

# Leukaemia Section

## Short Communication

### i(7)(q10)

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### Abstract

Isochromosome 7q, i(7)(q10), is a rare recurrent aberration found in various hematological neoplasms. In Mitelman's data base, i(7q) is the sixth most common isochromosome after i(17q), i(8q), i(1q), i(12p), and i(6p) in human neoplasms. The incidence of this abnormality, and genes involved are presented in this review.

#### Keywords

Chromosome 7; isochromosome; Hepatosplenic T-cell lymphoma; Shwachman Diamond syndrome; Acute lymphoblastic leukemia; Myeloid malignancies

### Identity

Isochromosome 7q consists of two identical copies of the long-arm (q) of chromosome 7 fused at the centromere but has lost the short-arm (p) 7p. The subsequent genetic imbalances of the karyotype with this abnormality results in loss of one copy of 7p and gain of 7q, thus neoplastic cells apparently suffer from an aberrant gene dosage effect (Martens, et al 1994).

### Clinics and pathology

#### Note

**Diseases** Hepatosplenic T cell lymphoma (HSTL); Shwachman-Diamond syndrome (SDS); Acute lymphoblastic leukemia (ALL); Myelodysplastic syndrome (MDS) and Acute myeloid leukemia (AML)

#### Disease

Shwachman Diamond syndrome (SDS)

#### Note

Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder, characterized by exocrine pancreatic insufficiency, skeletal abnormalities and bone marrow dysfunction.

The disease manifests with neutropenia, but anemia, thrombocytopenia, or aplastic anemia may as well occur. SDS patients have a high risk to develop myelodysplastic syndrome and/or acute myeloid leukemia (MDS/AML).

The frequency of leukemia in patients with this syndrome is as much as 36% by age 30 years and increases to 71% by age 50 years.

Around 90% of patients with clinical features of SDS have biallelic mutations in the SBDS gene that is mapped to chromosome 7q11.2 region.

The incidence of Shwachman-Diamond syndrome has been estimated at one case in 77,000 population using comparison cystic fibrosis data.

#### Cytogenetics

SDS patients often show acquired clonal chromosomal abnormalities in their bone marrow even in the absence of accompanying hematological disorders.

The most frequent is the i(7)(q10), which may account up to 44% of the cases with abnormal karyotype followed by monosomy 7 or 7q in 33% whereas the del(20)(q11) is found in around 16% of patients.

Recent reviews of the literature data have revealed that SDS with the i(7q) do not develop MDS or transform to AML, and rarely accumulate secondary chromosomal changes during the course of disease. In addition, i(7q) has been rarely seen in SDS patients who developed MDS/AML.



**Figure 1** Hyperdiploid karyotype from a child diagnosed with ALL showing i(7)(q10) i(7q), G-banding - Anwar N Mohamed; Insert: i(7)(q10), R- banding - Jean-Loup Huret (left), Courtesy Christiane Charrin (right).

## Genes

SBDS gene may play an important role in regulating the Fas-mediated apoptosis pathway and may be responsible for the reduced cellularity in the bone marrow and exocrine pancreas of patients with Shwachman-Diamond syndrome. Mutational analysis of SBDS gene revealed that SDS is caused by two common mutations, (c.183\_184TA>CT and c.258+2T>C), in exon 2 of the gene. As the SBDS gene is located on 7q11, bone marrow cells with the i(7)(q10) have three copies of this gene. In all eight cases studied the i(7)(q10) carried two copies of the c.258+2T>c mutation. They suggest that, as the c.258+2T>C mutation still allows the production of some amount of normal protein, this may contribute to the low incidence of MDS/AML in SDS patients with i(7q) (Minelli et al 2012).

## Prognosis

Studies suggests that SDS with i(7q) represents a much less aggressive disease with low risk to develop MDS/AML than SDS patients with -7/7q or complex karyotype. This finding has impacted the management of children with SDS, as hematopoietic stem cell transplantation is no longer considered in patients with the i(7q) (Cunningham et al 2003).

## Disease

Hepatosplenic T-cell lymphoma (HSTL)

### Note

HSTL is a rare and clinically aggressive subtype of peripheral T-cell lymphoma, recognized as a distinct clinico-pathological entity in the 2008 WHO classification. Patients are predominantly young men

usually present with isolated hepatosplenomegaly and thrombocytopenia due to malignant T-cell proliferation in the sinusoids of the liver, sinuses and red pulp of the spleen, and sinuses of the bone marrow (Belhadj et al 2003)

## Pathology

**Morphology:** The cells are monotonous, medium-sized lymphoid cells with round or slightly irregular nuclei, loosely condensed chromatin, and a moderate amount of pale cytoplasm. Mitotic activity is generally low. Histologic transformation to large cell or blastic morphology may occur with disease progression.

**Immunophenotype:** HSTL is derived from the cytotoxic memory T-cells responsible for innate immunity. Cells express CD2, surface CD3, and CD7 but CD56 expression is variable. CD4, CD5 and CD8 are not expressed. Most cases of HSTL express the gamma/delta T cell receptor (TCR), but rare cases express the alpha/beta TCR. The cytotoxic granule protein TIA-1 is expressed but perforin and granzyme B are absent.

## Cytogenetics

Conventional cytogenetics and fluorescence in situ hybridization (FISH) demonstrate that i(7q) is the primary chromosomal aberration in HSTL detected in almost all cases. The most common accompanying secondary alterations are trisomy 8, loss of sex chromosome, deletion of 11q and gain extra copies of i(7q). The increase number of i(7q) is associated with cytological features of HSTL

progression (Jonveaux P 1996; Alonsozana EL et al, 1997).

### Genes

The contribution of i(7q) aberration to the pathogenesis of HSTL has been addressed recently. Combined gene expression profiling and array-based comparative genomic hybridization (CGH) of several HSTL tumors recently reported by Travert et al showed downregulation of 7p genes, particularly CYCS, IKZF1, HUS1 and CBX3, and upregulation of 7q genes, including the putative oncogene PTPN12 (Travert et al 2012). Furthermore, Ferreiro et al studied six HSTL tumors positive for i(7q) including HSTL-derived cell line using high resolution array CGH; all exhibited a constant loss of 7p22.1p14.1 and gain of 7q22.11q31.1. On the other hand, the RNA-sequencing did not identify any disease-defining mutation or gene fusion suggesting that chromosome 7 genomic imbalances are the major events in the pathogenesis of HSTL. Based on the integrated genomic and transcriptomic data, Ferreiro et al assumed that loss of 7p sequences is critical for the development of HSTL. This aberration associates with an enhanced transcription of CHN2 and overexpression of  $\beta$ 2-chimerin, which likely affects the NFATC2 related pathway and leads to a proliferative response. Whereas gain of 7q correlates with upregulation of several genes, including ABCB1, RUNDC3B and PPP1R9A, providing growth advantage to lymphoma cells and contributing to their intrinsic chemo-resistance and aggressiveness (Finalet Ferreiro et al 2014).

### Prognosis

HSTL is a dismal disease. Treatment with various induction regimens has been unsatisfactory, with variable response rates, high relapse rates, and a short median survival of 8 months.

### Disease

Other lymphoproliferative neoplasms

#### Note

The incidence of isochromosome 7q in other peripheral T-cell lymphomas has not been well defined. In a single study, using two color FISH probes, i(7q) was identified in 4 tumor specimens from 94 cases; two cases of extranodal NK/T-cell lymphoma, nasal type, and two cases of anaplastic lymphoma kinase-negative anaplastic large cell lymphoma (Feldman et al, 2008). The biologic significance of i(7q) in ALK- ALCL and NKTL is unknown.

### Disease

Acute Lymphoblastic Leukemia (ALL)

#### Note

In a large collaborative study of a newly diagnosed pediatric ALL, i(7q) was reported in 0.8% of cases. Although i(7q) is found as sole structural abnormality in few cases, usually it accompanies other primary chromosomal changes most frequently hyperdiploidy followed by t(1;19), t(9;22), and t(4;11) (Figure 1). The leukemic cells with i(7q) have had B-lineage immunophenotype and there were no other distinguishing clinical or laboratory features in this group (Pui, et al, 1992). The prognostic significance of i(7q) in ALL is still undetermined.

### Disease

Myeloid malignancies

#### Note

In MDS and AML, i(7q) is very rare and mostly occurs in the setting of complex chromosomal changes. I(7q) was reported in a child of a transient MDS associated with a clonal marrow cytogenetic abnormality of isochromosome 7q. Without intervention, the bone marrow cytogenetics reverted to normal and there was complete hematologic recovery (Leung et al, 2003). Additionally, i(7q) has been reported as a sole acquired abnormality in three sporadic cases of Down syndrome with AML (Wong et al 2006).

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