

Fanconi Anemia via Sequencing of the *FANCD2* Gene (Test #884)

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, 15 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). 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 12 + FA genes including *FANCD2* (OMIM 613984). Most documented causative mutations in the *FANCD2* gene are missense/nonsense mutations, splicing mutations, or small deletions. Large deletions and duplications in the *FANCD2* gene are rare. Predominant mutations in the *FANCD2* are not yet apparent (www.rockefeller.edu/fanconi/mutate/).

Description of This Particular Test: This test involves bidirectional DNA sequencing of the 43 coding exons in the *FANCD2* gene (exons 2-44) plus ~50 bp of flanking non-coding DNA on either side of each exon. We will also sequence one (Test #100, \$190) or two (Test #200, \$340) exons in family members of patients with known mutations or to confirm research results.

Reference Sequences: Genomic: **NC_000003.11** mRNA: **NM_001018115.1** Protein: **NP_001018125.1 (CCDS 33696.1)**

Indications for Test: Patients with clinical features of FA, individuals with a family history of FA, and patients that develop aplastic anemia at any age even if they present no other physical abnormalities.

Sensitivity of Test: Mutations in the *FANCD2* gene are found in a significant fraction of patients with FA who do not have mutations in either the *FANCA*, *FANCC*, or *FANCG* genes.

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 the *FANCD2* Gene \$ 1780

CPT Codes

Test	83890	83891	83898	83904	83894	83912	Total
<i>FANCD2</i>	\$30 (x1)	\$40 (x1)	\$580 (x40)	\$860 (x40)	\$140 (x1)	\$130 (x1)	\$1780

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

Contact: Michael Chicka, PhD, michael.chicka@preventiongenetics.com, www.preventiongenetics.com