Genetic factors in lymphoproliferative malignancies. Focus on CHEK2 gene in lymphomas with comparison to distinct solid tumors.

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Summary of PhD thesis:

Background: The checkpoint kinase 2 gene (CHEK2) codes for an important mediator of DNA damage response pathway that among others interacts with the p53 protein. Mutations in the CHEK2 gene increase the risk of several cancer types, however, their role in non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) is not clear. The most frequent TP53 gene R72P polymorphism was analyzed in several studies in NHL but not in HL.

Methods: We have performed mutation analysis of the whole CHEK2 gene coding sequence in 340 NHL patients and the segment coding for CHEK2 forkhead-associated (FHA) domain in 298 HL patients and compared the results with our analyses of CHEK2 in breast, colorectal and pancreatic cancers. The TP53 R75P genotype was assessed in the same lymphoma populations. Both genes were analyzed using denaturing high-performance liquid chromatography.

Results: The overall frequency of CHEK2 alterations within FHA-coding region was significantly higher in NHL and HL patients (19/340 - 5.6%; 17/298 - 5.7%, respectively) compared to non-cancer controls (19/683 - 2.8%; p = 0.03 and 0.04, respectively). These alterations were associated with increased risk of lymphoma development (OR = 2.1; 95% CI 1.2-3.7; p = 0.01) and worse progression-free survival (PFS) in NHL patients (p = 0.008). Better overall survival in diffuse large B-cell lymphoma and PFS in all NHL patients was associated with CHEK2 IVS1+43dupA alteration (p = 0.02 and 0.01, respectively). We have identified the association of CHEK2 FHA alterations also with colorectal cancer risk (OR = 2.3; 95% CI 1.3-4.1; p = 0.003), but not with breast or pancreatic cancers. The TP53 R72P polymorphism did not influence lymphoma risk or survival.

Conclusions: Alterations in the CHEK2 gene FHA coding region represent moderate genetic predisposition factor increasing the risk of lymphoma and together with IVS1+43dupA alteration may modify lymphoma disease course.