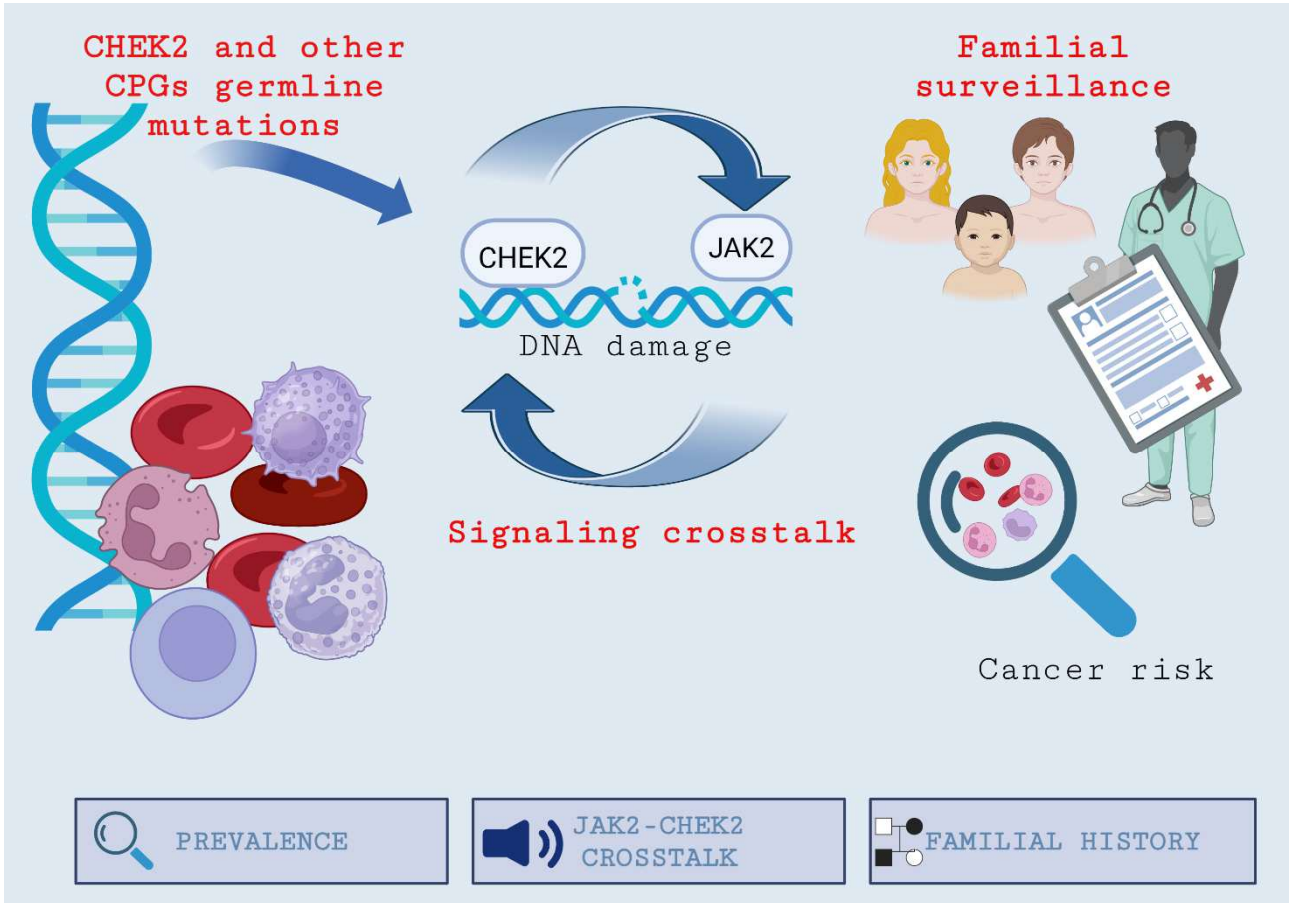
Title: "Hidden inheritance: germline variants fueling the onset of Ph-negative myeloproliferative neoplasms"

Elisa Rumi, Department of Molecular Medicine, University of Pavia; Unit of Molecular Hematology and Precision Medicine, Fondazione IRCCS Policlinico San Matteo Pavia

Research Theme/Topic: Hematology

Main Abstract:

There is increasing evidence that germline factors might favor the onset of myeloproliferative neoplasms (MPN). It was recently demonstrated that around 2% of patients with familial or early onset MPN carry loss of function germline CHEK2 mutations.
The project is based on these 3 hypotheses: 1) MPN onset might be favored by underlying germline mutations of DNA damage repair (DDR) genes or other cancer predisposition genes (CPGs) and these mutations might be associated with an higher risk of disease progression and secondary malignancies; 2) JAK2 mutant clones could preferentially expand on the background of CHEK2 germline mutations through a maladaptive rescue of mitosis and genome instability, promoting malignant transformation; 3) the identification of germline mutations in CHEK2 or other CPGs through genetic screening in relatives belonging to mutated families would allow an earlier diagnosis of solid cancers or of myeloid neoplasms through routinary surveillance.
The projects has 3 main aims: 1)To evaluate the prevalence of germline mutations of DDR genes and other CPGs in MPN and their correlation with the clinical phenotype; 2) to explore in hematopoietic stem and progenitor cells (HSPC) how germline CHEK2 variants synergize with the classical MPN driver mutations in JAK2 to promote clonal expansion and disease manifestation; 3) to test whether familial surveillance is able to preemptively identify solid cancers (such as breast, prostate and colon cancers) and myeloid disorders in presymptomatic relatives carrying DDR mutations or other CPGs mutations.
We will apply targeted next generation sequencing (NGS) in 800 patients affected with MPN (300 young/familial and 500 sporadic) and whole exome sequencing (WES) in 100 young/familial MPN patients tested negative for germline variants using the germline NGS panel. Then we will evaluate the prevalence of DDR mutations/other CPGs mutations and correlate them with the clinical phenotype. We will investigate the role of CHEK2 germline variants in human HSPCs and test the functional cooperation between CHEK2 germline and JAK2 somatic mutations. We will investigate the occurrence of solid cancers, clonal hematopoiesis (CH) and myeloid disorders in healthy relatives carrying DDR gene mutations or mutations of other CPGs through screening procedures.
Techniques: experience in recruiting patients with MPN, experience in NGS and WES, experience in translational research.


CHEK2 and other CPGs germline mutations
CHEK2
JAK2
DNA damage
Signaling crosstalk
Familial surveillance
Cancer risk
PREVALENCE
JAK2-CHEK2 CROSSTALK
FAMILIAL HISTORY