

Genetics of Neoplasia: Inherited Monogenic Defects Associated with Cancers

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Genetic alterations seem to be one of the major factor predisposing individual to cancers, while a wide range of genetic alterations in cancer development has already been described. In a notable recently published paper, entitled "Neoplasia from Genetic Point of View" (1), it is implied that several genetic pathways and critical cancer-predisposing genes contribute to cancer genesis through being undergone to wide range of gene mutations. However, it should also be added that there are a number of monogenic defects, named as primary immunodeficiency diseases (PIDs), which are associated with cancers (2).

The susceptibility to develop cancers in PIDs depends on several factors, including defective DNA damage response and dysregulated immune response (2). Among more than 200 known PIDs, there are some with defects in cellular and/or humoral immunity, such as X-linked lymphoproliferative disease (XLP), IL-2-inducible T-cell kinase (ITK) deficiency, epidermodysplasia verruciformis (EV), warts, hypogammaglobulinemia, infections and myelokathexis (WHIM) syndrome, autosomal recessive hyper-IgE syndrome (AR-HIES) in which genetic defects lead to increased susceptibility to specific viruses and consequently cancers (2).

XLP is an immunodeficiency disease, characterized by classical triad of fulminant infectious mononucleosis, dysgammaglobulinemia and lymphoma (3), caused by mutations in the Src homology domain-containing gene 1A (*SH2D1A*). The patients with XLP are at increased risk of developing lymphomas and other lymphoproliferative diseases, especially non-Hodgkin B-cell lymphomas (2,3). ITK deficiency (due to homozygous mutations of the *ITK* gene), clinically resembling XLP, is characterized by severe EBV associated immune dysregulation which may progress to Hodgkin lymphoma (2,3).

EV is manifested by disseminated cutaneous lesions

that carry a considerable risk for developing squamous cell carcinoma (2,4). Mutations of the genes *EVR1* and *EVR2* genes are the main cause of disease (4). As of its key role in HPV lifecycle, loss of function of EVER genes could contribute to HPV-mediated carcinogenesis (5). WHIM syndrome is an autosomal dominant syndrome, caused by mutations in the chemokine receptor *CXCR4* gene (6). In addition to HPV infections, EBV-associated lymphoproliferative disorders have also been reported in WHIM syndrome (7).

HIES is characterized by early onset bacterial infections predominantly involving skin and lungs in association with elevated serum IgE levels and eosinophilia (8,9). Mutations in dedicator of cytokinesis 8 (*DOCK8*) gene could lead to AR-HIES, which could be associated with a number of cancers (9); and finally, humoral immunodeficiencies, such as common variable immunodeficiency and X-linked agammaglobulinemia, which are commonly characterized by recurrent bacterial infections, could develop malignancies as well (10).

Finally, recent advances on identification of novel gene defects associated with PIDs led to new insights on genetics of infectious diseases as well as tumor development in PIDs. It seems that monogenic defects in some PIDs could have the main role in triad of immunodeficiency, susceptibility to recurrent infections, and predisposition to cancers (2).

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