Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section

Review

P2RY8 (purinergic receptor P2Y, G-protein coupled, 8)

Jill Mackarel, David Betts, Owen Smith

Our Lady's Children's Hospital, Crumlin, Dublin, Ireland

Published in Atlas Database: November 2014

Online updated version : http://AtlasGeneticsOncology.org/Genes/P2RY8ID49813chXp22.html

Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/62499/11-2014-P2RY8ID49813chXp22.pdf

DOI: 10.4267/2042/62499

Identity

Other names: P2Y8

HGNC (Hugo): P2RY8

Location: Xp22.33

Local order

The P2RY8 gene is located at the pseudoautosomal region 1 (PAR1) of chromosome X and chromosome Y.

Note

ChrX: 1581465-1656037 base pairs (hg19) from pter (74573 bases).
Orientation: minus strand.
ChrY: 1531465-1606037 (hg19).

DNA/RNA

Description

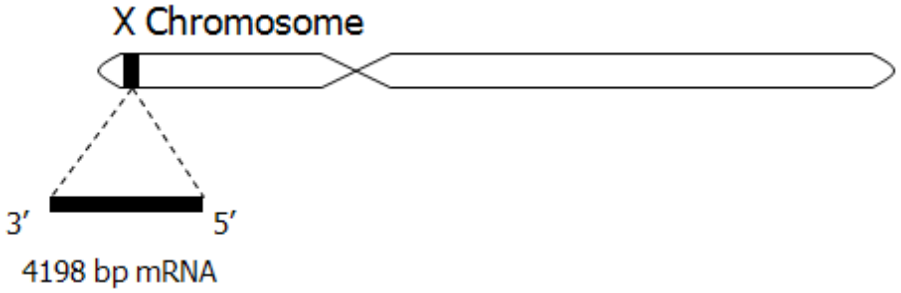
The P2RY8 gene is located on both chromosomes X and Y. It was discovered by Cantagrel and co-workers while investigating a pericentric inversion on the X chromosome, inv(X)(p22.3 q13.2), in a family with mental retardation. The gene is composed of 4 exons and the promoter region contains the regulatory transcription factor binding sites for CREB, POU3F1 and deltaCREB.

Transcription

The transcribed RNA has 4198 base-pairs and encodes a 359 amino acid protein. A second non-encoding transcript exists (splice variant) that has 407 base-pairs.

Pseudogene

Fusion gene: a 320-kb large interstitial deletion within the pseudoautosomal region 1 (PAR1) on chromosome X [del(X)(p22.33p22.33)] and chromosome Y [del(Y)(p11.32p11.32)] results in juxtaposition of the first non-encoding exon of P2RY8 to the CRLF2 coding region to form P2RY8-CRLF2 fusion which leads to over-expression of full-length CRLF2.



Schematic diagram of the human X chromosome indicating the location of the P2RY8 gene.

Protein

Description

The protein encoded by P2RY8 gene is composed of 359-amino acids and belongs to the P2Y family of G-protein coupled receptors that are preferentially activated by adenosine and uridine nucleotides. There are eight mammalian P2Y receptors known to date (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13 and P2Y14) and they are found in most human tissues. The specfic function of the P2RY8 receptor remains uncharacterised.

Expression

P2RY8 is highly expressed in lymphocytes, with weaker expression in heart, kidney and lung (Cantagrel et al., 2004). Adundant expression of P2RY8 has been demonstrated in bone marrow CD34+ cells in leukaemic patients (Fujiwara et al., 2007). However P2RY8 expression appears to be down-regulated during leucocyte differentiation: normal, mature peripheral blood leucocytes have been shown to have minimal expression, while an undifferentiated promyelocytic leukaemia cell line was shown to have moderate expression of P2RY8 that was down-regulated with induction of granulocyte differentiation (Adrian et al., 2000). Similarly, P2RY8 expression decreases during the differentiation of monocytes to macrophages (Hohenhaus et al., 2013).

Localisation

Cell membrane.

Function

Using retroviral expression screening for transforming genes in biphenotypic acute leukaemia, P2RY8 has been confirmed to have oncogenic potential (Fujiwara et al., 2007). The P2RY8-CRLF2 fusion is present in 5-7% of paediatric B-cell acute lymphoblastic leukaemia and > 50% of Down syndrome-associated acute lymphoblastic leukaemia (Mullighan et al., 2009; Russell et al., 2009; Cario et al., 2010; Hertzberg et al., 2010; Dyer et al., 2010) and has been identified as a poor prognostic factor associated with high risk disease with an increased risk of relapse (Cario et al., 2010; Ensor et al., 2011; Palmi et al., 2012; Attarbaschi et al., 2012; Yamashita et al., 2013). P2RY8-CRLF2 results in overexpression of full-length cytokine receptor-like factor 2 (CRLF2; also known as the thymic stromal lymphopoietin receptor), which together with IL7 receptor alpha forms a heterodimeric complex that acts at the functional receptor for thymic stromal lymphopoietin (reviewed in Roll and Reuther, 2010). CRLF2 alterations are associated with the presence of activating mutations in the JAK genes JAK1 and JAK2 (Russell et al., 2009; Mullighan et al., 2009; Hertzberg et al., 2010; reviewed in Roll and Reuther, 2010), as well as mutations of the lymphoid transcription factor gene IKZF1 (IKAROS) (Harvey et al., 2010).

Although P2RY8-CRLF2 fusions have been confirmed as a clear clinical risk factor in paediatric ALL, their precise role in the leukemic process remains to be elucidated with studies supporting involvement in the cellular transformation process but suggesting they function as a secondary capacity in driving the entire leukemic process (Morak et al., 2012).

Implicated in

B-acute lymphoblastic leukaemia (B-ALL) and Down syndrome-associated acute lymphoblastic leukaemia

Disease

As P2RY8-CRLF2 fusion in B-acute lymphoblastic leukaemia (B-ALL) and Down syndrome-associated acute lymphoblastic leukaemia (DS-ALL) (Mullighan et al., 2009; Russell et al., 2009; Cario et al., 2010; Hertzberg et al., 2010; Dyer et al., 2010).

Prognosis

Associated with increased relapse risk and overall inferior outcome (Cario et al., 2010; Ensor et al., 2011; Palmi et al., 2012; Attarbaschi et al., 2012; Yamashita et al., 2013).

Cytogenetics

Rearrangements are typically G- and R-band cryptic.

Hybrid/Mutated gene

An interstitial deletion of the pseudoautosomal region 1 (PAR1) of either of the sex chromosomes results in juxtaposition of the first noncoding exon of the P2RY8 gene to the first exon of CRLF2, such that CRLF2 expression from this chimeric locus is driven by the P2RY8 promoter.

Oncogenesis

Refer to protein function above.

Diffuse large B-cell lymphoma (DLBCL)

Note

Coding mutations in P2RY8.

Prognosis

Coding mutations were identified in 6 out of 55 patients (11%) with DLBCL using massively parallel whole-exome sequencing.

The impact of this mutation on prognosis remains unknown (Lohr et al., 2012).

Oncogenesis

The functional consequences of P2RY8 mutation in DLBCL remains to be determined.

References

Adrian K, Bernhard MK, Breitinger HG, Ogilvie A. Expression of purinergic receptors (ionotropic P2X1-7 and metabotropic P2Y1-11) during myeloid differentiation of HL60 cells. Biochim Biophys Acta. 2000 Jun 21;1492(1):127-38

Attarbaschi A, Morak M, Cario G, Cazzaniga G, Ensor HM, te Kronnie T, Bradtke J, Mann G, Vendramini E, Palmi C, Schwab C, Russell LJ, Schrappe M, Conter V, Mitchell CD, Strehl S, Zimmermann M, Pötschger U, Harrison CJ, Stanulla M, Panzer-Grümayer R, Haas OA, Moorman AV. Treatment outcome of CRLF2-rearranged childhood acute lymphoblastic leukaemia: a comparative analysis of the AIEOP-BFM and UK NCRI-CCLG study groups. Br J Haematol. 2012 Sep;158(6):772-7

Cantagrel V, Lossi AM, Boulanger S, Depetris D, Mattei MG, Gecz J, Schwartz CE, Van Maldergem L, Villard L. Disruption of a new X linked gene highly expressed in brain in a family with two mentally retarded males. J Med Genet. 2004 Oct;41(10):736-42

Cario G, Zimmermann M, Romey R, Gesk S, Vater I, Harbott J, Schrauder A, Moericke A, Izraeli S, Akasaka T, Dyer MJ, Siebert R, Schrappe M, Stanulla M. Presence of the P2RY8-CRLF2 rearrangement is associated with a poor prognosis in non-high-risk precursor B-cell acute lymphoblastic leukemia in children treated according to the ALL-BFM 2000 protocol. Blood. 2010 Jul 1;115(26):5393-7

Dyer MJ, Akasaka T, Capasso M, Dusanjh P, Lee YF, Karran EL, Nagel I, Vater I, Cario G, Siebert R. Immunoglobulin heavy chain locus chromosomal translocations in B-cell precursor acute lymphoblastic leukemia: rare clinical curios or potent genetic drivers? Blood. 2010 Feb 25;115(8):1490-9

Ensor HM, Schwab C, Russell LJ, Richards SM, Morrison H, Masic D, Jones L, Kinsey SE, Vora AJ, Mitchell CD, Harrison CJ, Moorman AV. Demographic, clinical, and outcome features of children with acute lymphoblastic leukemia and CRLF2 deregulation: results from the MRC ALL97 clinical trial. Blood. 2011 Feb 17;117(7):2129-36

Fujiwara S, Yamashita Y, Choi YL, Watanabe H, Kurashina K, Soda M, Enomoto M, Hatanaka H, Takada S, Ozawa K, Mano H. Transforming activity of purinergic receptor P2Y, G protein coupled, 8 revealed by retroviral expression screening. Leuk Lymphoma. 2007 May;48(5):978-86

Harvey RC, Mullighan CG, Chen IM, Wharton W, Mikhail FM, Carroll AJ, Kang H, Liu W, Dobbin KK, Smith MA, Carroll WL, Devidas M, Bowman WP, Camitta BM, Reaman GH, Hunger SP, Downing JR, Willman CL. Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. Blood. 2010 Jul 1;115(26):5312-21

Hertzberg L, Vendramini E, Ganmore I, Cazzaniga G, Schmitz M, Chalker J, Shiloh R, Iacobucci I, Shochat C, Zeligson S, Cario G, Stanulla M, Strehl S, Russell LJ, Harrison CJ, Bornhauser B, Yoda A, Rechavi G, Bercovich D, Borkhardt A, Kempski H, te Kronnie G, Bourquin JP, Domany E, Izraeli S. Down syndrome acute lymphoblastic leukemia, a highly heterogeneous disease in which aberrant expression of CRLF2 is associated with mutated JAK2: a report from the International BFM Study Group. Blood. 2010 Feb 4;115(5):1006-17

Hohenhaus DM, Schaale K, Le Cao KA, Seow V, Iyer A, Fairlie DP, Sweet MJ. An mRNA atlas of G protein-coupled receptor expression during primary human monocyte/macrophage differentiation and lipopolysaccharide-mediated activation identifies targetable candidate regulators of inflammation. Immunobiology. 2013 Nov;218(11):1345-53

Lohr JG, Stojanov P, Lawrence MS, Auclair D, Chapuy B, Sougnez C, Cruz-Gordillo P, Knoechel B, Asmann YW, Slager SL, Novak AJ, Dogan A, Ansell SM, Link BK, Zou L, Gould J, Saksena G, Stransky N, Rangel-Escareño C, Fernandez-Lopez JC, Hidalgo-Miranda A, Melendez-Zajgla J, Hernández-Lemus E, Schwarz-Cruz y Celis A, Imaz-Rosshandler I, Ojesina AI, Jung J, Pedamallu CS, Lander ES, Habermann TM, Cerhan JR, Shipp MA, Getz G, Golub TR. Discovery and prioritization of somatic mutations in diffuse large B-cell lymphoma (DLBCL) by whole-exome sequencing. Proc Natl Acad Sci U S A. 2012 Mar 6;109(10):3879-84

Morak M, Attarbaschi A, Fischer S, Nassimbeni C, Grausenburger R, Bastelberger S, Krentz S, Cario G, Kasper D, Schmitt K, Russell LJ, Pötschger U, Stanulla M, Eckert C, Mann G, Haas OA, Panzer-Grümayer R. Small sizes and indolent evolutionary dynamics challenge the potential role of P2RY8-CRLF2-harboring clones as main relapse-driving force in childhood ALL. Blood. 2012 Dec 20;120(26):5134-42

Mullighan CG, Collins-Underwood JR, Phillips LA, Loudin MG, Liu W, Zhang J, Ma J, Coustan-Smith E, Harvey RC, Willman CL, Mikhail FM, Meyer J, Carroll AJ, Williams RT, Cheng J, Heerema NA, Basso G, Pession A, Pui CH, Raimondi SC, Hunger SP, Downing JR, Carroll WL, Rabin KR. Rearrangement of CRLF2 in B-progenitor- and Down syndrome-associated acute lymphoblastic leukemia. Nat Genet. 2009 Nov;41(11):1243-6

Palmi C, Vendramini E, Silvestri D, Longinotti G, Frison D, Cario G, Shochat C, Stanulla M, Rossi V, Di Meglio AM, Villa T, Giarin E, Fazio G, Leszl A, Schrappe M, Basso G, Biondi A, Izraeli S, Conter V, Valsecchi MG, Cazzaniga G, Te Kronnie G. Poor prognosis for P2RY8-CRLF2 fusion but not for CRLF2 over-expression in children with intermediate risk B-cell precursor acute lymphoblastic leukemia. Leukemia. 2012 Oct;26(10):2245-53

Roll JD, Reuther GW. CRLF2 and JAK2 in B-progenitor acute lymphoblastic leukemia: a novel association in oncogenesis. Cancer Res. 2010 Oct 1;70(19):7347-52

Russell LJ, Capasso M, Vater I, Akasaka T, et al.. 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

Yamashita Y, Shimada A, Yamada T, Yamaji K, Hori T, Tsurusawa M, Watanabe A, Kikuta A, Asami K, Saito AM, Horibe K. IKZF1 and CRLF2 gene alterations correlate with poor prognosis in Japanese BCR-ABL1-negative high-risk B-cell precursor acute lymphoblastic leukemia. Pediatr Blood Cancer. 2013 Oct;60(10):1587-92

This article should be referenced as such:

Mackarel J, Betts D, Smith O. P2RY8 (purinergic receptor P2Y, G-protein coupled, 8). Atlas Genet Cytogenet Oncol Haematol. 2015; 19(12):705-707.