Partner and Localizer of BRCA2

Alternative Names
PALB2
FANCN Gene
FANCN

Record Category
Gene locus

WHO-ICD
N/A to gene loci

Incidence per 100,000 Live Births
N/A to gene loci

OMIM Number
610355

Mode of Inheritance
N/A to gene loci

Gene Map Locus
16p12.2

Description
PALB2 encodes a critical DNA repair protein that may be involved in tumour suppression. PALB2 functions by binding to and co-localizing with BRCA2, thereby permitting its stable intra-nuclear accumulation and preventing its proteasome-mediated degradation. The association of PALB2 with BRCA2 plays a key role as BRCA2 is essential for homologous recombination repair and tumour suppression. PALB2 also serves as the molecular scaffold in the formation of the BRCA1-PALB2-BRCA2 complex.

Mutations in the PALB2 gene impair its function and therefore its ability to carry out DNA repair. This results in a build-up of inter-strand crosslinks ultimately stalling DNA replication and causing either abnormal cell death or uncontrolled cell growth. Abnormal cell death leads to blood cell shortage and manifests as Fanconi anaemia while uncontrolled cell growth develops into cancers. Hence, mutations in the PALB2 gene are associated with breast cancer, pancreatic cancer and Fanconi anaemia. Breast cancer is a genetically and etiologically heterogeneous malignancy arising from the breast epithelial tissue. Women with a PALB2 mutation have an almost ten times higher risk of breast cancer than average. Pancreatic cancer is a malignant neoplasm that can arise from either the exocrine or endocrine regions of the pancreas. Fanconi anaemia is a rare blood disorder that results in bone marrow failure, organ defects, physical abnormalities and susceptibility to certain cancers. Similar to the BRIP1 gene, PALB2 is involved in the Fanconi anaemia pathway, downstream of FANCD2 ubiquitination.

Molecular Genetics
The 38 kb long PALB2 gene is made up of 14 exons. Its protein product is 113 kDa in size and made up of 1186 amino acids. Mutations associated with breast cancer are usually heterozygous deletions or transitions. PALB2 mutations are the second most common cause of hereditary pancreatic cancer. These are usually germline heterozygous mutations. Biallelic mutations in the PALB2 gene are associated with the Fanconi anemia complementation group N and an increased risk of early onset cancer.

Epidemiology in the Arab World

Saudi Arabia

Ghazwani et al. (2016) studied the underlying mutations affecting Fanconi anemia patients. Ten patients, all from consanguineous families and of Saudi Arabian origin, were recruited. Of these, 2 female infants were found to have a mutation in the PALB2 gene. The first female had a strong family history of cancer. The second infant had a sister who had died from acute myeloid leukaemia secondary to FA. A novel homozygous mutation in exon 13 of the PALB2 gene, c.3254del resulting in p.Leu1142Tyrfs*21, was detected in both patients. This variant was not found in 50 ethnically-matched non FA controls and in-situ analysis predicted it to be disease causing. Previous studies have found monoallelic loss of function mutations

adjacent to this variant to be associated with an increased risk of breast cancer. The study also found that unlike European FA cases, most Saudi FA mutations were in downstream FA pathway genes. As the FANCD2 monoubiquitination assay does not screen for these genes, the assay was considered ineffective in diagnosing most Saudi FA cases.

References

Ghazwani Y, AlBalwi M, Al-Abdulkareem I, Al-Dress M, Alharbi T, Alsudairy R, Alomari A, Aljamaan K, Essa M, Al-Zahrani M, Alsultan A. Clinical characteristics and genetic subtypes of Fanconi anemia in Saudi patients. Cancer Genet. 2016; 209(4):171-6.

Related CTGA Records

External Links

http://www.genecards.org/cgi-bin/carddisp.pl?gene=PALB2
http://www.breastcancer.org/research-news/abnormal-palb2-gene-increases-risk

Contributors

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