

Fanconi Anemia via Sequencing of the *PALB2/FANCN* Gene (Test #728)

Brief Description of Clinical Features: Fanconi Anemia (FA) (OMIM 227650) is characterized by a range of congenital abnormalities, bone marrow failure (aplastic anemia), pancytopenia, and predisposition to cancers (especially acute myelogenous leukemia (AML), and squamous cell carcinomas (SCC) of the head, neck, and gynecological tract). The FA phenotype is variable and often misdiagnosed. FA is considered a blood disease, however the name is a bit misleading as all systems of the body can be affected. Common clinical symptoms include radial ray defects (absent thumb or radius), skin pigmentation defects, short stature and other skeletal defects, microphthalmia, renal and urinary tract defects, genital defects, mental retardation, gastrointestinal malformations (atresia), congenital heart disease, and hearing and central nervous system defects (Tischkowitz and Hodgson *J Med Genet* 40:1-10, 2003; Dokal *Baillieres Best Pract Res Clin Haematol* 13:407-425, 2000). About one-third of FA patients have no obvious congenital abnormalities and are diagnosed only after developing hematological problems or after a family member is diagnosed (Giampietro et al. *Am J Med Genet* 68:58-61, 1997). In FA cells, chromosomes are hypersensitive to cross linking agents and highly susceptible to chromosome breakage, a hallmark of FA (Sasaki and Tonomura *Cancer Res* 33:1829-1836, 1973). The genetic instability of FA patients puts them at a particular high risk when exposed to ionizing radiation, environmental carcinogens, chemotherapeutic agents, and even diagnostic x-rays.

Genetics: FA is a genetically heterogeneous autosomal recessive disorder. To date, 14 FA or FA-like genes have been identified, but ~86% of all cases are attributed to mutations in three genes: *FANCA* (OMIM 607139) (~60%), *FANCC* (OMIM 227645) (~16%), and *FANCG* (OMIM 602956) (~10%) (Auerbach *Mutat Res* 668:4-10, 2009). Several populations have demonstrated a founder effect for FA, mainly for mutations in *FANCA*, *FANCC*, *FANCG* and *FANCD*, and targeted sequencing for these specific mutations is recommended if applicable (see individual Test Descriptions for details). In the United States and Europe, the incidence of FA is around 3 per million, and the carrier frequency is between 1 in 600 and 1 in 100 (see <http://www.fanconi.org/>). The remaining ~14% of FA cases are attributed to the additional 11+ FA genes including *PALB2* (also known as *FANCN*) (OMIM 610355). Numerous mutations, including small insertions, small and large deletions, premature termination, and splice-site mutations, are found throughout the *PALB2/FANCN* gene (<http://www.rockefeller.edu/fanconi/mutate/>). Mutations in *PALB2/FANCN* often result in very severe FA phenotypes. In relation to other FA patients, FA-N patients often develop leukemia at an earlier age, show increased spontaneous chromosomal breakage, and develop solid tumors (medulloblastoma, astrocytoma, and Wilms Tumors) that are rarely seen in other FA patients (Reid et al. *Nat Genet* 39:162-164, 2007).

Description of This Particular Test: This test involves bidirectional DNA sequencing of the *FANCN* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence one (Test #100) or two (Test #200) exons in family members of patients with known mutations or to confirm research results (\$190-340).

Reference Sequences: Exons: 13 Genomic: NC_000016.9 mRNA: NM_024675.3 Protein: NP_078951.2 (CCDS 32406.1)

Indications for Test: Patients with clinical features of FA or that develop aplastic anemia at any age even if they present no other physical abnormalities, and patients with a family history of FA or cancer, characteristic birth defects, or spontaneous chromosome breakage.

Sensitivity of Test: Mutations in FA genes account for >95% of all patients with FA.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *FANCN/PALB2* Gene \$980

CPT Codes

Test	83890	83891	83898	83904	83894	83912	Total
<i>FANCN</i>	\$30 (x1)	\$40 (x1)	\$290 (x18)	\$430	\$70 (x1)	\$120	\$980

Accreditation: CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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