NP_004548.3	
hs1	ANK 3	1700	1732	propagated from UniProtKB/Swiss-Prot (Q99466.2)	NP_004548.3	
hs1	EGF_CA	589	625	Calcium-binding EGF-like domain, present in a large number of membrane-bound and extracellular (mostly animal) proteins. Many of these proteins require calcium for their biological function and calcium-binding sites have been found to be located at the...; cd00054	NP_004548.3	CDD:28936
hs1	EGF_CA	931	965	Calcium-binding EGF-like domain, present in a large number of membrane-bound and extracellular (mostly animal) proteins. Many of these proteins require calcium for their biological function and calcium-binding sites have been found to be located at the...; cd00054	NP_004548.3	CDD:28936
hs1	EGF_CA	769	803	Calcium-binding EGF-like domain, present in a large number of membrane-bound and extracellular (mostly animal) proteins. Many of these proteins require calcium for their biological function and calcium-binding sites have been found to be located at the...; cd00054	NP_004548.3	CDD:28936
hs1	Notch	1254	1285	LNR domain; pfam00066	NP_004548.3	CDD:200970
hs1	Notch	1209	1246	LNR domain; pfam00066	NP_004548.3	CDD:200970
hs1	NODP	1378	>1415	NOTCH protein; pfam07684	NP_004548.3	CDD:191811
hs1	Notch	1165	1204	LNR domain; pfam00066	NP_004548.3	CDD:200970
hs1	ANK	1581	1721	ankyrin repeats; ankyrin repeats mediate protein-protein interactions in very diverse families of proteins. The number of ANK repeats in a protein can range from 2 to over 20 (ankyrins, for example). ANK repeats may occur in combinations with other...; cd00204	NP_004548.3	CDD:29261
hs1	LNR 3	1251	1294	propagated from UniProtKB/Swiss-Prot (Q99466.2)	NP_004548.3	
hs1	EGF_CA	314	353	Calcium-binding EGF-like domain, present in a large number of membrane-bound and extracellular (mostly animal) proteins. Many of these proteins require calcium for their biological function and calcium-binding sites have been found to be located at the...; cd00054	NP_004548.3	CDD:28936
hs1	EGF_CA	551	587	Calcium-binding EGF-like domain, present in a large number of membrane-bound and extracellular (mostly animal) proteins. Many of these proteins require calcium for their biological function and calcium-binding sites have been found to be located at the...; cd00054	NP_004548.3	CDD:28936

Multiple Protein Alignment DIOPT V6

NOTCH4

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hs1 ------------------------MQ-----PPSLLLLLL-------------------------LLLLCVS-------VVRPRGLLCGSFPEPCANGGTCLSLSLGQGTCQCAPGFLGET[61]
mm1 ------------------------MQ------PQLLLLL-------------------------LPLNFPVILT-------RVSSPELLCGGSPEPCANGGTCLRLSRGQGICQCAPGFLGET[62]
rn1 ------------------------MEGLGQGDPGRLGLGVKERGWIQHHAPGPHCGAGAAGQWPVGRYLVVVGHRFH-HLVSSSELLCGGSPEPCANGGTCLRLSQGQGTCQCAPGFLGET[96]
dr1 --------------------------MGNYSL----W-------------------------IFLSILYLVH-------NSEGLLCVDTHRPCENGGMCI-----DSRCLCRPGYIGSL[52]
dr2 ---------------------MGQLPGVSSGGVIL-------------------------LLICFLKTSY----------ALQCIDHEKPCVN-GTCVISSNGTHYCRCAPGFLGEY[60]
dr3 ------------------------------MHL---FF-------------------------VKLIVVISLNT------LTQGLEC---SEKCQNGGTCEPTADGRGECKCLDLYAGPA[53]
dm1 MQSQRSRRRSRAPNTWICFWINKMHAVASLPASL-PLLL-------------------------LTLAFANLPNTVRGTDTALVAASC--TSVGCQNGGTCVTQLNGKTYCACDSHYVGDY[93]
ce1 ----------------------------MRIPTI-CFLF-------------------------LLISLSKSLHI-----------------------GSCLGLI----------------[28]
                                                                        :  .                          * *
hs1 CQFPDPCQNAQLCQNGGSCQALLPAPLGLPSSPSPLTPSFLCTCLPGFTGERCQAKLEDPC-PPSFCSKRGRCHIQASGRPQCSCMPGWTGEQCQLRDFCSANPCVNGGVC--LATYPQI[178]
mm1 CQFPDPCRDTQLCKNGGSCQALLPTPPSSRSPTSPLTPHFSCTCPSGFTGDRCQTHLEELC-PPSFCSNGGHCYVQASGRPQCSCEPGWTGEQCQLRDFCSANPCANGGVC--LATYPQI[179]
rn1 CQFPDPCWDTQLCENGGSCQALLPTAPSSHSPTSPLTPHFSCTCPSGFTGDRCQSPLEELC-PPSFCSNGGHCSVQVSGRPQCSCEPGWTGEQCQLRDFCSANPCANGGVC--LATYPQI[213]
dr1 CQHLDPCHRSP-CLNAAACKSQ--VANSIP-------------------------------------------------QYTCVCQRGFRGQDCSLVDACATSPCANGARCTNWNNH--Y[118]
dr2 CHHSDPCNLLY-CKNGGECKVS---VAGVPG-------SPSCVCPLGFAGEHCEIQKNSTCYPNNPCTNGGKCLLLPNDQYKCQCALGWTGQHCEQEDACLSSPCANKGICNALPNR-EY[168]
dr3 CQFRNPCFQSP-CRNGGVCRLIT-SANKVD---------EVCNCSLGYTDRLCLTPTNNVC-LGAPCRNGGTCFLTSIHNYRCKCPPGWSGKTCQQADPCASNPCANGGQCSPEDSD--F[159]
```

Highlight from Integer (1~n) to Integer (1~n) for hs rn mm dr dm ce