FANCA Gene

Alternative Names
- FANCA
- Fanconi Anemia Complementation Group A Gene
- FACA
- FAA

OMIM Number
- 607139

Mode of Inheritance
- Autosomal recessive

Gene Map Locus
- 16q24.3

Description
Fanconi anemia (FA) is a rare autosomal recessive disease characterized by multiple congenital abnormalities, bone marrow failure and susceptibility to cancer. Fanconi anemia is genetically heterogeneous, with at least eight complementation groups (A-H), each presumably corresponding to a separate disease gene. Recently, the FANCA (Fanconi anemia complementation group A), FANCG and FANCF genes were cloned.

The study of the natural history of genotypically different Fanconi anemia patients is important to identify high-risk patients with poor hematological outcome as candidates for frequent monitoring and early bone marrow transplantation. The data of the International Fanconi Anemia Registry suggests that FA-C patients have poor survival compared with FA-A and FA-G and non-typed patients. Others also suggested that complete loss of the FANCA protein is associated with a severe phenotype, whereas patients with an altered protein have a milder phenotype with a later age onset of aplastic anemia, longer survival after diagnosis, and a lower prevalence of acute myeloblastic leukemia and myelodysplastic syndrome.

Molecular Genetics
FANCA has an open reading frame of 4,365 bp encoding a protein of 1,455 amino acids and is localized on chromosome 16q24.3. The gene is composed of 43 exons spanning about 80 kb of genomic DNA. The prevalence of the FA-A subtype is estimated to be 60±66%. FANCA mutations are the most prevalent, accounting for about two-thirds of all Fanconi anemia cases.

Epidemiology in the Arab World
Palestine
Tamary et al. (2004) investigated the molecular basis of Fanconi anemia (FANCA and FANCG) in three consanguineous families with nine patients and an additional unrelated patient. In two consanguineous families with five affected individuals, Tamary et al. (2004) applied SSCP analysis coupled with RT-PCR and DNA sequencing for the exons of the FANCA gene and identified two unique disease-causing mutations: a gross deletion of exons 6-31 and splice-site mutation IVS 42-2A-C. Sequence analysis of the FANCA gross deletion revealed recombination between two highly homologous Alu elements. cDNA analysis suggested that the IVS 42-2A-C substitution abolishes the 3’ splice-site and causes retention of intron 42 (173 bp) during pre-mRNA splicing. This change is predicted to cause retention of the 39 amino acids in the mature transcript, followed by a premature stop codon. The clinical
condition of eight patients with FANCA mutations was severe and accompanied with a variety of malformations such as microcephaly, hypoplastic thumbs, Klippel-Feil disease, deafness, and others.

Morocco
Tamary et al. (2000) investigated the molecular basis of Fanconi anemia in 13 unrelated non-Ashkenazi Jewish Fanconi anemia patients (including one compound heterozygote of Ashkenazi and non-Ashkenazi extraction). Using SSCP screening followed by DNA sequencing, Tamary et al. (2000) identified two mutations homozygously inherited in 10 Moroccan-Jewish patients. Patients also manifested a variety of malformations in the bicuspid aortic valve, thumbs, kidney, and others. The two mutations described in this patient group were novel (2172±2173insG in exon 24 and 4275delT in exon 43). A CCTG repeat sequence was observed in the vicinity of the (5 bp 50 to the) 2172±2173insG mutation. Tamary et al. (2000) calculated the frequency of the 2172±2173insG Moroccan mutation to be 1:200. They also noted that this mutation is associated with a milder disease with a lower frequency of malformations, and development of bone marrow failure and leukemia at an older age. Besides the 2172±2173insG mutation, Tamary et al. (2000) also identified the 890±893del in exon 10 of a Moroccan-Tunisian Jewish patient with Fanconi anemia and absent thumb. The 890±893del in exon 10 is also a novel mutation that also has a CCTG repeat sequence in the vicinity. Carriers of each mutation had identical haplotypes suggestive for a common founder for each mutation [See also: Morocco > Tamary et al., 2000].

Tunisia
Tamary et al. (2000) investigated the molecular basis of Fanconi anemia in 13 unrelated non-Ashkenazi Jewish Fanconi anemia patients (including one compound heterozygote of Ashkenazi and non-Ashkenazi extraction). Using SSCP screening followed by DNA sequencing, Tamary et al. (2000) identified the 2574C-G (S858R) mutation in exon 27 of a Tunisian-Jewish patient. The patient inherited the mutation homozygously and also exhibited hearing loss. In addition, Tamary et al. (2000) also identified the 2172±2173insG mutation and 890±893del in exon 10 of a Moroccan-Tunisian Jewish patient with Fanconi anemia and absent thumb [See also: Morocco > Tamary et al., 2000].

References

Contributors
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