Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Gene Section
Review

CRLF2 (Cytokine receptor like factor 2)

Dafné Moreno-Lorenzana, RocÍo Juárez-Velázquez, Daniel Martínez-Anaya, Patricia Péez-Vera

Laboratorio de Genética y Cáncer. Instituto Nacional de Pediatría (DML, RJV, DMA, PPV); Cátedra CONACYT-Instituto Nacional de Pediatría (DML); Posgrado en Ciencias Biológicas, Universidad Nacional Autónoma de México (DMA). / e-Mail pperezvera@yahoo.com

Published in Atlas Database: February 2019
Online updated version : http://AtlasGeneticsOncology.org/Genes/CRLF2ID51262chXp22.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/70641/02-2019-CRLF2ID51262chXp22.pdf
DOI: 10.4267/2042/70641

Abstract

CRLF2 is a member of type I cytokine receptor family. CRLF2 forms a functional complex with IL-7 receptor α chain and thymic stromal lymphopoietin, this complex induces the activation of signal transducers and activators of transcription proteins. The overexpression of CRLF2 induced by genetic rearrangements has been described in acute lymphoblastic leukemia.

Keywords
CRLF2; Cytokine receptor; TSLP; Jak-Stat pathway.

Identity

Other names: CRL2, TSLPR

HGNC (Hugo): CRLF2

Location: Xp22.33 and Yp11.2, negative strand. ENSG00000205755

Local order

CRLF2 is located on chromosome X and Y, on the short arm and lies between RPL14P5 (ribosomal protein L4 pseudogene 5) and CSF2RA (colony stimulating factor 2 receptor alpha subunit). Entrez Gene ID: 64109

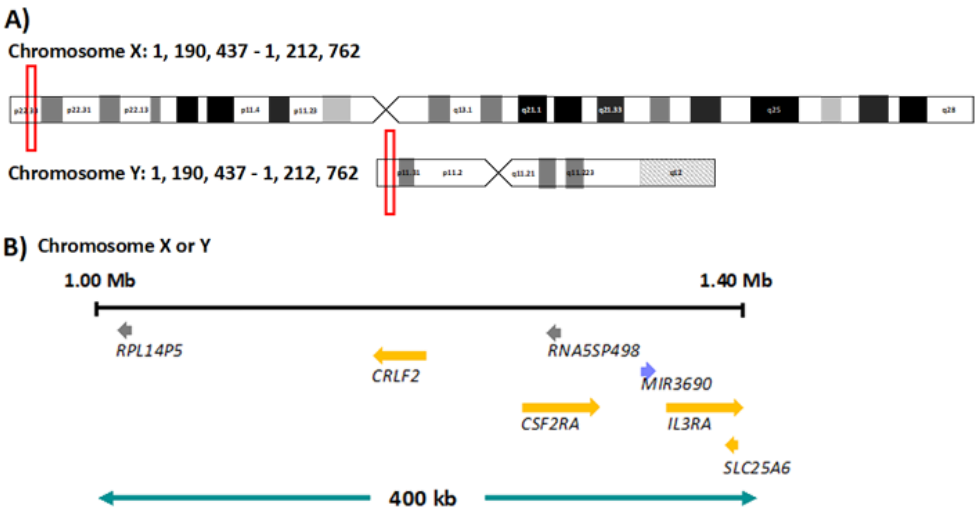

Figure 1. A) Chromosomal location of CRLF2 gene. B) Mapping of CRLF2 gene and local order on genomic context of the chromosome X and Y.

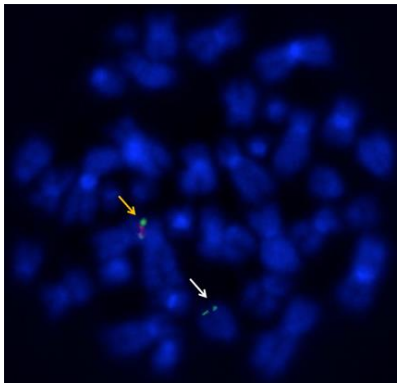

Figure 2. Chromosomes obtained from MHH-CALL-4 cell line positive to IGH/CRLF2 translocation detected by fluorescence in situ hybridization (FISH). The der(Y) chromosome is lost in the cell line. Metaphase hybridized with CRLF2 break-apart probe (Cytocell Aquarius) with a normal chromosome X (green-red signal, yellow arrow), and der(14) (green signal, white arrow).

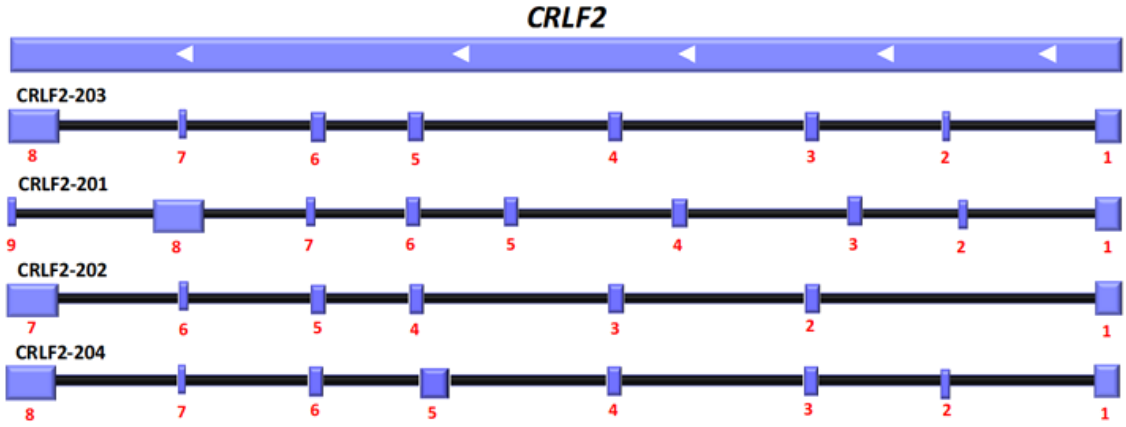

Figure 3. CRLF2 gene encodes four transcript variants: two with 8 exons, one with 9 exons, and one with 7 exons (exons are represented by violet boxes and introns by black line). ENSG00000205755, Entrez Gene ID: 64109

DNA/RNA

Description

CRLF2 gene is located in reverse strand of pseudo-autosomal region 1 (PAR1) in X and Y chromosomes. CRLF2 encompasses 22kb of DNA and give rise to four transcript variants with different lengths: 1.6, 1.5, 1.0 and 1.7 kb. ENSG00000205755

Transcription

CRLF2 gene encodes a member of type I cytokine receptor family and generate four transcript variants (Table 1). Three generate protein coding transcripts and one generates a non-sense mediated decay transcript.

According with gene expression array data CRLF2 is expressed, from highest to lowest, in: cervix > lung > bladder > small intestine > esophagus > stomach > skin > prostate > uterus > vagina > testes > colon > spleen > mammary gland > thyroid > whole blood.

It has been reported that in pathological conditions the transcription rate of CRLF2 is altered. CRLF2 overexpression (fold change > 2) is found in: microbial infection, immunodeficiency syndromes (X-linked hyper IgM syndrome), autoimmune diseases (arthritis), and cancer (esophagus dysplasia, papillary thyroid carcinoma and acute lymphoblastic leukemia). The CRLF2 subexpression (fold change < 2) has been reported only in cancer (myelodysplastic syndrome, non-small cell lung carcinoma, hepatobiliary carcinoma, colorectal carcinoma, pancreatic adenocarcinoma and breast carcinoma). ENSG00000205755; UniProt Q9HC73; neXtProt NX_Q9HC73

Table 1. Transcript variants and proteins

Name (RefSeq)	Exons	Coding Exons	Transcript Length	Protein Length	Type of transcript
CRLF2-203 (NM_022148)	8	8	1, 639 bp	371 residues	Protein coding
CRLF2-201	9	8	1, 545 bp	371 residues	Protein coding
CRLF2-202 (NM_001012288)	7	6	1, 013 bp	259 residues	Protein coding
CRLF2-204 (NR_110830)	8	5	1, 789 bp	232 residues	Non-sense mediated decay

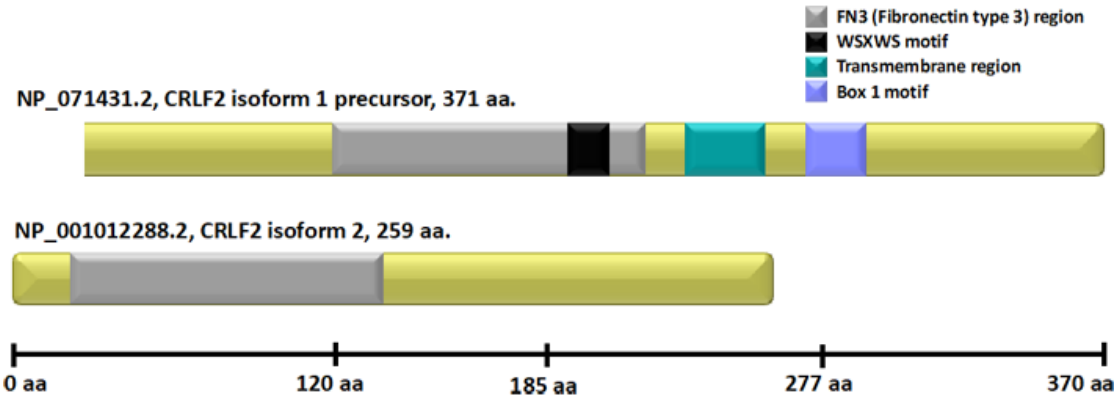

Figure 4. Isoform 1 is a single-pass type I membrane protein, have a length of 371 aa. Protein sequence includes four main regions: FN3 (Fibronectin type 3), encompassed from 109 to 207 aa; WSXWS motif, encompassed from 200 to 204 aa; Box 1 motif encompassed from 261 to 269 aa; Transmembrane region encompassed from 232 to 252 aa. Isoform 2 is a secreted protein an only have FN3 region, encompassed from 7 to 76 aa.

Protein

Description

CRLF2 gene encodes a member of the type I cytokine receptor family. CRLF2 has three protein coding transcripts: CRLF2-201, CRLF2-202, CRLF2-203 and CRLF2-204.

CRLF2-203 and CRLF2-201 transcript variants generate the longer isoform of 371 amino acids (42 kDa), also called isoform 1.

Isoform 1 has the protein regions that characterize this family gene: FN3 (Fibronectin type 3) region, WSXWS motif, Box 1 motif, and transmembrane region. Post-translational modifications of CRLF2 protein include glycosylation at asparagine residues (Asn169, Asn55 and Asn47) and phosphorylation at isoleucine (Ile271) and tyrosine (Tyr74) residues.

The other isoform, called isoform 2, is encoded by the transcript variant CRLF2-202. This isoform is shorter, 259 amino acids (26.6 kDa), at N-terminus compared with isoform 1 because lacks an alternate exon which results in translation initiation at a downstream start codon. ENSG00000205755; UniProt Q9HC73, Q9HC73-2, Q4V300; neXtProt NX_Q9HC73

Expression

CRLF2 protein is present in intestine, bone marrow, spleen, thymus, and is more abundant in dendritic cells. neXtProt NX_Q9HC73

Localisation

CRLF2 isoform 1 is a cell membrane protein and CRLF2 isoform 2 is a secreted protein.

Function

CRLF2 forms a functional complex with IL-7Rα (IL-7 receptor α chain) and TSLP (thymic stromal lymphopoietin).

Functional complex activation induces different signals depending on the type of cell and also exerts multiple functions. Heterocomplex is involved in a plethora of physiologic and pathologic immune functions, including: tolerance, allergy, autoimmune diseases and cancer. (Tsilingin et al., 2017).

CRLF2 is expressed mainly in dendritic cells and also hematopoietic cells including T cells, B cells, granulocytes, and mast cells.

Heterocomplex main function is the differentiation to T helper type 2 (Th2) cells. CRLF2-activated dendritic cells express OX40 ligand and trigger naive $CD4^+$ to differentiate into inflammatory Th2 cells and the expansion of allergen-specific Th2 memory cells (Lin et al., 2018).

According with phosphoproteome analysis in diverse cell types, after TSLP binds to the CRLF2/IL-7Rα heterocomplex, the phosphorylation of Janus kinase1 (JAK1) and 2 (JAK2) activates signal transducers and activators of transcription (STATs) proteins, including: STAT1, STAT3, STAT4, STAT5A, STAT5B and STAT6. Heterocomplex also activates other signaling molecules such as PI3K/AKT/MTOR pathway, SRC / TEC pathway, MAPK3 / MAPK1 (ERK1/2), NF-kB, MAPK8 / MAPK9 (JNK1 JNK2), and p38/MAPK activation (Zhong Jun et al., 2012; Zhong Jun et al., 2014).

In allergy or autoimmune disease has been described high expression of TSLP and overstimulation of TSLP/CRLF2/IL-7Rα complex. Tezepelumab is a human monoclonal antibody that blocks functional complex and is successfully used in asthma treatment (Van Rompaey et al., 2012).

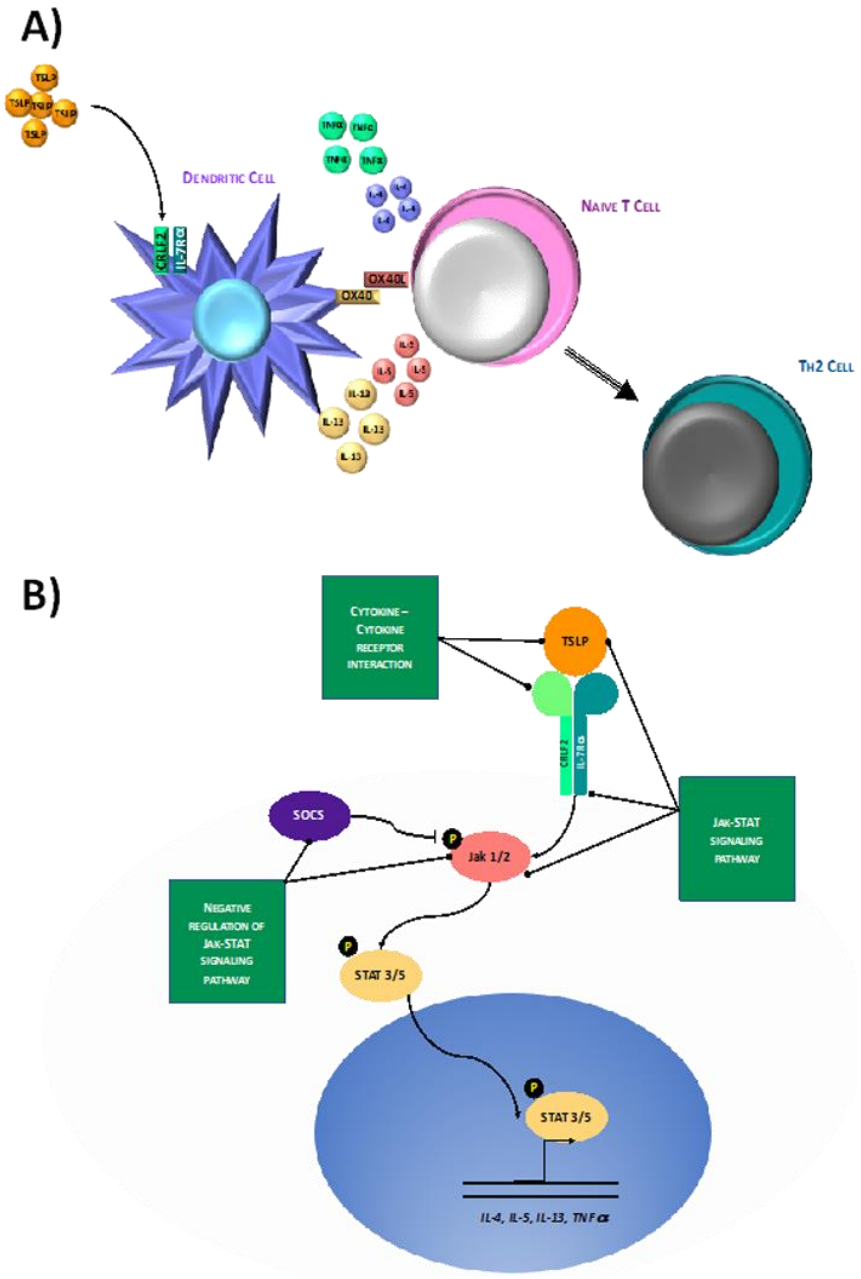

Figure 5. A) TSLP /CRLF2/ IL7R complex activation is implicated in Th2 differentiation. TSLP binds to CRLF2/IL-7Rα heterodimer in dendritic cells and promotes the expression of OX40 ligand (TNFSF4 (CD252)) and IL13, IL5, IL4 and TNF to induce Th2 differentiation. B) TSLP/CRLF2/IL-7Rα complex activation in dendritic cells. Activation of CRLF2 was described by first time in dendritic cells. This scheme exemplifies the main nodes involved.

The role of functional heterocomplex in cancer is still controversial, in certain neoplasia plays a pro-tumorigenic role, whereas in others, a protective role.

For example, in cervix, breast, and pancreas cancer has been describe an increase of metastasis associated with an overstimulation of TSLP/CRLF2/IL-7Rα. On the other hand, in colon and skin carcinoma, functional heterocomplex has been associated with better prognostic. In addition to above, CRLF2 gene has genetic alterations that promote cell survival in cancer.

The genetic rearrangements P2RY8/CRLF2 and IGH/CRLF2, generate CRLF2 overexpression, and the mutation Phe232Cys, encodes CRLF2 proteins capable of forming homodimers and self-activation, both described in acute lymphoblastic leukemia (Varricchi et al., 2018; Zhong Jun, 2014).

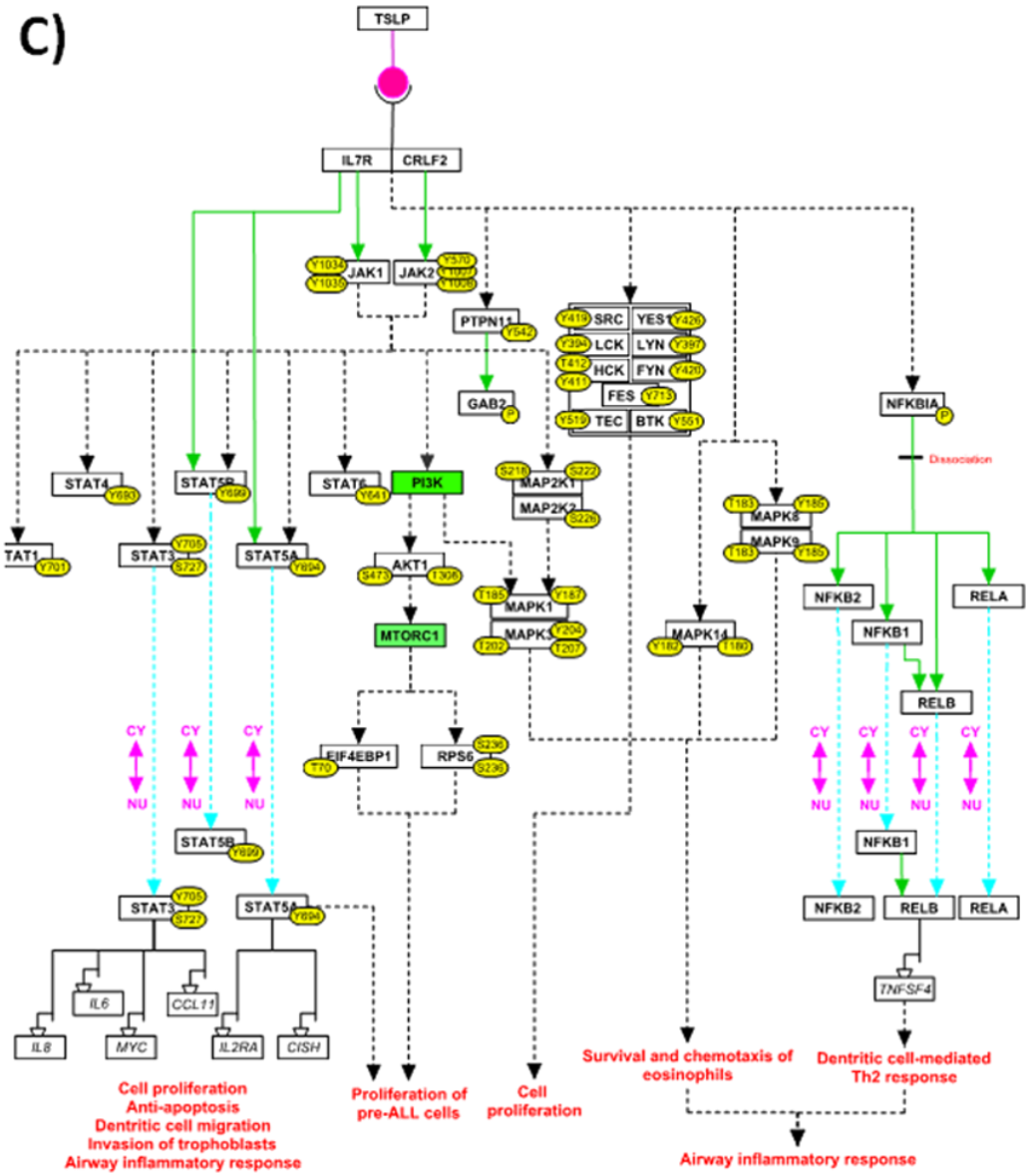

Figure 6. C) Phosphoproteomic analysis reveals multiple targets in TSLP/CRLF2/IL-7Rα pathway in different cell types. This scheme shows experimental curated data obtained from NetSlim.

Homology

Table 2. CRLF2 Orthologues

Name	Organism
CRLF2	P. troglodytes
CRLF2 (ENSCAFG00000011034)	C. lupus
LOC529792 (ENSBTAG00000020242)	B. taurus
Crlf2 (ENSMUSG00000033467)	M. musculus
Crlf2 (ENSRNOG00000049828)	R. novergicus
LOC418668 (ENSGALG00000016696)	G. gallus

Mutations

See Figure 7.

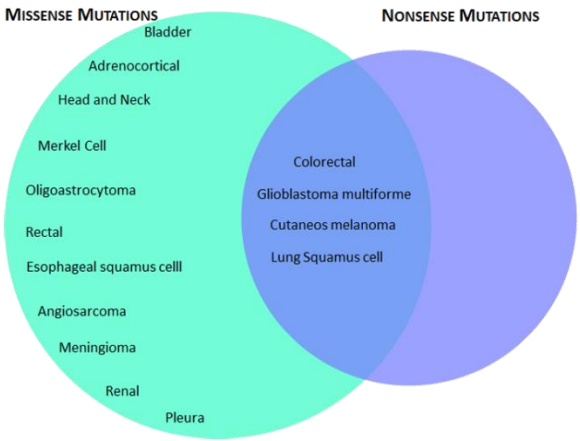

Figure 7. Mutations in CRLF2 have been identified in a wide range of cancer types. Most of them are missense mutations (green), nonsense mutations are also represented (violet).Somatic

CDS Mutation	Cancer Type	Type of Mutation
c.315C>A	Bladder Carcinoma	Missense
c.357C>A	Bladder Carcinoma	Missense
c.193G>A	Bladder Carcinoma	Missense
c.89T>A	Bladder Carcinoma	Missense
c.33C>G	Diffuse Large B Cell Lymphoma	Missense
c.415T>C	Diffuse Large B Cell Lymphoma	Missense
c.349C>T	Osteosarcoma	Missense
c.330T>C	Colon Carcinoma	Missense
c.384G>A	Colon Carcinoma	Missense
c.33C>G	Colon Carcinoma	Missense
c.159G>A	Rectum Carcinoma	Missense
c.474C>T	Adenocarcinoma	Missense
c.372C>T	Adenocarcinoma	Missense
c.411G>A	Adenocarcinoma	Missense
c.603C>T	Adenocarcinoma	Missense
c.405G>A	Adenocarcinoma	Missense
c.669G>A	Adenocarcinoma	Missense
c.642T>C	Adenocarcinoma	Missense
c.642T>C	Endometrioid Carcinoma	Missense
c.321C>T	Lung Carcinoma	Missense
c.384G>A	Pleura Carcinoma	Missense
c.456C>T	Melanoma	Missense
c.411G>A	Melanoma	Missense
c.468C>T	Melanoma	Missense
c.123C>T	Melanoma	Missense
c.630G>A	Melanoma	Missense
c.534G>A	Melanoma	Missense
c.438C>T	Melanoma	Missense
c.383C>T	Merkel Cell Carcinoma	Missense
c-.335G>T	Merkel Cell Carcinoma	Missense
c.604G>A	Urinary Tract Carcinoma	Missense
c.742C>A	Urinary Tract Carcinoma	Missense
c.208C>A	Neuroblastoma	Missense
c.139A>T	Glioma	Missense
c.404C>T	Glioma	Missense
c.365C>T	Glioma	Missense
c.598C>A	Glioma	Missense
c.404C>T	Glioma	Missense
c.313C>T	Glioma	Missense
c.74G>A	Glioma	Missense
c.632G>A	Glioma	Missense
c.445G>A	Meningioma	Missense
c.660G>T	Breast Carcinoma	Missense
c.734C>T	Breast Carcinoma	Missense
c.526G>C	Breast Carcinoma	Missense
c.297C>G	Cervix Carcinoma	Missense
c.658G>C	Cervix Carcinoma	Missense
c.566C>T	Endometrium Carcinoma	Missense
c.536A>T	Endometrium Carcinoma	Missense
c.643C>T	Endometrium Carcinoma	Missense
c.7C>T	Endometrium Carcinoma	Missense
c.496A>C	Endometrium Carcinoma	Missense
c.373G>A	Endometrium Carcinoma	Missense
c.346T>C	Endometrium Carcinoma	Missense
c.495A>C	Endometrium Carcinoma	Missense
c.248G>T	Kidney Carcinoma	Missense
c.526G>A	Liver Carcinoma	Missense
c.105C>G	Liver Carcinoma	Missense
c.671C>T	Acute Myeloid Leukemia	Missense
c.695T>G	B Cell Acute Lymphoblastic Leukemia	Missense
c.2T>A	Mantle Cell Lymphoma	Missense
c.340G>C	Marginal Zone Lymphoma	Missense
c.228C>T	Head and Neck Carcinoma	Missense
c.764G>A	Melanoma	No sense
c.764G>A	Melanoma	No sense
c.755G>A	Head and Neck Carcinoma	No sense
c.755G>A	Melanoma	No sense
c.451C>T	Melanoma	No sense
c.628C>T	Pancreas	No sense
c.137G>A	Colon Carcinoma	No sense
c.620C>G	Intestinal Adenocarcinoma	No sense
c.91C>T	Glioblastoma Multiforme	No sense
c.73G>T	Adenocarcinoma	No sense
c.54G>A	Head and Neck Carcinoma	No sense
c.25G>T	Lung Carcinoma	No sense

Table 3 CRLF2 mutations in cancer

Catalogue of Somatic Mutations in Cancer; cBioPortal for Cancer Genomics

Implicated in

Hematological malignancies

Oncogenesis

The t(X;14)(p22;q32) or t(Y;14)(p11;q32) rearrange CRLF2 with immunoglobulin heavy chain gene forming IGH/CRLF2 rearrangement. With P2Y purinoceptor 8 gene (P2RY8), located also in the pseudoautosomal (PAR1) region of X or Y chromosomes, CRLF2 forms a rearrangement through the interstitial deletions del(X)(p22p22) or del(Y)(p11p11). Both abnormalities are associated with B-precursor acute lymphoblastic leukemia (pre-B ALL) and Down syndrome pre-B ALL (Entrez Gene ID: 64109; Russell LJ et al., 2009).

It has been referred similar deletions in the PAR1 region involving the interleukin 3 receptor subunit alpha (IL3RA) gene or the colony stimulating factor 2 receptor alpha subunit (CSF2RA) gene and CRLF2, indicating that the breakpoints are variable between patients. Interestingly, one patient has been reported with the CSF2RA/CRLF2 rearrangement and IGH/ EPOR (Yano M et al., 2015). These rearrangements produce the overexpression of CRLF2 by the juxtaposition of this gene within the gene promoter of P2RY8, AKAP17A (SFRS17A), or ASMT (Russell LJ et al., 2009). Biallelic deletions of the PAR1 region, including CSF2RA and CRLF2 genes, have been reported in mantle cell lymphoma (Nieländer I et al., 2008).

In addition, four fusions with CRLF2 have been also reported: 1) CHRFAM7A /CRLF2 with the cholinergic receptor, nicotinic, alpha 7, exons 5-10 and he family with sequence similarity 7A, exons A-E fusion gene (CHRNA7) located in 15q13 (Fusion gen ID: 7161); 2) CRLF2/ U2AF1 with the U2 small nuclear RNA auxiliary factor 1 gene (U2F1), associated with myelodysplastic syndrome, and located in 21q22.3 (Fusion gen ID: 8499); 3) GOLGA8A /CRLF2 with the golgin A8 family member A gene (GOLGA8A) in 15q14 (Fusion gen ID: 15056); 4) WDR27 /CRLF2 with the WD repeat domain 27 gene (WDR27) in 6q27 (Fusion gen ID: 41824).

Pulmonary alveolar proteinosis

A recessive pattern of another similar homozygous deletion, that disrupts CSF2RA, CRLF2, and IL3RA gene, was found in a boy with pulmonary alveolar proteinosis, an accumulation of surfactant in the alveoli. Surfactant is cleared by alveolar macrophages, and granulocyte-macrophage colony-stimulating factor (GM-CSF) and its signaling is necessary for this process. GM-CSF activates Jak-Stat pathway inducing phagocytic functions of alveolar macrophage and catabolize surfactant (Chiu CY et al., 2017).

References

Chiu CY, Su SC, Fan WL, Lai SH, Tsai MH, Chen SH, Wong KS, Chung WH. Whole-Genome Sequencing of a Family with Hereditary Pulmonary Alveolar Proteinosis Identifies a Rare Structural Variant Involving CSF2RA/CRLF2/IL3RA Gene Disruption. Sci Rep. 2017 Feb 24;7:43469

Lin SC, Cheng FY, Liu JJ, Ye YL. Expression and Regulation of Thymic Stromal Lymphopoietin and Thymic Stromal Lymphopoietin Receptor Heterocomplex in the Innate-Adaptive Immunity of Pediatric Asthma. Int J Mol Sci. 2018 Apr 18;19(4)

Nieländer I, Martín-Subero JI, Wagner F, Baudis M, Gesk S, Harder L, Hasenclever D, Klapper W, Kreuz M, Pott C, Martinez-Climent JA, Dreyling M, Arnold N, Siebert R. Recurrent loss of the Y chromosome and homozygous deletions within the pseudoautosomal region 1: association with male predominance in mantle cell lymphoma. Haematologica. 2008 Jun;93(6):949-50

Russell LJ, Capasso M, Vater I, Akasaka T, Bernard OA, Calasanz MJ, Chandrasekaran T, Chapiro E, Gesk S, Griffiths M, Guttery DS, Haferlach C, Harder L, Heidenreich O, Irving J, Kearney L, Nguyen-Khac F, Machado L, Minto L, Majid A, Moorman AV, Morrison H, Rand V, Strefford JC, Schwab C, Tönnies H, Dyer MJ, Siebert R, Harrison CJ. Deregulated expression of cytokine receptor gene, CRLF2, is involved in lymphoid transformation in B-cell precursor acute lymphoblastic leukemia. Blood. 2009 Sep 24;114(13):2688-98

Tsilingiri K, Fornasa G, Rescigno M. Thymic Stromal Lymphopoietin: to cut a long story short Cell Mol Gastroenterol Hepatol. 2017; 3(2):174-182

Van Rompaey D, Verstraete K, Peelman F, Savvides SN, Augustyns K, Van Der Veken P, De Winter H. Virtual screening for inhibitors of the human TSLP: TSLPR interaction Sci Rep. 2017; 1: 17211

Varricchi G, Pecoraro A, Marone G, Criscuolo G, Spadaro G, Genovese A, Marone G. Thymic stromal lymphopoietin isoforms, inflammatory disorders and cancer Front Immunol. 2018; 9: 1595

Yano M, Imamura T, Asai D, Kiyokawa N, Nakabayashi K, Matsumoto K, Deguchi T, Hashii Y, Honda YK, Hasegawa D, Sasahara Y, Ishii M, Kosaka Y, Kato K, Shima M, Hori H, Yumura-Yagi K, Hara J, Oda M, Horibe K, Ichikawa H, Sato A. Identification of novel kinase fusion transcripts in paediatric B cell precursor acute lymphoblastic leukaemia with IKZF1 deletion Br J Haematol. 2015;171(5):813-7

Zhong J, Kim MS, Chaerkady R, Wu X, Huang TC, Getnet D, Mitchell CJ, Palapetta SM, Sharma J, O'Meally RN, Cole RN, Yoda A, Moritz A, Loriaux MM, Rush J, Weinstock DM, Tyner JW, Pandey A. TSLP signaling network revealed by SILAC-based phosphoproteomics Mol Cell Proteomics. 2012;11(6):M112.017764

Zhong J, Sharma J, Raju R, Palapetta SM, Prasad TS, Huang TC, Yoda A, Tyner JW, van Bodegom D, Weinstock DM, Ziegler SF, Pandey A. TSLP signaling pathway map: a platform for analysis of TSLP-mediated signaling Database (Oxford).2014:bau007.

This article should be referenced as such:

Moreno-Lorenzana D ,2, Juárez-Velázquez R, Martínez-Anaya D,3, Péez Vera P. CRLF2 (Cytokine receptor like factor 2). Atlas Genet Cytogenet Oncol Haematol. 2020; 24(1):1-7.