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P994 GERMLINE SINGLE-NUCLEOTIDE VARIANTS (SNV) IN THE JAK-STAT PATHWAY GENOME OF ADOLESCENT AND YOUNG ADULTS (AYA) AND NON-AYA PATIENTS WITH *BCR::ABL* NEGATIVE MYELOPROLIFERATIVE NEOPLASM (MPN)

Topic: 15. Myeloproliferative neoplasms - Biology & Translational Research

Alice Diepers*[1,2], Susann Schulze[2], Nadja Jäkel[2], Danny Misiak[1], Christina Zahn[1], Claudia Spohn[3], Regina Moeller[3], Dietrich Kämpfe[4], Maik Schwarz[5], Katrin Nerger[1], Bayram Edemir[1,6], Haifa Kathrin Al-Ali[1,2]

[1]Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany; [2]University Hospital Halle (Saale), Halle (Saale), Germany; [3]Hämatologisch-Onkologische Gemeinschaftspraxis, Halle (Saale), Germany; [4]Praxis Fuer Haematologie Und Onkologie, Luedenscheid, Germany; [5]Paracelsus Medizinisches Versorgungszentrum, Schwerpunktpraxis Für Hämatologie Und Onkologie, Schoeneck, Germany; [6]Witten/Herdecke University, Witten, Germany

Background:

Phenotype driver mutations (mut.) in *JAK2*, *CALR*, and *MPL* and JAK-STAT pathway dysregulation characterize MPN. Germline SNV have been associated with susceptibility to various cancers. Little is known about germline SNV in the JAK-STAT genome as causal mediators of *BCR::ABL* negative MPN.

Aims:

To present germline SNV in the *JAK2*, *CALR*, *MPL*, and 7 STAT-family genes in AYA and Non-AYA from the MARY project of the East German Study Group for Hematology and Oncology (OSHO)

Methods:

After signed informed consent, phenotype data and blood samples were collected [n=122: AYA (<39 y)=45, Non-AYA (>40 y)=77]. Besides whole transcriptome sequencing (RNA-seq) from blood derived RNA, WES from blood and FACS sorted CD3+ cells derived DNA was performed on an Illumina NovaSeq 6000 at Novogene. At the Core Facilty Imaging of the MLU Halle-Wittenberg (www.medizin.uni-halle.de/cfi), raw reads were quality checked (FastQC, version 0.11.9), low quality reads clipped off (Cutadapt, version 2.8), processed reads aligned (HiSat2 [https://doi.org/10.1038 /nmeth.3317] ,version 2.1.0) to the human genome (UCSC hg38), indexed (samtools, version 1.10), and used for variant calling (bcftools, version 1.10.2) mpileup pipeline. Annotation was performed (Ensembl VEP [doi:10.1186/s13059-016-0974-4], version 108.1) using Ensembl GRCm38.108 [https://doi.org/10.1093/nar/gkab1049], and merging/summarizing of variant and annotation data was performed via an in-house R script. MARY was approved by the ethical committee and funded by Incyte.

Results:

Median age in AYA and Non-AYA was 32.5 and 52 years respectively. Diagnoses were ET in 54 (44%), PV in 33 (27%), and PMF in 28 (23%) pts. *JAK2* exon 14, *CALR*, and *MPL* mut. were detected in 77%, 11%, and 1.7%. 11 (9%) pts were triple negative. Thyroid dysfunction (23%), thrombosis (37%) and a family history of thrombosis (43%) were similar across age. ET (p<0.001), thrombosis after diagnosis (p=0.05), *CALR* mut., and a triple negative genotype (p=0.004) were higher in AYA.

All pts harbored *JAK2* protein coding SNV (median n=44). In 93% and 71% of pts, a median of 27 and 8 SNV in *CALR* and *MPL* were detected respectively. *MPL* SNV correlated with triple negative genotype (p=0.03). Irrespective of phenotype driver mut., *JAK2* SNV correlated negatively with *CALR* and *MPL* SNV in AYA (p=0.02) and positively in non-AYA (p=0.03). Of 5 germline *CALR* and *MPL* SNV detected in >50% of pts, 3 were purely

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germline while somatic rs2974752 and rs1049481,COSV57131545 were found in further pts without the germline counterpart (**Table 1**). Median *STAT1* (n=370), *STAT2* (n=70), *STAT4* (n=75), *STAT5A* (n=28), *STAT5B* (n=127), and *STAT6* (n=127) SNV were comparable across age. *STAT3* SNV were less in AYA (mean n=451) vs Non-AYA (mean n=573) (p=0.02). In AYA, *CALR* SNV correlated with *STAT1* (p=0.04) and *STAT5B* SNV (p=0.02) while in Non-AYA, *JAK2* SNV correlated with *STAT3* and *STAT4* SNV (p=0.02) and a negative association between *STAT1* and *STAT5B* SNV was found (p=0.04). Irrespective of the number of *STAT* SNV, the percentages of protein coding to nonsense-mediated-decay, and intron retention biotypes within a gene were entirely constant across all pts. A negative association between protein coding *STAT3* SNV and protein coding *STAT4* SNV in non-AYA was found (p<0.001).

Summary/Conclusion:

The recurrent germline mut. in JAK-STAT pathway genes establish a linkage to map certain DNA regions that may be responsible for the MPN trait in AYA and Non-AYA. The integration of RNA-seq data will document the functional role of these genes and their potential cooperative activity with the classical phenotype driver mut.

Table 1. Germline and Somatic Genetic Variations (SNV) in *MPL* and *CALR* Genes in > 1% of Patients

		Gene			
		MPL		*CALR*	
	Percent	Germline SNV	Somatic SNV	Germline SNV	Somatic SNV
Frequency of genetic variations (SNV) in the entire cohort* * Phenotype driver mutations are excluded	**≥ 1 - 5%**	rs2069378; rs839993,CRO43164; rs12058355; rs911161496,COSV100196353; rs56701833; rs1760669; rs200460456; rs1051097,COSV60522559; rs1749959; rs114338202; rs59776175; rs35732878; rs1199038; rs839996	rs 2069378; rs839993,CRO43164; rs12058355; rs911161496,COSV100196353; rs76186025; rs56701833; rs1760669; rs1749959; rs77612379; rs114338202; rs111888775; rs1199038	rs2965220; rs4987202,COSV100330635; rs34598385; rs5016037; rs532493020; rs769694323; rs28365950; rs4987202,COSV100330635	rs2965220; rs765476509, COSV57116551,COSV57118194 rs5016037; rs891822005
	≥ 5 - 20%	rs16830693,COSV65244224; rs710252; rs41269541,COSV65245731; rs1273191,CMO10063,COSV65244707	rs17499601; rs1749961; rs59776175; rs710252; rs839996	rs1010222; rs2974751; rs56290054; rs11558955,COSV57120330	rs1049481,COSV57131545; rs2974752; rs35819755; rs1010222; rs2974751
	≥ 20 - 50%			rs35819755	
	≥ 50%	rs1760670,COSV65245058; rs839995		rs2974750; rs1049481,COSV57131545; rs2974752	

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