

Fanconi Anemia via Sequencing of the *FANCC* Gene (Test #722)

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)). FA is primarily considered a blood disease, but all systems of the body can be affected. Other features commonly observed include radial ray defects (absent thumb or radius), skin pigmentation defects, short stature, microphthalmia, renal and urinary tract defects, genital defects (males), 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).

Genetics: FA is a genetically heterogeneous autosomal recessive disorder. To date, 14 FA or FA-like genes have been discovered, 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%) (see <http://www.fanconi.org/>; and 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 estimated between 1 in 600 and 1 in 100 (see <http://www.fanconi.org/>). A notable exception are the Ashkenazi Jews. In this population, almost all cases of FA are attributed to a splice site mutation in *FANCC*, denoted IVS4+4A>T, the carrier frequency for which is ~ 1 in 90 (Verlander *Blood* 86:4034-4038, 1995; Whitney et al. *Nat Genet* 4:202-205, 1993). Causative mutations in *FANCC*, including splice-site variants, insertions, deletions, missense, and premature termination mutations, have been reported throughout the coding region (see <http://www.rockefeller.edu/fanconi/mutate/>). The IVS4+4A>T mutation, and R548X and L554P mutations in exon 14, all correlate with very severe FA marked by a high frequency of congenital birth defects and early onset anemia. In contrast, other mutations in *FANCC*, such as 322delG and Q13X in exon 1 and R185X in exon 6, correlate with a milder phenotype, fewer birth defects and later onset of hematological disorders (Gillio et al. *Blood* 90:105-110, 1997).

Description of This Particular Test: This test involves bidirectional DNA sequencing of the *FANCC* 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:

Gene:	Exons	Genomic: NC_	mRNA: NM_	Protein: NP_	CCDS:
<i>FANCC</i>	15	000009.11	000136.2	000127.2	35071.1

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: FA via *FANCC* accounts for ~ 16% of all FA cases.

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 *FANCC* Gene

Test	CPT Codes						Total
	83890	83891	83898	83904	83894	83912	
	Ascertainment	DNA Isolation	Amplification	Sequencing	Separation	Report	
<i>FANCC</i>	\$30 (x1)	\$40 (x1)	\$240 (x14)	\$370 (x14)	\$50 (x1)	\$ 90 (x1)	\$820

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

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