Fanconi's anemia

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Abstract
An autosomal recessive disease associated with chromosomal instability, Fanconi's anemia (FA) is remarkable by its phenotypic heterogeneity, which includes bone-marrow failure, a variety of congenital malformations, a propensity to develop acute myeloid leukemia (AML) and cellular hypersensitivity to DNA cross-linking agents. This property has allowed the study of the mechanisms underlying the disease and also contributes to making the clinical diagnosis. FA has been found in all ethnic groups. Its frequency has been estimated to be 1/350,000 births. FA is characterized clinically by pancytopenia, progressive aplastic anemia, diverse congenital malformations and, above all, a marked predisposition to develop AML. The congenital anomalies include skeletal malformations, hyperpigmentation, urogenital, renal and cardiac anomalies. The hematological disorders resulting from bone marrow dysfunction (thrombocytopenia, progressive pancytopenia) usually appear around a mean age of 7 years, but they can arise very early, at birth, or, even more rarely, very late around 40 years of age. Bone-marrow or umbilical cord-blood transplantations are the main treatment, relatively effective, of the hematological failure typical of FA. Even if it is not yet effective, it seems that cellular therapy with isolated and characterized stem cells is a promising approach for FA patients. Analysis by in situ somatic hybridization, followed by the search for complementation for the cytotoxic response to DNA cross-linking agents, using lymphoblastoid cell lines, led to the identification of 8 complementation groups (FANCA-FANCH), each of which was thought to represent a unique gene. To date, 6 FANC genes have been cloned.A unified and precise understanding of the biochemical events responsible for FA is still lacking. The functions of the different FANC genes remain unknown.

Key-words
Fanconi's anemia, bone-marrow failure, acute myeloid leukemia, bone-marrow transplantation, *FANC* genes

Name of the disease
Fanconi's anemia

Definition
An autosomal recessive disease associated with chromosomal instability, Fanconi's anemia (FA) is remarkable by its phenotypic heterogeneity, which includes bone-marrow failure, a variety of congenital malformations, a propensity to develop acute myeloid leukemia (AML) and cellular hypersensitivity to DNA cross-linking agents. FA is manifested in children by a progressive hematopoietic deficiency.

Differential diagnosis
FA belongs to a group of diseases associated with chromosomal instability. These genetically determined disorders are collectively called chromosome break-up syndromes or DNA-repair disorders. They are characterized by a susceptibility to chromosomal anomalies, with a higher frequency of aberrations, spontaneous or induced by exposure to diverse agents that damage DNA (Taniguchi *et al.*, 2002). One of the defining characteristics of FA is hypersensitivity to the cytotoxic and clastogenic effects of DNA cross-linking agents, such as mitomycin C, diepoxybutane (DEB), cisplatin, photoactivated psoralens, etc. This property has allowed the study of the mechanisms underlying the disease and also contributes to making the clinical diagnosis. The other genetic diseases, such as ataxia telangiectasia variant V1 also known as the Nijmegen syndrome, which, like FA, have spontaneously elevated frequencies of chromosomal anomalies, are not hypersensitive to cross-linking agents. Thus, this feature can be used to obtain a reliable and sensitive diagnosis of FA (d'Andrea and Grompe, 1997; Auerbach *et al.*, 1998; Buchwald and Moustacchi, 1998).

Frequency
FA has been found in all ethnic groups. Its frequency has been estimated to be 1/350,000 births (Auerbach *et al.*, 1989; Verlander *et al.*, 1995). The disease has been found to have a higher frequency in two ethnic groups: Ashkenazi Jews and the Afrikaans population of South Africa. Thus, in the Cape of Good Hope region, the incidence of homozygous forms is 1/22,000 births and reflects the allelic frequency of around 1/77 (as opposed to 1/300 in the general population (Rosendorff *et al.*, 1987). The International Fanconi Anemia Registry (New York, USA) was established in 1982 to collect a maximum of information on the clinical, hematological and genetic bases of FA (Auerbach *et al.*, 1991; Butturini *et al.*, 1994). The early diagnosis based on cytogenetic analysis of sensitivity to DEB has increased the number of recorded cases.

Clinical description
In 1927, Guido Fanconi, a Swiss pediatrician, described a family with 3 boys who had diverse malformations at birth and developed severe pancytopenia between the ages of 5 and 7 years.
Subsequently, numerous FA cases have been described without congenital malformations (approximately 33%) but with only progressive hematological failure. Inter- and intrafamilial clinical heterogeneity is also broad (Fanconi, 1967; Auerbach *et al.*, 1991; Young and Alter, 1994). FA is characterized clinically by pancytopenia, progressive aplastic anemia, diverse congenital malformations and, above all, a marked predisposition to develop AML.
The congenital anomalies include skeletal malformations, hyperpigmentation, urogenital, renal and cardiac anomalies (Young and Alter, 1994). The hematological disorders resulting from bone marrow dysfunction (thrombocytopenia, progressive pancytopenia) usually appear around a mean age of 7 years, but they can arise very early, at birth, or, even more rarely, very late around 40 years of age (Young and Alter, 1994). The signs evocative of FA before the appearance of hematological abnormalities are: pre- and postnatal growth retardation, diverse skeletal malformations (including the sometimes asymmetrical absence of thumbs, microphthamia, typically small face), a high insulin/glucose ratio, and/or hypogonadism sometimes associated with infertility.
The incidence of AML varies from 19 to 37%, depending upon the genetic complementation group affected. Carriers of the *FANCG* gene have the highest rate of AML (Faivre *et al.*, 2000).
Other types of cancers can develop in FA patients, principally hepatocellular carcinomas or squamous cell carcinomas of the mouth (Auerbach *et al.*, 1998).

Treatment
Bone-marrow or umbilical cord-blood transplantations are the main treatment, relatively effective, of the hematological failure typical of FA. The improvements of blood counts achieved with androgens are transitory and accompanied by a risk of hepatic toxicity and malignant transformation. The results of bone-marrow transplantation have been substantially improved by changing the protocol of immune suppression applied prior to the grafting. This protocol takes into consideration of the hypersensitivity of FA patients to cyclophosphamide and ionizing radiation

(Gluckman *et al.*, 1994). HLA compatibility obviously remains a major factor of transplantation success.
Umbilical cord blood offers a potential source of hematopoietic stem cells for FA patients without an HLA match (Broxmeyer *et al.*, 1989; Gluckman *et al.*, 1989).
Even if it is not yet effective, it seems that cellular therapy with isolated and characterized stem cells is a promising approach for FA patients.
For about the past 8 years, gene therapy has been the object of research and trials without any definitive outcome. The targeting of retroviral vectors carrying the cloned genes of interest (such as *FANCA* and *FANCC*, which represent the most frequently mutated groups of genes, *i.e.* 80% of the patients) is not very effective and is still poorly controlled (Walsh *et al.*, 1994; Liu, 1998; Liu *et al.*, 1999; Noll *et al.*, 2001). Preclinical protocols are currently being tested.

Etiology
Analysis by *in situ* somatic hybridization, followed by the search for complementation for the cytotoxic response to DNA cross-linking agents, using lymphoblastoid cell lines, led to the identification of 8 complementation groups (*FANCA–FANCH*), each of which was thought to represent a unique gene. However, it was found that the group H line belonged to complementation group A, bringing to 7 the number of genes implicated in FA (Strathdee *et al.*, 1992; Joenje *et al.*, 1997, 2000). In 2001, Timmers *et al.* demonstrated that complementation group D was composed of 2 distinct genes, *FANCD1* and *FANCD2*, thereby again bringing the number of genes to 8. To date, 6 *FANC* genes have been cloned (**Table 1**) *(FANCA, FANCC, FANCD2, FANCE, FANCF and FANCG)*. The corresponding proteins share very few homologies, among themselves or with other known proteins (Lo Ten Foe *et al.*, 1996; de Winter *et al.*, 2000a). It was recently shown that FANC proteins interact to form multimeric nuclear complexes; a mutation in one of the *FANC* genes prevents the formation of functional complexes (de Winter *et al.*, 2000b; Medhurst *et al.*, 2001). Interaction of FANCD2 with BRAC1 (the protein associated with the hereditary form of breast cancer), in conjunction with other observations, has suggested that this complex plays a role in repair by sealing breaks in double-stranded DNA (Garcia-Higuera *et al.*, 2001). Moreover, the two unidentified subtypes B and D1 have been shown to contain biallelic mutations in *BRCA2* and express truncated BRCA2 protein (Howlett *et al.* 2002). Taken together, these observations link FA genes with *BRCA1* and *BRCA2* in a common pathway. In addition, one of the proteins, FANCC, partially located in the cytoplasm, might play a role in the control of apoptosis pathways induced by interferon-γ and tumor necrosis factor (TNF)-α (Rosselli *et al.*, 1992, 1994; Bagnara *et al.*, 1993). This protection of hematopoietic cells would result from the intervention of *FANCC* in response to oxidative damage (Kruyt *et al.*, 1998, 2000; Rousset *et al.*, 2002).
Interstitial deletions of the long arm of chromosome 9 (9q) overlapping with the *FANCC* locus have been reported. The somatic loss of one or two alleles of the *FANC* genes could predispose the non-FA or heterozygous FA carrier to malignant transformation.

Table 1. Characteristics of FANC genes and their products (Moustacchi and Papadopoulo, 2001).

Gene	Localization	Exon	Protein(kDa)	Reference
FANCA	16q24.3	40	1455	Lo Ten Foe et al., 1996
FANCB	?	?	?	
FANCC	9q22.3	14	588	Strathdee et al., 1992
FANCD2	3p25	44	1451(155/162)	Timmers et al., 2001
FANCE	6p21–22	10	536	de Winter et al., 2000a/b
FANCF	11p15	1	374	de Winter et al., 2000a/b
FANCG/XRCC9	9p13	14	622	de Winter et al., 1998

Genetic counselling
Counselling should adhere to the standards established for all autosomal recessive diseases.

Prenatal diagnosis
It is possible to examine the sensitivity to DNA cross-linking agents of amniotic cells taken from heterozygous mothers.

Unresolved questions
A unified and precise understanding of the biochemical events responsible for FA is still lacking. The functions of the different *FANC* genes remain unknown. The overall similarity of the clinical and, above all, cellular phenotypes lead us to think that these proteins participate in the same major metabolic network.

A strict correlation between the severity of the disease and the genes responsible or the type of mutation in these genes has not yet been elucidated, even though it has been observed that carriers of intervening sequence (IVS) or exon 14 mutations in the *FANC* genes have hematological anomalies and a higher frequency of AML.
It cannot be excluded that the *FANC* genes play a specific role in the appearance of AML.

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