City of Hope

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Assay Summary

PALB2 (Partner and localizer of BRCA2) Gene Mutation Analysis

Fanconi Anemia Complementation Group N, Pancreatic Cancer Susceptibility, and Breast Cancer Susceptibility

Synopsis

Partner and localizer of BRCA2 (PALB2, OMIM *610355) was originally identified as a BRCA2-interacting protein that is crucial in physically and functionally connecting BRCA1 and BRCA2 to form a "BRCA complex" [1]. The integrity of the "BRCA complex" is essential for the maintenance of genomic stability via recombinational repair and the avoidance of cancer and Fanconi anemia (FA). Germline monoallelic (heterozygous) mutations in *PALB2* are associated with increased risk of breast and pancreatic cancer, whereas biallelic mutations in *PALB2* lead to FA[1,3,4,10]. The PALB2 gene consists of 13 exons and maps to chromosome 16p12.2.

Fanconi anemia is a recessive chromosomal instability syndrome with both autosomal and X-linked inheritance that currently includes 13 subtypes. Biallelic mutations in *PALB2* gene lead to Fanconi anemia subtype N[5]. The phenotypes associated with biallelic *BRCA2* and *PALB2* mutations are markedly similar to each other. *PALB2*-related FA have a typical FA phenotype with growth retardation and variable congenital malformations. Furthermore, *PALB2*-related FA phenotype is associated with an unusually severe predisposition to childhood solid tumors.

PALB2 gene has been recently identified as the second most important susceptibility gene for **familial pancreatic cancer** (FPC) after BRCA2[10]. Jones et al. identified 3 (3.1%) truncating mutations in PALB2 in 96 American familial **pancreatic cancer** patients[10]. Each of these mutations produced a different stop codon. Some FPC patients with the PALB2 mutation had an associated history of breast cancer but not all. In another recent European study, Slater et al. found truncating mutations in 3 out of 81 (3.7%) European pancreatic cancer families, which all included breast cancers[2].

PALB2 is also a **breast cancer** susceptibility gene. Rare germline monoallelic mutations in *PALB2* have been reported to confer as much as 5-9 fold increase risk for breast cancer.[4,6,8,11] Number of monoallelic *PALB2* truncating mutations and a novel PALB2 gene deletion were identified in women with a strong family history of **breast cancer** and negative mutations in BRCA1 and BRCA2.[1,8,9] There are also several founder *PALB2* mutations reported in the literature. A French Canadian founder mutation 2323C > T has been reported in 2/356 (0.5%) unselected patients with early-onset breast cancer .[7] *PALB2* mutations have now been found in patients in many countries with frequencies varying from 0.6 to 2.7% in familial breast cancer cases.[3]

Indications for testing

1) Individuals with strong family history of cancers (breast, prostate, and pancreatic) suggestive of BRCA2 but who tested negative for mutations in *BRCA2*.
2) Patients with FA phenotype who tested negative for other FA genes.
3) Blood relatives of individuals with a mutation in PALB2.

Methodology

Full gene sequencing of *PALB2*: Coding exons and associated intron junctions are captured and enriched using custom Agilent SureSelect technology. Next-generation sequencing is performed on Illumina MiSeq. Additional Sanger sequencing is performed for any regions with insufficient depth of coverage or for

verification of suspect variant calls. Targeted testing for known familial mutation is performed by Sanger sequencing.

Limitations

This method will not detect mutations located in regions of the genes that are not analyzed (non-coding exon sequences, intron sequences other than the splice junctions, and upstream and downstream sequences). The method also will not detect inversions. Some sequence alterations that may be detected (such as those causing missense or synonymous changes) will be of unknown clinical significance. Interpretation of test results should be in the context of the patient's diagnosis, ethnicity, clinical and family histories, and other laboratory test results.

Specimen Requirements

Blood samples: 2 tubes with a total of 6 ccs in ACD (yellow top) or EDTA (lavender top) tubes.

Keep at ambient temperature and ship by overnight courier. Samples must be received in our laboratory within 72 hours of draw.

Note:

i) for infants, a minimum of 3 ccs is sufficient.

ii) we accept DNA; at least 10 micrograms is required.

Test Request Form (TRF)

a) A completed CMDL TRF is required for each specimen. Please submit the completed TRF with the specimen. Complete testing and billing information must be provided before the specimen is processed.

b) General Cancer Patient Information Form: Include a completed General Cancer Patient Information for the proband and a complete pedigree.

Order Codes	***CPT Codes***	***TAT***
PALB2-SEQ (PALB2 gene, full gene sequencing by NGS)	81406, G0452	3 wks
PALB2-CAS (PALB2 gene, targeted mutation analysis, known mutation)	81403, G0452	2 wks

References

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2. Slater EP et al. *Clin Genet.* 201078(5):490-4.
3. Tischkowitz M et al. *Cancer Res.* 2010;70(19):7353-9.
4. Xia B et al. *Nat Genet.* 2007;39:159–61.
5. Moldovan GL et al. *Annu Rev Genet.*2009;43:223–49.
6. Byrnes GB et al. *Breast Cancer Res.* 2008;10:208.
7. Foulkes WD et al. *Breast Cancer Res.* 2007;9:R83.
8. Rahman N, *Nat Gene.* 2007;39:165–7.
9. Dansonka-Mieszkowska A et al. *BMC Med Genet*. 2010; 11:20
10. Jones S et al. *Science*. 2009;324 (5924):217.
11. Antoniou, et al. N Engl J Med. 2014;371(6):497-506.

NOTE: This test is performed pursuant to a license agreement with Roche Molecular Systems, Inc.