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A Genetic Approach to Hereditary Cancers

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ABSTRACT

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Cancer: It is a disease characterized by the development of abnormal cells that divide in an uncontrolled manner and are capable of destroying by spreading to normal tissues. The main abnormality in cancer development is the continuous and uncontrolled proliferation of cancer cells. Loss of control in these cells is the result of the accumulation multiple cell regulatory system abnormalities. Development of cancer at the cellular level; it is a multistep process involving the selection and mutation of cells that proliferate, increase invasion and metastasis capacity. This change is due to the successive accumulation of changes in genes that enable the continuation of genetic integrity, cell death, and control of cellular proliferation [1]. Cancers can occur sporadically and hereditary in individuals. Sporadic cancers; which is caused by damaged accumulated in the DNA due to the environment and aging effect, constitutes approximately 80% of all cancers. This type of cancer, which is mostly seen in older ages, is unlikely to have an inherited mutation. Even if there are many cases of cancer in the family of the individual with cancer, this does not indicate hereditary transmission. Sporadic cancers can be largely prevented by lifestyle changes. Hereditary cancers; certain types of cancer occur in certain genes and are caused by the inherited transmission of disease-related permanent changes to subsequent generations. The incidence of these cancers is 5-10% in all cancer cases. They are seen at an earlier age than sporadic cancers. These cancers may occur in the individual, in multiple organs and/or at multiple points of the same organ [2].

Hereditary Cancer Syndromes

Cancer develops due to environmental agents (chemical carcinogens, radiation, viruses, etc.) and inherited genetic factors (germline mutations). If an individual has a hereditary cancer syndrome due to an inherited mutation, there may be an increased risk of developing certain tumors that may develop relatively early. In many of the known hereditary malignant syndromes, the affected genes are usually associated with the repair of DNA damage or control of the cell cycle. Due to the widespread presence of malignancies in the population, and because the mutation screening is laborious and expensive, extreme care must be taken in the selection of individuals for molecular genetic analysis. Detailed information of the applicant (proband) for genetic counseling is learned, at least three generations of family history are questioned, and pedigree analysis is performed. The history of the prosthetic and the drawn pedigree analysis usually leads to suspicion of a defined "hereditary cancer syndrome ve and, if adequate criteria are met, it is decided to carry out genetic analysis to investigate relevant gene mutations.

"Increased Risk of Hereditary Cancer Susceptibility "in which situations should it think?

If an individual has multiple primary tumor foci in the same organ, multiple primary tumor foci in different organs or bilateral primary tumors of the double organs, this may be due to a genetic basis. Also, if in an individual identifies early diagnosis of cancer, a rare histological type of cancer cell, rare cancer (breast cancer in man, etc.), congenital defects and rare diseases with inherited precursor or cutaneous lesions, hereditary cancer syndrome should be suspected. Sometimes an individual's family history may suggest the presence of hereditary cancer syndrome. For example; if one of the first-degree relatives has a tumor of the same or similar type, tumors of the similar region in ≥2 first-degree

relatives, ≥2 first-degree relatives, tumors of known hereditary cancer syndromes, rare tumors in ≥2 first-degree relatives, and ≥2 relatives in two generations in the case of tumors of the region or etiologically related regions, a genetic cause should be investigated [3]. Hereditary cancers are inherited by certain genes and are usually autosomal dominant with incomplete penetrance. There are several genes that are known today and whose changes can cause hereditary cancer syndrome and each of the hereditary cancer syndromes to which these genes are responsible has certain characteristic tumor spectra (Table 1) [4].

Table 1: Gene(s) responsible for hereditary cancer syndromes and expected tumor spectrum.

Inheritance Pattern	Hereditary Cancer Syndromes	Gene(s)	Expected Tumor Spectrum
Autosomal Dominant Heredity	Hereditary Nonpolyposis Colorectal Cancer (HNPCC)	MLH1, MSH2, MSH6, PMS2, EPCAM	Colon, Endometrial, Gastric, Small Intestine etc.
	Hereditary Breast and Ovarian Cancer	BRCA1, BRCA2	Breast, Ovarian, Prostate, Pancreas Cancer etc.
	Neurofibromatosis Type 1	NF1	Neurofibroma, Optic nerve glioma, Neurofibrosarcoma
	Multiple Endocrine Neoplasia Type 2 (MEN2a)	RET	Medullary thyroid cancer, pheochromocytoma, hyperparathyroidism
	Familial Adenomatous Polyposis (FAP)	APC	Polyposis tumors in upper gastrointestinal tract, desmoids
	Von Hippel-Lindau Disease	VHL	Clear cell renal cancer disease and other, usually benign tumors
	Li-Fraumeni Disease	TP53	Sarcoma, breast cancer, brain tumors, leukemia etc.
Autosomal Recessive Heredity	MUTYH-associated polyposis (MAP)	MUTYH	Colon cancer, colonic adenoma
	Ataxia telangiectasica	ATM	Non-Hodgkin Lymphoma, Leukemia
	Fanconi Anemia	FANCA-H	Hematologic neoplasms

Which genetic tests to select in the family tree and who will perform genetic analysis should be determined by the Medical Genetic Specialist. During the genetic counseling, learning in detail the organs in which the primary tumors of the proband family reside will facilitate the selection of the responsible gene. For this reason, a family history of at least 3 generations of proband should be questioned in detail. Diagnosis and age of cancer patients, risk factors that may cause diagnosis for each patient in the pedigree should be questioned. According to the results of genetic testing, individuals or family members are informed about susceptibility to certain types of cancer and genetic counseling is provided. When a disease-related gene variant is detected, in which organ systems this gene increases the risk of malignancy and the risk increase rates, the genetic transition pattern of the gene should be explained in detail with the literature. For all organs that may increase the risk of malignancy, a multidisciplinary approach to proband is referred to the relevant departments. In the family of the proband, family work (co-segregation analysis) is carried out following a certain algorithm to screen for the disease-related variant of the gene that is inherited in the genealogy analysis of those likely to be affected.

Most of these syndromes conform to the autosomal dominant inheritance pattern, i.e. first-degree relatives (mother, father, children, and siblings) have a 50% risk for this mutation. The relatives of the patient should be reminded in genetic counseling that family work tests are susceptibility tests and that only those who want to learn the risks. Identification of a patient's cancer-causing mutation provides a reliable predictive diagnosis for patients' relatives. This means that when family members at risk are screened for the presence of the mutation in question, it can be determined whether they inherit the increased risk of cancer. The most important objective here is to ensure that family members with mutations are enrolled in a specific monitoring program for relevant cancer syndrome. Besides, if the clinical mutation in a family cannot be detected in the proband, it is not possible to perform predictive testing on other healthy members of the family. Family members who do not have a mutation are not included in the cancer intensive cancer screening and monitoring program.

As a result; many features, such as tumors occurring simultaneously or at different times in the patient, age at onset of the disease earlier than expected, and the presence of multiple relatives affected, indicate the presence of hereditary cancer syndrome. In these cases, it would be beneficial for the patient and relatives to receive genetic counseling, if necessary, to perform additional diagnostic procedures and analyzes, and to receive individual recommendations for early diagnosis/screening tests. Targeted examinations can be used to diagnose possible cancer early and, if necessary, to improve prognosis by removing precursor cancerous lesions. In summary; defining "hereditary cancer syndrome de in an individual will enable the individual and his / her family members at risk to be included in a cancer intensive cancer screening, monitoring, and prevention program. For this reason, individuals with suspected hereditary cancer syndrome should consult with a genetics specialist and get genetic counseling.

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