POLYMORPHISMS AND EXPRESSION OF GENES ASSOCIATED WITH JAK/STAT SIGNALING IN PATIENTS WITH MYELOPROLIFERATIVE NEOPLASM

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Myeloproliferative neoplasms, encompassing essential thrombocythemia, primary myelofibrosis, and polycythemia vera, represent a subset of hematological disorders within the Philadelphia-negative subgroup. The molecular network involved in the JAK/STATs signaling pathway has been demonstrated involved in the genetic landscape of Myeloproliferative disorders in several studies. Deubiquitinating genes such as CYLD and A20 are known as negative regulators of immune reactions. In this study, we assessed the expression levels of CYLD, A20, SHPs, and STATs genes by q-PCR. Additionally, genotyping via Kompetitive Allele Specific PCR (KASP) was employed to discern the genotypes of 5 variants within the A20, JAK2, HLA, and OR10Q2P genes. Furthermore, levels of inflammatory cytokines and cancer antigen 125 (CA-125) were quantified using enzyme-linked immunosorbent assay (ELISA). Results showed that mRNA levels of CYLD, A20 and SHP-1 were significantly lower in all Myeloproliferative neoplasms patients, while expressions of SHP-2, STAT1 and STAT6 were significantly enhanced in Essential thrombocythemia patients when compared to controls. Concentrations of inflammatory cytokines IL-6, TNF-α, IL-1β as well as the cancer antigen protein CA-125 were elevated in Myeloproliferative neoplasms cases. Genotyping results explored that rs10974947 in JAK2, rs200878487 in A20, and rs2281389 in HLA had higher frequencies in PMF cases compared to controls. Importantly, two novel associations as our knowledge, between the variant HLA rs2281389 (p = 0.004, OR = 2.6, 95% CI = 1.36–4.85) and OR10Q2P rs12289961 – a LPXN-nearby variant (OR = 1.95, 95%CI = 1.01–3.75) with Polycythemia vera were detected in this studied population. These data suggested that A20, JAK2, HLA and LPXN genes may have important functions in disease phenotypes. Nevertheless, further functional studies on these genes should be carried out for a better understanding of Myeloproliferative neoplasms pathogenesis.

***Key word**: A20, CYLD, myeloproliferative neoplasms, SHP, STATs, HLA.*

ПОЛІМОРФІЗМИ ТА ЕКСПРЕСІЯ ГЕНІВ, АСОЦІЙОВАНИХ ІЗ СИГНАЛЬНИМИ ШЛЯХАМИ JAK/STAT, У ПАЦІЄНТІВ З МІЄЛОПРОЛІФЕРАТИВНИМИ НОВОУТВОРЕННЯМИ

Мієлопроліферативні новоутворення, серед яких ідіопатична тромбоцитемія, первинний мієлофіброз та поліцитемія, становлять підгрупу гематологічних розладів у межах підгрупи без наявності філадельфійської хромосоми. Участь молекулярної мережі, задіяної в сигнальному шляху JAK/STAT, була продемонстрована в декількох дослідженнях генетичного ландшафту мієлопроліферативних розладів. Такі гени деубіквітинування, як *CYLD* та *A20*, відомі як негативні регулятори імунних реакцій. У цьому дослідженні ми оцінили рівні експресії генів *CYLD, A20, SHP* та *STAT* за допомогою кількісної ПЛР. Крім того, було застосовано генотипування за допомогою конкурентної алель-специфічної ПЛР (KASP) для визначення генотипів 5 варіантів у межах генів *A20, JAK2, HLA* та *OR10Q2P*. Більше того, було використано імуноферментний аналіз (ІФА) для кількісного визначення рівнів запальних цитокінів та ракового антигену 125 (CA-125). Результати показали, що рівні мРНК *CYLD, A20* і *SHP-1* були значно нижчими у всіх пацієнтів з мієлопроліферативними новоутвореннями, тоді як експресія *SHP-2, STAT1* і *STAT6* була значно підвищена у пацієнтів з ідіопатичною тромбоцитемією порівняно з контролем. У випадках мієлопроліферативних новоутворень концентрації запальних цитокінів IL-6, TNF-α, IL-1β, а також білка-антигену раку CA-125 були підвищеними. Результати генотипування показали, що *rs10974947* в JAK2, *rs200878487* в A20 та *rs2281389* в HLA мали вищу частоту у випадках МПН порівняно з контролем. Важливо, що в досліджуваній популяції було виявлено дві нові асоціації між варіантом *HLA rs2281389* (p = 0,004, OR = = 2,6, 95% CI = 1,36–4,85) та *OR10Q2P rs12289961* – варіантом, близьким до LPXN (OR = 1,95, 95% CI =

= 1,01–3,75), з поліцитемією. Ці дані свідчать про те, що гени *A20, JAK2, HLA* та *LPXN* можуть відігравати важливу роль у формуванні фенотипу захворювання. Тим не менш, для кращого розуміння патогенезу мієлопроліферативних новоутворень необхідно провести подальші функціональні дослідження цих генів.

Ключові слова: *A20*, *CYLD,* мієлопроліферативні новоутворення, *SHP, STAT, HLA.*

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