LEOPARD Syndrome (Multiple Lentigine Noonan Syndrome)

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ABSTRACT

LEOPARD is a syndrome characterized by sensorineural hearing loss and abnormal genitalia in addition to dysmorphic facial features, including diffuse brown spots, cardiac abnormalities, short stature, pectus deformity, widely spaced eyes, and ptosis. LEOPARD consists of the initials of the findings obtained in the cases: Lentigines, Electrocardiographic abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retardation of growth and Deafness. This syndrome is autosomal dominant. In the syndrome, 4 mutations have been identified in this process from the investigated chromosomes to genes. These are PTPN11, RAF1, BRAF and MAP2K1. While these mutations cause amino acid changes in the genotype, they reveal visible clinical findings in the phenotype. It is also called Multiple Lentigine Noonan Syndrome due to its similarity with Noonan syndrome. Too many dark brown spots are present in individuals with LEOPARD syndrome as a distinctive clinical finding from Noonan syndrome.

Keywords: Amino acid, chromosome, lentigin, LEOPARD syndrome, mutation, Noonan syndrome, signaling pathway.

This name was changed to LEOPARD because it was long and was thought to frighten children. In addition, studies have shown that the disease is autosomal dominant inherited. This suggested that it was a genetic disorder.

Symptoms seen in LEOPARD Syndrome are: brown spots (Lentigine), hypertrophic cardiomyopathy in addition to cardiac abnormalities, weak linear growth/short stature, dysmorphic facial features including pectus deformity, widely spaced eyes and ptosis plus sensorineural hearing loss, abnormal genital area (e.g. in male cryptorchidism (missing testicle)). When these symptoms are seen in the clinic, a pre-diagnosis can be made.

GENETIC STRUCTURE OF LEOPARD SYNDROME

The diagnosis of LEOPARD syndrome is made by visible clinical signs, or by identification of a...
pathogenic variant in one of four genes (PTPN11, RAF1, BRAF, and MAP2K1) if clinical findings are insufficient.°\[7\]

LEOPARD SYNDROME AND THE FOUR GENE

The PTPN11 gene is responsible for making a protein called SHP2. This protein helps regulate the RAS/MAPK signaling pathway. This signal pathway has characteristics such as the growth and division of cells, the maturation process of cells to perform certain functions, cell movement and self-destruction (apoptosis) of cells. During embryonic development, SHP2 protein is very important in the development of the heart, blood cells, bones and many other tissues.°[8,9]

Multiple lentigines caused by PTPN11 gene mutations are one of two mutations that make up about 65 percent of noonan syndrome cases. Two different mutations occur in the SHP2 protein with the change of amino acids. One of these mutations is the replacement of tyrosine and cysteine, and the other is the replacement of threonine and methionine.°[8,9]

Approximately 85% of patients diagnosed with definite LEOPARD syndrome have a mutation in the PTPN11 gene located on the 24.1 location of the 12th chromosome q (long) arm. The PTPN11 gene encodes the PTPase (SHP2) protein, which contains the SRC homology 2 (SH2) domain. SH2 has two subdomains (N-SH2 and C-SH2). These domains characterize and activate protein tyrosine phosphatase (PTP) domain. SHP2 functions as cytoplasmic signal converter, playing a specific role for growth factors, multiple receptors for cytokines and hormones and in the RAS-mitogen-activated protein kinase (MAPK) pathway. So far 11 different PTPN11 mutations have been reported in exons 7, 12 and 13 (Tyr279Cys/Ser, Ala461Thr, Gly464Ala, Thr468Met/Pro, Arg498Trp/Leu, Gln506Pro and Gln510Glu/Gly). Two of these (Tyr279Cys and Thr468Met) occur in approximately 65% of cases.°[10-13]

Sporadic tumors (including leukemia and solid tumors) that occur in the absence of NSML (LEOPARD Syndrome) or other findings of Noonan syndrome contain somatic pathogenic variants in PTPN11 that are not found in reproductive cells; therefore, predisposition to these tumors is not inherited. PTPN11 cancer are benign tumors.\[2\]

BRAF

Sithanandam et al.°[7] Succeeded in cloning BRAF from the cDNA library in 1990 using a BRAF kinase-specific oligomer. The BRAF gene has 651 amino acids and its total molecular weight is 72.5 kD.°[14] The Braf gene is located on the long arm (7q34) of chromosome 7 and consists of 18 exons. The pathological allelic BRAF variants that cause to LS are Thr241Pro and Leu245Phe. Germline mutations in this gene are also associated with cardiofaciocutaneous syndromes and generate somatic mutations.°[5,15]

RAF1

When the RAF1 gene is mutated, it causes the resulting RAF1 protein to be constantly active and stimulate other protein kinases in the same signaling pathway that help control cell division. This mutation can cause cells to divide and grow uncontrollably. RAF1 gene mutations are more frequently associated with causing multiple lentigine syndrome and Noonan syndrome than with causing cancer.°[16]

The heterozygous 1837C> G mutation in the RAF1 gene has been associated with both LEOPARD syndrome and NS.°[17] RAF1 is the flux factor of the RAS signal, which encodes the MAPK protein with 648 amino acids in the signal pathway and contains three domains, CR1, CR2 and CR3. Both Noonan syndrome and LEOPARD syndrome are associated with mutations in PTPN11 and RAF1. The percentage of this mutation is higher in patients. Therefore, especially these mutations are paid attention when examining patients.°[18]

MAP2K1

This syndrome occurs as a result of a mutation in the 15th chromosome long (q) arm of the MAP2K1 gene. MAP2K1 gene MEK1, protein kinase stimulates to make a protein. This protein is part of a signaling pathway called the RAS/MAPK pathway, which transmits chemical signals from outside the cell to the cell’s nucleus. The RAS/MAPK signal helps control the growth and division of cells, specific functions of the cell and the process by which cells mature to perform cell movement and self-destruction (apoptosis) of cells. The MEK1 protein kinase appears to be essential for normal development before birth and for survival after birth.°[19]

Binding of extracellular ligands such as growth factors, cytokines, hormones and dual specific protein kinase that functions as an essential component of
the MAP kinase signal transduction pathway to cell surface receptors activates RAS and this initiates RAF1 activation.[20-22]

Subsequently, RAF1 also activates the dual specific protein kinases MAP2K1/MEK1 and MAP2K2/MEK2. Both MAP2K1/MEK1 and MAP2K2/MEK2 function specifically in the MAPK/ERK cascade. A threonine and a tyrosine structure catalyze a tyrosine structure found in the extracellular signal regulated kinases MAPK3/ERK1 and MAPK1. The combination of ERK2, MAPK/ERK cascade leads to activation and further transmission of the signal. BRAF1 activates based on KSR1 or KSR2. Depending on the cellular context, transcription leads to various biological functions such as cell growth, adhesion, survival, and differentiation through metabolism and cytoskeletal rearrangement. The MAP2K1 gene interacts with RAF and BRAF.[20-22]

The identified MAP2K1 gene mutation occurs as a result of the replacement of Glutamic acid and Glycerin in the MEK1 protein. This change results in increased activation of the RAS/MAPK signaling pathway in cells throughout the body. Increased signaling interferes with the normal development of many organs and tissues, leading to the characteristic features of Multiple Lentigine Noonan syndrome.[23]

OTHER CLINICAL SYNDROMES WITH SIMILAR LEOPARD SYNDROME

Williams syndrome: There is a microdeletion at 11.23 The long arm of chromosome 7 (q) containing the elastin gene (ELN), 80% of patients show coronary heart disease (mostly supravalvular aortic stenosis). There is facial dysmorphism (facial anomaly). 15% of patients have hypercalcemia. A variable degree of mental retardation and developmental delay can also be seen.[24]

Watson syndrome: There are Cafe-au-lait (coffee with milk) spots, short stature, mental retardation and pulmonary stenosis. There is a neurofibromin (NF) mutation. Lisch (iris spot) nodule is not expected.[25]

Cardiofasiocutaneous syndrome (CFC): There are Congenital heart diseases, LEOPARD and Noonan-like appearance, short stature, mental retardation, ectodermal and gastrointestinal anomalies. It is caused by a spontaneous mutation of all three genes in the mitogen-activated protein kinase (MAPK) pathway.[26,27]

Costello syndrome: As in LEOPARD and Noonan syndrome, there is feeding difficulty in infancy. There are papillomas around the mouth and nose. There is growth retardation and an increased risk of malignancy. There is a mutation in the HRAS gene at 11p13.1.[28,29]

Declaration of conflicting interests
The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding
The authors received no financial support for the research and/or authorship of this article.

REFERENCES


