Atypical deletion of 5q in myelodysplastic syndromes (MDS) with retained commonly deleted regions (CDR) in MDS

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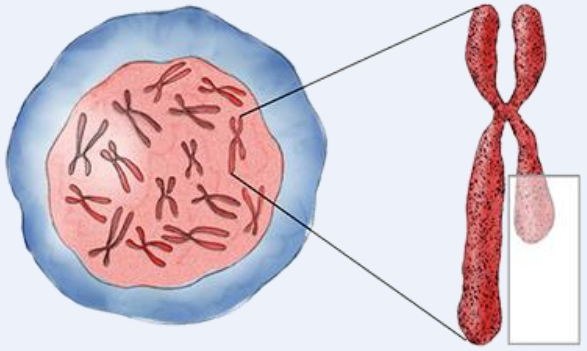
Introduction

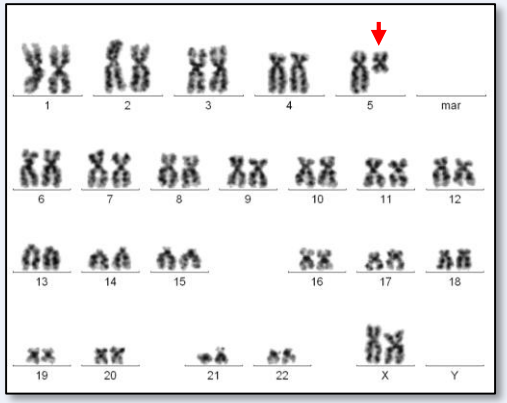
The interstitial deletion of the long arm of chromosome 5 – del(5q) - is a recurrent cytogenetic aberration in bone marrow cells of patients with myelodysplastic syndromes (MDS). The extent of the del(5q) varies in individual cases, but chromosome region 5q31 is deleted in most of them.

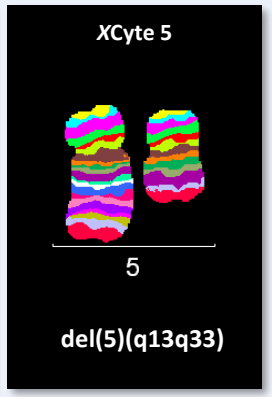
Two different commonly deleted regions (CDRs) have been identified: the proximal 5q31.2 region is associated with a high-risk MDS, and the distal CDR 5q32–5q33 is involved in the pathogenesis of MDS with isolated del(5q) [1]. However, rare cases of atypical deletions of 5q that do not include defined CDRs have also been reported [2,3].

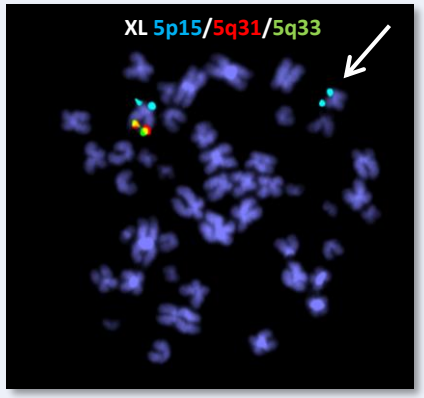
The aim of this study was to determine the frequency and clinical significance of atypical deletions of 5q in a large cohort of MDS patients.

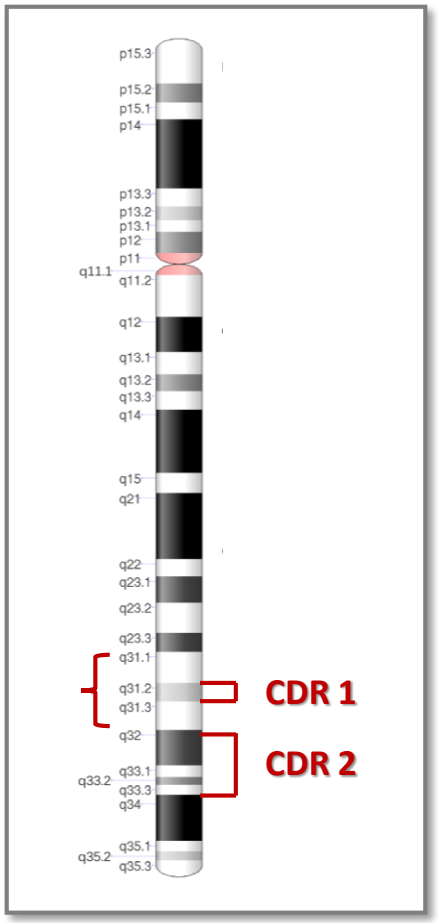


https://www.revlimid.com/mds-patient/about-myelodysplastic-syndromes/ what-is-myelodysplastic-syndromes/









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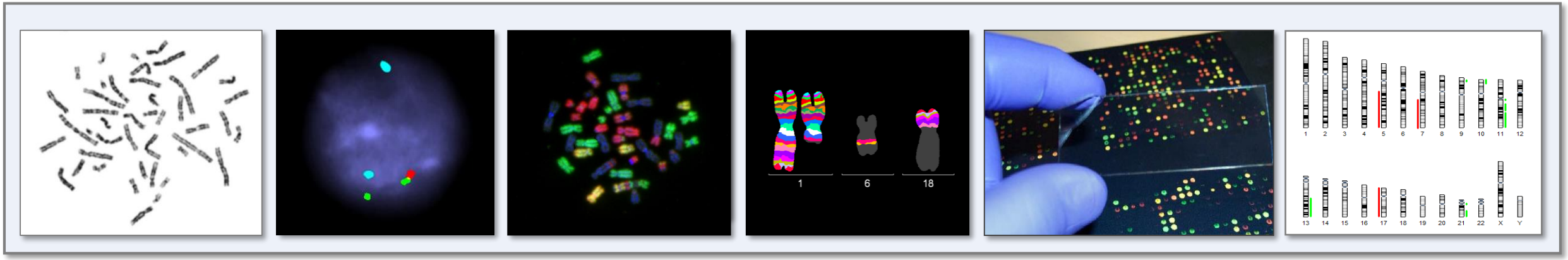
Methods

In the 1993-2019 we examined bone marrow cells of 3 714 MDS patients with combination of cytogenomics techniques (retrospective and/or prospective analysis).

- **Conventional cytogenetic analysis (G-banding)** → karyotype at the time of diagnosis and during the disease
- **I-FISH (Vysis DNA Probes, Abbott / XL Probes MetaSystems)** → confirmation of del(5)(q31); monitoring the size of the pathological clone; verification of aberrations detected with conventional cytogenetic analysis
- **mFISH (MetaSystems)** → analysis of structural and/or complex chromosomal aberrations
- **mBAND (MetaSystems)** → analysis of the extent of del(5q); identification of breakpoints
- **aCGH/SNP (CytoChip Cancer SNP 4x180K, Illumina / SurePrint G3 Cancer CGH+SNP Microarray, 4x180K, Agilent)** → analysis of the size of del(5q) and other unbalanced aberrations



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Results

No.	Sex	Age	WHO 2016	HGB g/L	ANC x10^9/L	PLT 10^9/L	BM blasts (%)	IPSS-R score	IPSS-R category	Date of dg	Date of death	OS* months	Karyotype (G-banding, mFISH/mBAND)	FISH 5q31/q33	aCGH deletion size (Mb)
1	F	66	MDS-EB 2	na	na	na	na	na	na	1993	1994	12	45,XX,t(2;11)(p16;q24),-7,**del(5)(q12.1q23.3)**[3]/46,XX[3]	negative	71.9
2	F	61	AML-MRC	**14.3**	**2.20**	**140**	**1.6**	1	very low	1996	2019	271	46,XX,**del(5)(q14.2q21.3)**[4]/46,XX[25]	negative	27.7
3	F	59	MDS-SLD	**8.3**	**2.76**	**172**	**0.4**	2	low	2015	2015	6	46,XX,**del(5)(q14.2q31.1)**[11]/46,XX[8]	negative	53.19
4	M	83	sMDS-U	**11.2**	**4.58**	**193**	**0.2**	1	very low	2019		8	46,XY,**del(5)(q14.3q22.2)**[20]	negative	25.46
5	F	76	MDS-U	**9.0**	**5.10**	**66**	**0.0**	4.5	intermediate	2014	2015	9.5	46,XX,**del(5)(q14.3q23.1)**,r(18)(p11.21q22.3),del(20)(q11.21q13.3)[15]	negative	30.75
6	F	66	MDS/MPN-U	**12.2**	**11.00**	**50**	**2**	1.5	very low	1999	2000	13.5	46,XX,**del(5)(q14.3q23.2)**[20]	negative	39.53
7	M	73	MDS-SLD	**9.4**	**4.30**	**147**	**0.9**	2	low	2010	2010	12	46,XY,**del(5)(q14.3q23.2)**[19]/46,XY[3]	negative	37.49
8	M	72	sMDS-U	na	na	na	na	na	na	2011	2011	11	46,XY,**del(5)(q14.1q23.3)**[6]/46,XY[27]	negative	53.7
9	M	77	AML-MRC	**11.9**	**1.54**	**126**	**0.8**	3	low	2017	2017	1	45,XY,**del(5)(q14.3q31.1)**,dic(18;20)(p11.1;p11.1)[18]/46,XY[2]	negative	43.92

na = data not available

** calculated from the date of the first bone marrow examination*

✓ **del(5q) was detected in 920/3714 patients (24,8%). Most of them had large deletions spanning whole 5q31 region and both defined CDRs.**

✓ **Atypical deletions with retained CDRs were identified in 9/920 cases (1%; four males, five females; median age, 72 years).**

✓ **In six cases del(5q) was a sole abnormality, in three patients it was detected in combination with additional chromosomal aberrations.**

✓ **Of the nine patients, eight died (median OS 11.5 months) and one patient lives (8 months from diagnosis).**

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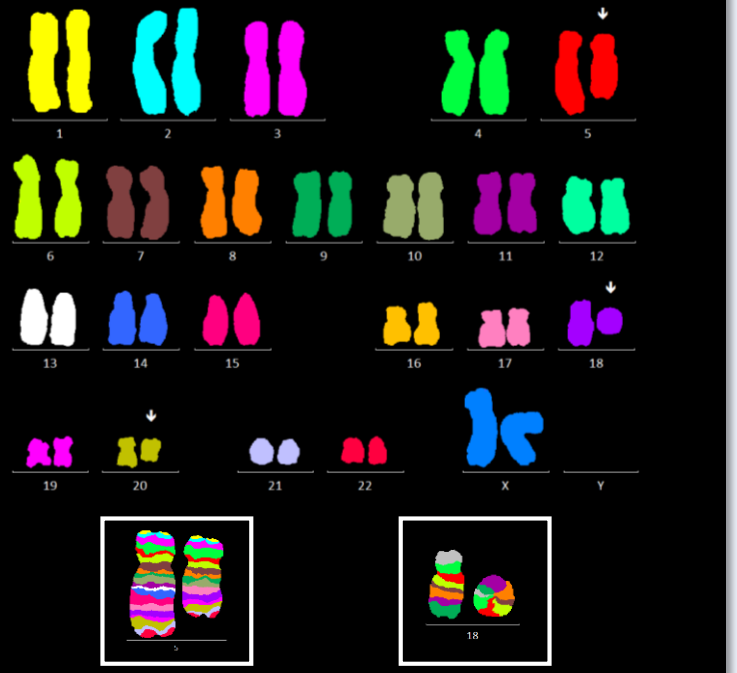
Results

Patient No. 5



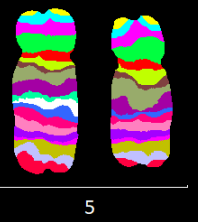
del(5)(q14.3q23.1) r(18)(p11.21q22.3)

46,XX,del(5)(q14.3q23.1),r(18)(p11.21q22.3),del(20)(q11.21q13.3)

Patient No. 3

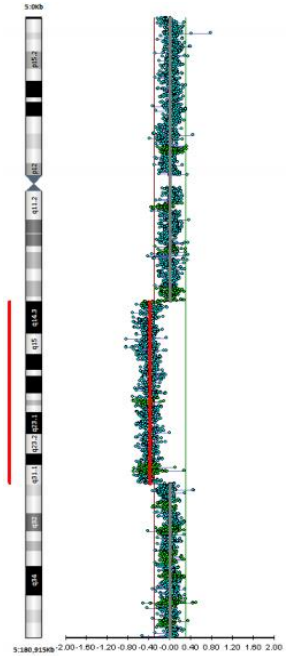
del(5)(q14.2q31.1)

Patient No. 4



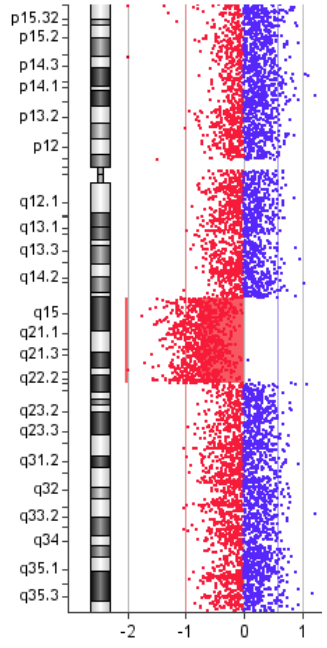
del(5)(q14.3q22.2)

Patient No. 3



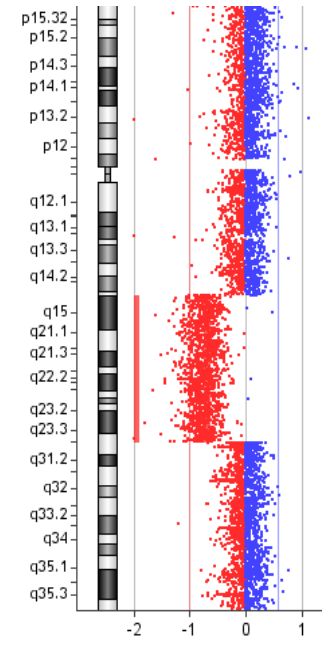
del(5)(14.2q31.1)

Patient No. 4



del(5)(14.3q22.2)

Patient No. 9



del(5)(14.3q31.1)

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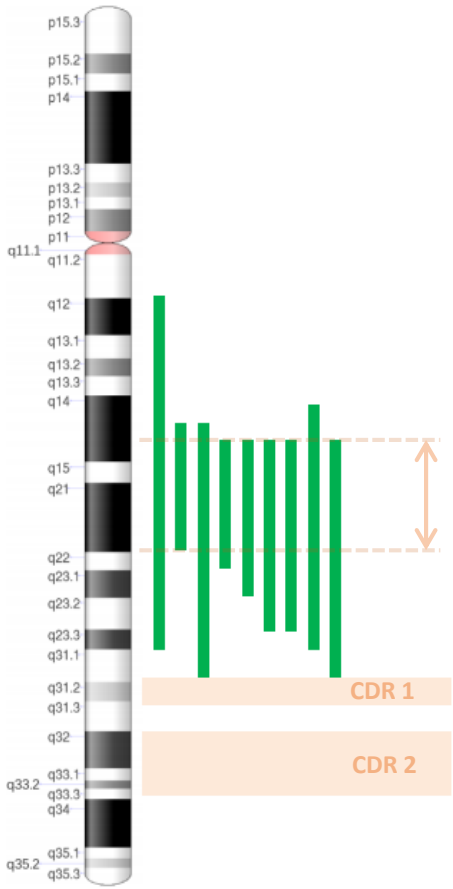
Range of deletions (aCGH/SNP)



- ✓ In all nine cases, deletions were localized **proximally** to the **5q31 region** and **both CDRs**.
- ✓ The size of the deleted segments ranged from **25.46** to **71.90 Mb** (median **39.53 Mb**) and the region **5q14.3 - q21.3 (26.79 Mb)** was deleted in all nine patients.
- ✓ Many candidate genes, whose haploinsufficiency could lead to malignant transformation, have been identified in this region (for example ***CCNH***, ***CHD***, ***MAN2A1***, ***ARRDC3***, ***ELL2***, *etc.*).

Conclusions

- Our results suggest that del(5q) may occur outside the defined CDRs.
- Although these findings are extremely rare, they show that also genes located outside known CDRs highly probably contribute to the malignant progression of MDS.
- The identification of these genes will lead to better understanding of the MDS pathogenesis and may contribute to identification of new therapeutic targets.

References:

1. *Ebert BL. Molecular dissection of the 5q deletion in myelodysplastic syndrome. Seminars in Oncology 2011;38(5):621-626.*
2. *Douet-Guilbert N, et al. Three rearrangements of chromosome 5 in a patient with myelodysplastic syndrome: an atypical deletion 5q, a complex intrachromosomal rearrangement of chromosome 5, and a paracentric inversion of chromosome 5. Cancer genetics and Cytogenetics 2010;203:303-308.*
3. *Brezinova J, et al. Deletion of the long arm but not the 5q31 region of chromosome 5 in myeloid malignancies. Leukemia Research 2012;36:e43-e45.*

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There are no relevant conflicts of interest to disclose.