t(X;14)(p22;q32) or t(Y;14)(p11;q32) IGH/CRLF2

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Abstract
Review on t(X;14)(p22;q32) or t(Y;14)(p11;q32) with data on the genes involved, and clinics.

Keywords
IGH; CRLF2, B cell precursor Acute Lymphoblastic Leukemia (ALL), Ph-like, BCR/ABL1-like ALL.

Clinics and pathology

Disease
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR/ABL1-like ALL (Arber et al. 2016)

Etiology
The translocation IGH/CRLF2 involves a CpG break at CRLF2 and a V(D)J break at IGH locus, and produce overexpression of the CRLF2 protein (Schmäh et al. 2017).

Epidemiology
Reports about the IGH/CRLF2 prevalence have been obtained from selected and unselected patients, mostly from retrospective cohorts; as a consequence contrasting results have been informed. The Medical Research Council (MRC) found IGH/CRLF2 in 1% of paediatric patients (Ensor et al. 2011); in adults with Ph-like this translocation has been detected in 57.6% of cases (Roberts et al. 2017). A recent study reports in ALL children and adolescents (1-18 years-old) the higher incidence of IGH/CRLF2 in patients with median age of 14 years (Schmäh et al. 2017). Another report describes a cohort of pre B-ALL patients, ranging from 1-60 years-old, with IGH/CRLF2 in 37.2% of cases (Russell et al. 2017). In general, the prevalence of IGH/CRLF2 increases with age.

Clinics
ALL with BCP immunophenotype with rearrangement involving a cytokine receptor, included in the BCR/ABL1-like ALL subgroup.

Treatment
The IGH/CRLF2 translocation results in kinase-activating lesion that causes the constitutive activation of the Jak2/STAT5 signalling pathway. The patients that harbour IGH/CRLF2 ALL could benefit from the treatment with Ruxolitinib, which blocks Jak2/STAT5 pathway (Figure 5). This treatment could potentially improve their survival (Harrison 2013).

Prognosis
IGH/CRLF2 is associated with high risk National Cancer Institute (NCI) characteristics in contrast to P2RY8/CRLF2 positive patients. IGH/CRLF2 is also present in patients with high levels of minimal residual disease (MRD) ($\geq 10^{-3}$) which are consider MRD-slow early responders, based on this the group is prone to suffer relapses (Schmäh et al. 2017; Attarbaschi et al. 2012).
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Cytogenetics

Cytogenetics morphological

Figure 1. CRLF2 Flow cytometry analysis in an ALL patient with IGH/CRLF2 rearrangement. The figure shows the strategy applied to analyze by flow cytometry the CRLF2 overexpression and activation in blasts population (CD34+ CD19+), compared with unstained control (A). In this patient almost 100% of blasts are positive to CRLF2 protein, (B) and its signaling pathway is active since the phosphorylation of STAT5 at tyrosine residue (pY694) is present and (C) was reversible by the Jak2 inhibitor Ruxolitinib.

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. (A) Metaphase hybridized with CRLF2 break-apart probe (Cytocell Aquarius) with a normal chromosome X (yellow arrow) and the der(14) (green arrow). (B) Metaphase hybridized with IGH break-apart probe (Vysis-Abbott) with the normal chromosome 14 (yellow arrow) and the der(14) (red arrow).

t(X;14)(p22;q32) or t(Y;14)(p11;q32) IGH/CRLF2 is a cryptic rearrangement (Figures 2 and 3). It is present in patients with extra copies of the X chromosome produced by high hyperdiploidy in 19.8% of cases. To date, only one patient who presented both a PAR1 deletion (P2RY8/CRLF2) and IGH/CRLF2 translocation has been reported (Harvey et al. 2010). Recently, two patients with coexistence of IGH/CRLF2 and BCR/ABL1 rearrangements have been described. One patient presented both rearrangements in different clones (Russell et al. 2017); the other case showed the translocation t(Y;14) harbouring the CRLF2 rearrangement in 90% of interphases, and presented BCR/ABL1 fusion in a subset of the CRLF2-rearranged cells (Jain et al. 2017).

IGH/CRLF2 positive cells also have a high frequency (94%) of additional deletions which may reflect chromosomal instability (Schmäh et al. 2017). The most common deletions in addition to this rearrangement are found in IKZF1 (53%), ADD3 (46%) and SLX4IP (41%). Similar to patients P2RY8/CRLF2 positive, deletions in JAK1/ JAK2 (17%) are also present (Russell et al. 2017). Although IGH/CRLF2 is part of the BCR/ABL1-like ALL subtype this rearrangement is not associated with it in all cases; however, those patients with the rearrangement in coexistence with JAK2 mutations have been found that present the expression signature of the subtype (Herold et al. 2017). Although in Down syndrome patients the P2RY8/CRLF2 deletion is more frequent, IGH/CRLF2 rearrangement is also observed (35% vs. 20% respectively) (Russell et al. 2017).
Figure 3. (A-B) FISH in interphase nuclei with the IGH break apart-probe, and (C-D) with the CRLF2 break-apart probe. The yellow arrows indicate normal alleles and the red and green arrows indicate monoallelic breakages.

Genes involved and proteins

IGH (immunoglobulin heavy locus)

Location
14q32.33
Protein-coding gene. Others names: D (diversity) region of heavy chains; J (joining) region of heavy chains; immunoglobulin heavy chain variable region; immunoglobulin heavy diversity group; immunoglobulin heavy diversity locus; immunoglobulin heavy joining cluster; immunoglobulin heavy joining group; immunoglobulin heavy polypeptide, joining region; immunoglobulin heavy variable cluster; immunoglobulin heavy variable group. Other symbols: IGHDY1; IGH@; IGD1; IGHV; IGHD@; IGHJ@; IGHV@; IGH1@

DNA/RNA
The genomic location of IGH starts at 105,536,746 pb from 14pter and ends in 106,879,844 pb from 14pter. The size is 1,343,098 bases, with minus strand orientation NC_000014.9

CRLF2 (cytokine receptor like factor 2)

Location
It is located at the PAR1 of chromosome X, Xp22.33, and chromosome Y, Yp11.
Protein-coding gene. Other names and symbols: Thymic Stromal Lymphopoietin Protein Receptor, TSLP Receptor, Thymic Stromal-Derived Lymphopoietin Receptor, Cytokine Receptor-Like 2. Others symbols: TSLPR, CRL2, CRLF2Y.

DNA/RNA
The genomic location of CRLF2 gene in chromosome X starts at 1,187,549 bp from Xpter, and ends at 1,212,815 bp from Xpter. The size is 25,267 bases, with minus strand orientation NC_018934. CRLF2 has 3 transcripts variant; the transcript variant 1 has 1606 pb mRNA NM_022148.2, this variant encodes the longer isoform NM_022148.2 (Schmäh et al. 2017); the transcript variant 2 has 1503 pb mRNA NM_001012288.2, this variant lacks an alternate exon which results in translation initiation at a downstream start codon compared to variant 1, the resulting isoform is shorter at the N-terminus compared to isoform 1 (Russell et al. 2017); the transcript variant 3, uses an alternative splice junction at the 5′end of an exon, and contains another alternate exon compared to variant 1, this variant is a non-coding mRNA NR_110830.1.

Protein
The cytokine receptor-like factor 2 has a size of 371 amino acids, with a molecular mass of 42013 Daltons. Cytokine receptor-like factor 2 is a transmembrane protein with an extracellular domain of 210 residues, and an intracellular domain of 119 residues (Zhang et al. 2001). CRLF2 heterodimerizes with IL7R constituting a functional receptor (Figure 5) (Rochman et al. 2010; Bugarin et al. 2015).

Somatic mutations
The CRLF2 711T>G (Phe232Cys) mutation has been found in ALL blasts. The CRLF2 Phe232 residue is near to the junction of the extracellular and transmembrane domains. The Phe232Cys mutation confers a constitutive dimerization through the cysteine residues inducing cell growth. This mutation also promotes the up-regulation of downstream transcriptional targets of the Jak2/STAT5 pathway (Figure 5) (Yoda et al. 2010).

Result of the chromosomal anomaly

Hybrid gene
The IGH/CRLF2 rearrangement results from a cryptic translocation t(X;14)(p22;q32) or t(Y;14)(p11;q32) involving the PAR1 region, which is located in the short arm of both sex chromosomes and the immunoglobulin heavy chain locus located in the chromosome 14 (Figure 3). Represent the 20-26% of IGH translocations in B cell precursor ALL and the principal consequence is a deregulated
transcription of CRLF2 by the physical juxtaposition with the IGH transcriptional enhancers (Figure 4) (Dyer et al. 2010; Chaparo et al. 2013; Jeffries et al. 2014; Yoda et al. 2010; Tsai et al. 2010).

**Description**

IGH/CRLF2 translocation can result of an aberrant D-J or V-DJ recombination that involves the cryptic recognition signal sequence (RSS) in the pseudoautosomal region (Figure 4). As a result, the IGH-J or IGH-DJ regions becomes adjacent to the CRLF2 entire reading frame and the der(14) carries the junctions between IGH segments and the centromeric region of CRLF2 (Dyer et al. 2010; Chaparo et al. 2013; Yoda et al. 2010; Tsai et al. 2010).

The breakpoints occur approximately 8 to 16 Kb upstream to the CRLF2 translation start site and, there is a 311 bp cluster from positions 1,307,403 to 1,307,713 which contains 6 out of 19 described breakpoints. Tsai et al., 2010 report that 7 of 19 CRLF2 breakpoints are at 5'or 3'sides of CpG dinucleotide sequences. Similar to the IGH-BCL2 rearrangement, at least 18 of the 19 IGH breaks in the IGH/CRLF2 translocation are compatible with standard V(D)J recombination, the IGH junction is within 30bp 5'of an RSS and this junctions contain non templated nucleotide additions consistent with the activity of terminal deoxynucleotide transferase (Dyer et al. 2010; Chaparo et al. 2013; Yoda et al. 2010).

**Transcript**

There is no a chimeric transcript. Usually the rearrangement relocates the CRLF2 entire coding sequence without mutation under transcriptional control of IGH enhancer and the gene is overexpressed (Dyer et al. 2010).

**Detection**

The IGH/CRLF2 translocation involves the disruption of both loci, based on this FISH technique using IGH and CRLF2 break-apart probes allows the detection of the rearrangement (Figure 3). These probes mark the centromeric region of each gene of red color and the telomeric region of green color. A normal cell with intact IGH and CRLF2 shows in each cell two close red (R) and green (G) fused (F) signals (2F); in a cell with the translocation, one normal F signal is conserved and one red and one green are present as a result of the breakage (1F1R1G pattern). In abnormal metaphases the hybridization with IGH break-apart probe shows a der(14) with one centromeric red signal and one telomeric green signal moved to the derivative chromosome X or Y (Russell et al. 2009). Harvey et al. 2010 reported the IGH/CRLF2 detection using a single fusion extra signal probe consisting of two bacterial artificial chromosomes (BAC) clones flanking CRLF2 labeled with red fluorochrome, and a third BAC clone centromeric to IGH labeled with green fluorochrome. In this assay an IGH/CRLF2 positive cell shows the 1F2R1G pattern.

Yoda et al. 2010 amplified the IGH/CRLF2 junction on der(14) by PCR using a common IGHJ primer and spaced primers 5' of the CRLF2 coding sequence.

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**Figure 4.** The IGH/CRLF2 translocation. (A) IGH locus. The IGH breakage can occur between the variable (V-H) and diversity (D-H) regions, the orange diamonds represent the transcriptional enhancers. (B) PAR1 region. The breakage can occur 8Kb to 12Kb upstream to CRLF2. (C) The derivative chromosome 14 carries the CRLF2 juxtaposition with IGH transcriptional enhancers and (D) the derivative chromosome X or Y hold the IGH telomeric region.
Figure 5. PATHWAY: IGH/CRLF2 rearrangement increases the expression of CRLF2. CRLF2 signaling pathway involves the activation of Jak2/STAT5 and PI3k/Akt/mTOR that are related with increase in proliferation and survival of leukemic cells. Other cellular mechanism activated by Akt is apoptosis inhibition. Additionally, CRLF2 can activate Src family members which create a feedback positive loop with Abl, and activate molecules implicated in cellular adhesion and survival (TSLP Signaling Pathway n.d.).

**Fusion protein**

There is not a fusion protein

**Oncogenesis**

The overexpression of CRLF2 due to the IGH/CRLF2 translocation results in its homodimerization at cellular membrane. This leads directly to constitutive activation of JAK2/STAT5, PI3k/ MTOR andSRC signaling pathway, causing the leukemic blast proliferation and survival (Figures 3 and 5) (Zhong et al. 2014). Nevertheless, the IGH translocation is not enough for the establishment of the neoplastic phenotype, concurrent activation of synergistic oncogenes and loss of tumor suppressor gene functions are necessary (Moorman et al. 2012). In the near future, inhibitors for the JAK2 pathway, Ruxolitinib, and for Src pathway, Dasatinib, could be used in order to counteract oncogenic effect caused by IGH/CRLF2 in ALL patients.

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