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Blood 142 (2023) 4610–4612

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Early-Onset Myelodysplastic Syndromes (MDS) with Ring Sideroblasts (RS) without *SF3B1* Mutations in Adults: Enrichment with Germline Variants in Genes Responsible for Congenital Sideroblastic Anemias

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Introduction:
Acquired mutations in *SF3B1* gene in myeloid neoplasms are classically associated with the presence of RS in Pearl Stain, ineffective erythropoiesis, and favorable prognosis. Nevertheless, in up to 20-25% of adults diagnosed with MDS with RS (WHO 2017), mutations in *SF3B1* are not found, and molecular grounds for the presence of RS remain to be ascertained. The objective of our study was to investigate whether the presence of RS could be associated with germline variants in genes responsible for congenital sideroblastic anemia (CSA).
Methods:
Patients diagnosed with de novo MDS between 16-60 years of age without previous organ dysfunction were recruited from 32 centers of GEMSD since 2016. Whole exomes were sequenced using HiSeq4000-NovaSeq6000-Illumina, paired tumor-germline samples. Mean depth was 100x, with 150 million reads per sample and quality Q30a>95%. Variants were analyzed using a bioinformatics pipeline: filtering intronic and synonymous variants and those with a population frequency >1%. The mutational state of *SF3B1* was determined by Sanger Sequencing and Next Generation Sequencing (NGS). Germline variants were categorized according to American College of Molecular Genetics (ACMG) criteria. The list of genes related to CSA explored in this study is shown in Table 1.

Results:
Among 239 cases of adults diagnosed with early-onset MDS (mean age at diagnosis: 48 years, range 16-60), 58 (24%) patients presented with RS in bone marrow (mean RS: 28%). Of these 58 patients, acquired mutations in *SF3B1* were not found in 32 (55%). Nine out of these 32 (25%) harbored a germline variant (two variants in one case) in genes responsible for CSA (Table 2): *SLC25A38* (n=2), *STEAP3* (n=2) *FECH*, *ALAS2*, *GLRX5*, *SLC19A2*, *TRNT1* and *IARS2*. This frequency was statistically higher than in the *SF3B1* and RS mutated group (n=23), with only one case with a germline variant in a CSA gene (p=0.013). It was also higher than in the non-RS cases (n=181), with only one case in this group (p<0.001). Using the Fisher's exact test, commonly used to perform enrichment, the odds ratios were also significant (p=0.033 and p<0.0001), respectively.
Among patients with RS, those carrying a CSA gene germline variant were younger (43 vs. 54 years, p=0.04), had a higher rate of neutropenia (1.8 vs. 2.6 x 10E9/L, p=0.02), and thrombocytopenia (151 vs. 259 x 10E9/L, p=0.03) than MDS-RS patients with *SF3B1* mutated. Furthermore, MDS-RS with a germline variant in CSA genes had a lower mean percentage of RS than patients who acquired the mutation in *SF3B1* (14% vs. 38%; p=0.003).
Conclusions:
In our series, the frequency of MDS-RS without *SF3B1* mutations is higher in early-onset adult MDS than the one reported in MDS in advanced age. Whole exome analysis allowed us to describe, for the first time, a significant enrichment of variants in genes causing CSA in young adults with RS and without acquired mutation in *SF3B1*.

Disclosures Tormo: *Pfizer:* Honoraria; *AbbVie:* Honoraria; *Astellas:* Honoraria; *BMS:* Honoraria; *MSD:* Honoraria. **Bosch:** *BeiGene:* Consultancy; *Roche:* Honoraria; *Lilly:* Consultancy; *Mundipharma:* Consultancy, Honoraria; *Gilead:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *AstraZeneca:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria; *Karyospharm:* Other; *Celgene:* Consultancy, Honoraria; *Roche:* Consultancy, Honoraria. **Diez-Campelo:** *BMS/Celgene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Advisory board fees; *Gilead Sciences:* Other: Travel expense reimbursement; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *GSK:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Jerez:** *Novartis:* Consultancy; *Astrazeneca:* Research Funding; *GILEAD:* Research Funding; *BMS:* Consultancy.

CSA GENES
ALAS2
SLC25A38
ABCB7
GLRX5
PUS1
YARS2
SLC19A2
TRNT1
FECH
COASY
HEPHL1
PAFAH2
STEAP3
IARS2
SARS2

Table 1. List of genes responsible for CSA which were interrogated for the presence of mutations in 236 WES tumor-germline matched MDS cases with a diagnosis between 16 and 60 years.

	AGE	%RS BM	GERMLINE VARIANT	CHR	NUCLEOTID EXCHANGE	AMINOACID CHANGE	VAF (%)	MAF	CADD	REVEL	ACMG	OTHER CONCOMITANT GERMLINE VARIANTS
RS-*SF3B1*^{MUT}	30	95	*TRNT1*	3	c.1292T>C	p.Ile431Thr	53	0,01	24	0,152	VUS	*ATM, VWDE, IL17RA*
RS-*SF3B1*^{WT}	19	17	*FECH*	18	c.380A>G	p.Glu127Gly	50	<0,01	26	0,876	VUS	*MLH1, TXNDC11, NPAT*
	28	40	*SLC25A38*	3	c.683G>T	p.Gly228Val	49	<0,01	29	0,915	LP	*RYR1, NF1*
			ALAS2	X	c.509G>A	p.Arg170His	44	<0,01	29	0,977	LP	
	49	24	*GLRX5*	14	c.185C>T	p.Pro62Leu	59	<0,01	25	0,370	VUS	*JAK2*
	32	2	*SLC19A2*	1	C.926A>G	p.Tyr309Cys	44	<0,01	29	0,874	VUS	*ATP10B*
	50	4	*SLC25A38*	3	c.415G>T	p.Val139Phe	44	<0,01	24	0,624	LP	*TRERF1*
	60	2	*TRNT1*	3	c.1292T>C	p.Ile431Thr	35	0,01	24	0,152	VUS	*TSPAN3*
	35	6	*STEAP3*	2	c.1217C>T	p.Ser406Phe	57	<0,01	32	0,850	VUS	*MLH1, BRIP1*
	19	17	*STEAP3*	2	c.1096C>T	p.Arg366Trp	53	<0,01	25	0.716	VUS	*none*
	54	5	*IARS2*	1	c.2126T>G	p.Arg471Pro	41	<0,01	25	0.631	VUS	*DDX41*

Table 2. Germline variants in genes related to CSA in 58 cases of early onset MDS-RS in adults. Ten out of eleven variants were present in the subset of patients without *SF3B1* mutations.

Figure 1

https://doi.org/10.1182/blood-2023-185836