BRCA1 & BRCA2 MUTATION COMPREHENSIVE PANEL

BRCA1 & BRCA2 MUTATION COMPREHENSIVE PANEL
(Sequencing)
Mutations detected

Chromosome	Position	Gene	RS ID	Result
13	32906729	BRCA2	rs144848	Suspected Deleterious
13	32929387	BRCA2	rs169547	Suspected Benign
17	41223094	BRCA1	rs1799966	Unknown
17	41244000	BRCA1	rs80357956:rs16942	Unknown
17	41244435	BRCA1	rs80357920:rs16941	Unknown
17	41244936	BRCA1	rs799917:rs80357962	Unknown
17	41245471	BRCA1	rs4986850	Unknown

Note:

1. Genetic counseling is recommended before ordering this test.
2. This assay analyzes sequencing of all exons and immediately adjacent intronic regions of BRCA1 & BRCA2. It does not detect all large genomic rearrangements.
3. Classification of the variants includes single nucleotide variants (SNV), multi nucleotide variants (MNV), short insertion and short deletion. This reflects current state of scientific understanding at the time of report issue.
4. This test is for research purposes only and results must be interpreted in context of clinical findings and other laboratory data.
5. Test results were analyzed according to previously known clinical data from SNPEDIA, CLINVAR (based on CLINAAC ID) database. SIFT score, Polyphen score, Grantham score and Phylop score (provided by ion reporter V4.2) were considered to classify the mutants. The Breast Cancer Information Core (BIC) database from National Human Genome Research Institute has also been consulted. The information in these databases may pertain to Caucasian population as they are most well studied.

Interpretation

RESULT	REMARKS
No Mutation Detected	BRCA1 & BRCA2 mutation not detected in the sample submitted
Unknown	Mutation detected but significance unknown
Benign	Mutation detected but harmless as per current literature
Suspected Benign	Mutation detected but clinical harmlessness not established

Suspected Deleterious	Mutation detected but clinical harmfulness not established
Deleterious	Mutation detected clinically harmful and patient is at significantly increased risk for developing Breast & / or Ovarian cancer as compared to general population

Comments

Hereditary Breast Cancer accounts for about 5-10% of female breast cancer and 4-40% of male breast cancer. The most common cause is mutations in the BRCA1 & BRCA2 genes which are tumor suppressor genes located on chromosome 17 and 13 respectively. Mutations in these genes also account for 15% of all ovarian cancers. More than1600 mutations are inherited in an autosomal dominant manner and have been identified in each of these genes. The mutations occur in an estimated 1:300 to 1:800 people. However the frequency is higher in Ashkenazi Jews. BRCA1 and BRCA2 mutations are primarily linked to Hereditary cancer of breast, ovary & fallopian tube and Primary papillary serous carcinoma of peritoneum.

Individuals suitable for testing

- Early onset Breast cancer <=50 years of age
- Bilateral Breast cancer & / or Ovarian cancer
- Strong family history of Breast & / or Ovarian cancer
- Earliest family member with the diagnosis of Breast and Ovarian cancer should be tested first of all.

Disclaimer

- A Negative result implying non-detection of mutation / deletion indicates a likely Benign polymorphism. These results reduce but do not eliminate the possibility of hereditary cancer as rare genetic abnormalities may not be detected by this assay. Thus a negative result is not very informative when the carrier status of other family members is either unknown or negative.
- A Deleterious / Suspected deleterious result indicates a likely pathogenic mutation with an increased risk for BRCA1 or BRCA2 associated cancer including breast, ovarian, fallopian tube or peritoneal in a female. In a male it indicates an increased risk of breast or prostate cancer. Genetic testing of close family members is recommended.
- Variants of Unknown significance - As per current literature, the significance of these mutations is unknown
- The accuracy and completeness of this information may vary due to variable information available in different databases
- The mutations have not been confirmed using Sanger sequencing and/or alternate technologies and additional testing might be required if clinically indicated
- Test results must be interpreted in context with clinical findings, family history and other laboratory data

Mutations detected

1. chr13:32906729 (Asn372His; BRCA2)
   In a separate study, homozygotes (G;G)were determined to have a 1.31x increased risk for breast cancer greater risk compared to (T;T) genotypes. This SNV has been found in the epithelial ovarian cancer patients according to SNPedia. The heterozygous has been linked weakly with breast cancer. According to Clinvar database, conflicting data was observed from different submitters. According to SIFT score this mutation can be tolarated. According to BIC database this mutations is classified as class I mutation (non-pathogenic/low clinical significance). Based on available data, it is the opinion of the BIC steering committee that this sequence change is neutral or of little clinical importance.
   Some sequence changes of this type may be associated with modest increases in cancer risk.
2. chr13:32929387 (Val2466Ala; BRCA2)
   According to SIFT score this mutation can be tolarated. According to SNPedia, the valine variant was associated with ovarian cancer in one patient, but was later reported as a benign polymorphism in the Yoruba population. According to Clinvar database, conflicting data was observed from different submitters. According to BIC database the Valine variant is considered as class I mutation (nonpathogenic/low clinical significance). The homozygous Alanine variant did not reveal any clinical significance.
3. chr17:41223094 (Ser1634Gly; BRCA1)
   According to SIFT score this mutation is suspected as deleterious. According to SNPedia, this SNP, a variant in the BRCA1 gene, is 1 of 25 SNPs reported to represent independently minor, but cumulatively significant, increased risk for breast cancer. According to Clinvar database, this mutation is benign or likely benign. Classification of this mutation according to BIC database is pending.
4. chr17:41244000 (Lys1183Arg; BRCA1)
   Has been found in one a tissue which had adenocarcinoma.According to SNPedia, It is one of the 25 SNP's which represent independently minor but cumulatively significant risk of breast cancer. According to SNPedia, the risk (minor) allele is (G). According to Clinvar database, this mutation is benign/likely benign. According to BIC database classification of the mutation is still pending. Based on available data, it is the opinion of the BIC steering committee that this sequence change is neutral or of little clinical importance.
   Some sequence changes of this type may be associated with modest increases in cancer risk.
5. chr17:41244435 (Glu1038Gly; BRCA1)
   According to SNPedia, there is no definite link to breast caner with this mutation. According to Clinvar database, this mutation is benign or likely benign. According to BIC database classification of the mutation is still pending. Based on available data, it is the opinion of the BIC steering committee that this sequence change is neutral or of little clinical importance.
   Some sequence changes of this type may be associated with modest increases in cancer risk.
6. chr17:41244936 (Pro871Leu; BRCA1)
   According to SNPedia, polymorphisms in the BRCA1 and ABCB1 genes modulate menopausal hormone therapy associated breast cancer risk in postmenopausal women (PMID: 19672706). This missence mutation is not addressed by Clinvar database. According to BIC database this mutations is classified as class I mutation (non-pathogenic/low clinical significance). Based on available data, it is the opinion of the BIC steering committee that this sequence change is neutral or of little clinical importance. Some sequence changes of this type may be associated with modest increases in cancer risk.