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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Clinical and Molecular Spectrum of Somatic Mosaic States in *DDX41* mutant Germline Predisposition Syndromes

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Introduction:
Germline DEAD-box RNA helicase-1 mutant (DDX41) predisposition syndrome (*DDX41*-MT-GPS) is one of the most frequent hereditary predisposition syndromes in adults with myeloid neoplasms (MN-2-5%). Somatic mosaicism involving the unmutated *DDX41* allele (e.g., R525H) as a potential mechanism for myeloid evolution has been reported in 39-50% of patients (pts). In addition, given the later age of onset, somatic mosaic states composed of age-related clonal hematopoiesis (ARCH) (e.g., *DNMT3A*, *ASXL1*, *TET2*, and *TP53*), with reported frequencies less than expected in MDS and AML, have been documented. We conducted this study to define the somatic mosaic landscape in *DDX41*-MT-GPS .

Methods:
After approval from the Mayo Clinic IRB the prospective GPS database was queried for pts with *DDX41*-MT GPS. Germline confirmation was conducted on skin fibroblast-, or hair follicle-derived DNA. Somatic CH testing was conducted using a targeted NGS panel as previously described. Given the high frequency of variants of undetermined significance (VUS), comparisons were made between pathogenic (*DDX41* ^{path}) and *DDX41* ^{VUS}.

Results: We identified 106 pts with *DDX41*-MT-GPS, of which 83 (78%) met criteria for MN, 16 (15%) for CH/CCUS (clonal cytopenias of undetermined significance), while 7 (6%) were unaffected carriers.

Somatic mosaicism in DDX41-GPS patients without MN
Sixteen *DDX41*-MT pts without MN met criteria for CH/CCUS (*DDX41* ^{path} [n=4] and *DDX41* ^{VUS} [n=12]; median age 69 years (yrs) (range [R], 19-78) (*DDX41* ^{path} [69 yrs] and *DDX41* ^{VUS} [67 yrs], p=0.85), with a male predilection (75%). Four (25%) pts had somatic *DDX41* MT (R525H [n=3] and A376T [n=1]) with median variant allele frequency (VAF) 10.5% (R, 5-27); 2 (50%) pts with germline *DDX41* ^{path} had R525H (VAF; 5% and 13%) and 1 (8%) pt each with germline *DDX41* ^{VUS} had R525H (VAF 5%) and A376T (VAF 27%) somatic variants, respectively. Abnormal cytogenetics (CG) were observed in 2/13 evaluable (15%) pts ([+8 and del20q]) in the germline *DDX41* ^{path} group only (p= 0.05). ARCH co-mutations were observed in 11 (69%) pts, not significantly (NS) different between *DDX41* ^{path} (75%) and *DDX41* ^{VUS} (75%), p= 0.66. Individual co-mutations: *DNMT3A* (25% vs 16%, p= > 0.99), *ASXL1* (25% vs 8%, p=0.71), *TET2* (25% vs 8%, p= >0.99), and *JAK2* (0% vs 8%, p= >0.99) were NS different between the two groups.

Somatic mosaicism in DDX41-GPS patients with MN
Eight-three pts met criteria for MN (*DDX41* ^{path} [n=43] and *DDX41* ^{VUS} [n=40]; median age 67 yrs (range [R], 27-92), with a male predilection (58%). Fifty-four (65%) pts had MDS (*DDX41* ^{path} [55%] and *DDX41* ^{VUS} [45%], p=0.55) and 29 (35%) had AML (*DDX41* ^{path} [41%] and *DDX41* ^{VUS} [59%], p=0.65). Overall, 15 (18%) pts had somatic *DDX41* MT; 12 (80%) pts with *DDX41* ^{path} and 3 (20%) pts with *DDX41* ^{VUS} (p= 0.003). The median VAF of somatic *DDX41* MT was 12% (R, 5-37), NS different between *DDX41* ^{path} (10.5%) and *DDX41* ^{VUS} (12%) (p=0.08). The most common somatic *DDX41* MT was R525H (66% [n=10]), significantly associated with *DDX41* ^{path} (9/10 [90%]), p=0.01. ARCH was observed in 17 (20%) pts, significantly higher in *DDX41* ^{path} (76%)

compared to *DDX41* ^{VUS} (24%), p= 0.03. Abnormal CG were observed in 10/73 evaluable (14%) pts (-Y [n=2], del 20 [n=3], del 5q [n=2], del 7q [n=1], t (3;8) [n=1] and complex CG [n=1]), higher in *DDX41* ^{path} (70%) compared to *DDX41* ^{VUS} (30%) with p value >0.99.

We compared the spectrum of CH between *DDX41* MT CH/CCUS and MN pts (**Table 1**) and found no difference in the proportion of pts with somatic *DDX41* MT (p= 0.52) and ARCH/myeloid MT (p= 0.56). The individual occurrences of *DNMT3A* (p= 0.49), *ASXL1* (p= 0.71), *TET2* (p=0.59), *JAK2* (p>0.99) and *TP53* (p= 0.56) mutations were NS different between the two groups (**Figure 1**).

Conclusion:

We define the somatic mosaic landscape in *DDX41*-MT GPS and demonstrate that somatic mutations involving the other allele, especially R525H, are seen in ~20% of pts (>80% of R525H present in MN). The frequency and composition of ARCH and myeloid driver mutations was lower than expected for the age of presentation, in comparison to *de novo* and secondary MDS/AML and occurred more frequently in *DDX41* ^{path} compared to *DDX41* ^{VUS}. Forty-two % (n=41), including 37% with MN, did not have somatic mosaicism, underscoring the fact that mechanisms of leukemia progression remain to be defined in subsets of affected pts.

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Variable	Overall (n=99)	CHIP/CCUS (N= 16)	Myeloid Neoplasm (N= 83)	P value
Age years, median(range)	66 [19-92]	69 [19-78]	67 [27-92]	0.89
Gender (male), n (%)	60 (60%)	12 (75%)	48 (58%)	0.69
***DDX41* pathogenic**	48 (48%)	4 (25%)	43 (52%)	0.003
***DDX41* VUS**	51 (51%)	12 (75%)	40 (48%)	0.01
Somatic *DDX41*	19 (19%)	4 (20%)	15 (18%)	0.52
R525H	12 (12%)	3 (19%)	10 (12%)	0.78
***DDX41* somatic VAF %**	12 [5-37]	10.5 [5-27]	12 [5-37]	0.67
Co-mutations	39 (39%)	11 (69%)	28 (34%)	0.56
ASXL1	9 (9%)	2 (12.5%)	7 (8%)	0.71
DNMT3A	12 (12%)	3 (19%)	8 (11%)	0.49
TET2	4 (4%)	2 (12.5%)	2 (2.5%)	0.59
JAK2	5 (5%)	1 (6%)	4 (5%)	>0.99
CBL	2 (2%)	1 (6%)	1 (1%)	>0.99
Spliceosome mutations	2 (2%)	0	2 (2.5%)	0.55
IDH 1/2	2 (2%)	0	2 (2.5%)	0.55
CEBPA	2 (2%)	0	2 (2.5%)	0.56
TP53	2 (2%)	0	2 (2.5%)	0.56
FLT3 ITD	1 (1%)	0	1 (1%)	>0.99
CSF3R	1 (1%)	0	1 (1%)	>0.99
RAS	1 (1%)	0	1 (1%)	>0.99
EZH2	4 (4%)	0	4 (5%)	0.30
Abnormal cytogenetics[a]	14 (16%)	2 (15%)	10 (14%)	0.74
NI	13	3	10	

NI; no information available, VUS; variant of undetermined significance, VAF; variant allele frequency

[a]2 patients had chromosomal abnormality without somatic co-mutations

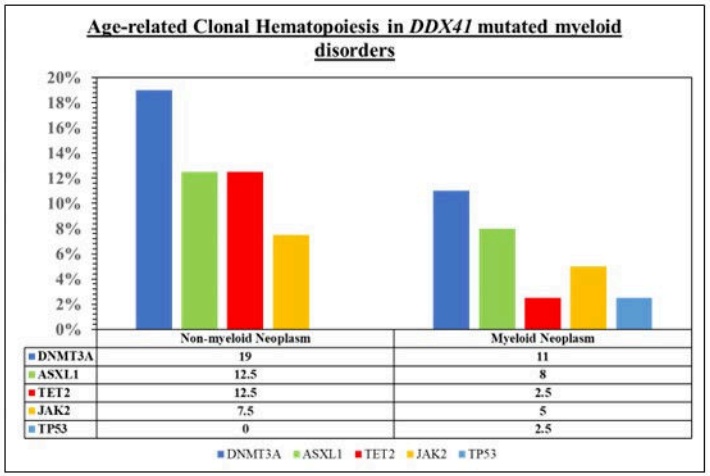

Figure 1