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POSTER ABSTRACTS

631.CHRONIC MYELOID LEUKEMIA: BIOLOGY AND PATHOPHYSIOLOGY, EXCLUDING THERAPY

Signaling Pathway Gene Set Enrichment Analysis in Whole Exome Sequencing Data from Discordant Identical Twins Unveils Relevant Pathways As a Clue to Understand Somatic Mutation Acquisition and Clonal Evolution in Myeloproliferative Neoplasms

Eduard Mas Marin, PhDMSc,BSc,PharmD,BA[1], *Sabrina Mir, BS*[2], *Eli M Soyfer, MS*[3], *Jane H Chen, BS*[4], *Jianhong C Heidmann, BS*[5], *Simran Bhardwaj*[6], *Gajalakshmi Ramanathan, PhD*[6], *Angela G. Fleischman, MDPhD*[5]

[1] University of California, Irvine, IRVINE, CA
[2] School of Medicine, University of California, Irvine, Irvine, CA
[3] Medicine, Biological Chemistry, University of California, Irvine, Irvine, CA
[4] University of California, Irvine, Irvine
[5] Division of Hematology/Oncology, University of California, Irvine, Irvine, CA
[6] University of California, Irvine, Irvine, CA

Although the role of classic driver mutations (i.e., *JAK2*, *MPL*, and *CALR*) in myeloproliferative neoplasm (MPN) development is well characterized, additional somatic mutations likely modulate the phenotype. Recurrent somatic mutations, such as those in *TET2*, *DNMT3A*, *ASXL1* genes are commonly identified in MPN using targeted myeloid panels, however identification of somatic mutations using an unbiased approach may unveil novel pathways involved in MPN pathogenesis.

We performed whole exome sequencing of blood samples of three sets of discordant identical twins in which one twin has MPN and the other twin is unaffected. The twin sets included all MPN subtypes (1 polycythemia vera, 1 essential thrombocythemia, 1 primary myelofibrosis). We also performed whole exome sequencing on additional family members, including the mother and father of the PV twin and the brother of the ET twin. Sequencing information from the discordant identical twins is a unique opportunity to identify somatic mutations in the affected twin that may contribute to MPN pathogenesis, and also to potentially identify clonal hematopoiesis in the unaffected twin.

We mapped all the identified genetic variants to the affected genes, and we filtered all the genes mapped to those variants depending on whether they were present either in the MPN-affected twin or in the unaffected counterpart for further gene set enrichment pathway analysis. The gene set enriched signaling pathways from identified genetic variants for each condition-exclusive (either MPN or unaffected twin) allows us to identify and prioritize key pathways in MPN development in terms of somatic mutations acquisition. Furthermore, besides performing the analysis within each single MPN set, we analyzed the gene sets resulting from combining the different families allowing us not only to identify pathways at each single MPN type level but also among the different MPN diseases (PV, ET, and MF). We divided all the enrichment analyses into coding and silent variants to obtain a higher degree of pathway refinement.

In single discordant twin sets we identified several pathways that may play an important role within MPN pathogenesis such as defective mismatch DNA repair, facilitated mitotic progression, extracellular matrix degradation, MAPK signaling, FGFR signaling, *O*-glycosylation of proteins, collagen metabolism and laminin interactions, neutrophil degranulation, interleukin-33 signaling, Rho GTPases and cGMP regulation, and nuclear pore complex (NPC) assembly. Interestingly, only when we analyze all the MPN-types together all the statistically significant pathways resulting from coding variants correspond only to DNA repair, specifically defective mismatch repair (PMS2, MLH1, MutSα, MutSβ, and TP53). Our findings reveal that DNA repair genes might occupy a central role within MPN acquisition and development, whereas at the same time each single MPN clinical entity might possess its own distinct mechanisms differentiating each one from the others.

Disclosures Fleischman: *Pharmaessentia, CTI:* Speakers Bureau; *GSK, Incyte, CTI:* Consultancy.

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