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Research Article

Molecular analysis of the most prevalent mutations of the *FANCA* and *FANCC* genes in Brazilian patients with Fanconi anaemia

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Abstract

Fanconi anaemia (FA) is a recessive autosomal disease determined by mutations in genes of at least eleven complementation groups, with distinct distributions in different populations. As far as we know, there are no reports regarding the molecular characterisation of the disease in unselected FA patients in Brazil. Objective: This study aimed to investigate the most prevalent mutations of *FANCA* and *FANCC* genes in Brazilian patients with FA. Methods: Genomic DNA obtained from 22 racially and ethnically diverse unrelated FA patients (mean age ± SD: 14.0 ± 7.8 years; 10 male, 12 female; 14 white, 8 black) was analysed by polymerase chain reaction and restriction site assays for identification of *FANCA* (Δ3788-3790) and *FANCC* (Δ322G, IVS4+4A → T, W22X, L496R, R548X, Q13X, R185X, and L554P) gene mutations. Results: Mutations in *FANCA* and *FANCC* genes were identified in 6 (27.3%) and 14 (63.6%) out of 22 patients, respectively. The disease could not be attributed to the tested mutations in the two remaining patients enrolled in the study (9.1%). The registry of the two most prevalent gene abnormalities (Δ3788-3790 and IVS4 + 4 → T) revealed that they were present in 18.2% and 15.9% of the FA alleles, respectively. Additional *FANCC* gene mutations were found in the study, with the following prevalence: Δ322G (11.4%), W22X (9.1%), Q13X (2.3%), L554P (2.3%), and R548X (2.3%) of total FA alleles. Conclusion: These results suggest that mutations of *FANCA* and *FANCC* genes are the most prevalent mutations among FA patients in Brazil.

Key words: Fanconi anaemia, DEB test, molecular diagnosis, *FANCA*, *FANCC*.

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Introduction

Fanconi anaemia (FA) is an autosomal recessive disease characterised by a very high frequency of bone marrow failure and many other manifestations, including but not restricted to severe birth defects and marked predisposition to malignancies, especially acute myeloid leukaemia and, to a lesser extent, solid tumours (Young and Alter, 1994; Alter and Young, 1998; Alter, 2003).

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FA cells exhibit spontaneous chromosomal instability and hypersensitivity to DNA cross-linking agents such as diepoxybutane (DEB) and mitomycin C (Auerbach and Wolman, 1976) and the resulting increase in chromosome breakage provides the basis for a diagnostic test (Auerbach, 1993).

Complementation analysis by cell fusion and correction of cross-linker hypersensitivity has delineated at least eleven complementation groups (A, B, C, D1, D2, E, F, G, L, I, J) (Joenje and Patel, 2001; Meetei *et al.*, 2003) and seven genes have been cloned (*FANCA*, *C*, *D2*, *E*, *F*, *G and L*) (Strathdee *et al*., 1992; Whitney *et al*., 1993; Lo Tem Foe *et al.,* 1996; De Winter *et al.*, 1998; De Winter *et al.*, 2000;

Timmers *et al.*, 2001; Meetei *et al.*, 2003). Four FA-D1 patients were shown to possess biallelic mutations in the breast cancer susceptibility gene BRCA2 (Levitus *et al.*, 2003). *FANCA* and *FANCC* mutations are the most prevalent, accounting for approximately 65% and 5-15% of FA patients (Tischkowitz and Hodgson, 2003).

The prevalence of distinct FA gene mutations is variable in different populations (Tischkowitz and Hodgson, 2003). *FANCA* mutations are more common in Afrikaners (Tipping *et al.*, 2001) and *FANC* in Ashkenazi Jews and Japanese (Yamashita *et al.*, 1996; Gillio *et al.*, 1997; Futaki *et al.*, 2000; Tamary *et al.*, 2003).

The relationship between the complementation group and mutation type and the clinical outcome of the patients with disease is controversial. Patients with *FANCA* and *FANCG* mutations appear to constitute a high risk group according to some authors (Faivre et *al.*, 2000). In contrast, The International Fanconi Anaemia Register revealed a significantly earlier onset of bone marrow failure and poorer survival rates for complementation group C compared with groups A and G. Moreover, there was no significant difference in the time for haematologic or nonhaematologic neoplasm development between FA groups of patients (Kutler *et al.*, 2003).

The ethnic origin of the Brazilian population is highly heterogeneous, consisting of indigenous Amerindians and immigrants from Europe, Africa, and Asia (Alves-Silva *et al.*, 2000; Carvalho-Silva *et al.*, 2001).

The Δ3788-3790 and IVS8-2A > G gene mutations were found in a group of Brazilian FA patients seen at a single bone marrow transplantation service, and were described as the most common *FANCA* and *FANCG* Brazilian mutations by the International Fanconi Anemia Registry (IFAR) (Levran *et al.*, 1997; Auerbach *et al.*, 2003). As far as we know, there are no reports regarding the molecular analysis of FA in unselected populations of our country. Therefore, this was the aim of the study presented herein.

Material and Methods

Eligibility requirements

All unrelated patients with confirmed FA, attended at the Medical Genetic and the Haematology services of UNICAMP and Haemotherapy Centres of several Brazilian Universities, were considered as fully eligible for the present study. The diagnosis of the disease was based on clinical and laboratory data, including haematological analysis, bone marrow aspiration and biopsy, and was confirmed by DEB test. The study protocol was approved by the local Research Ethics Committee.

DEB test

The DEB test was performed at the Cytogenetics Laboratory of the Haematology and Haemotherapy Centre of the State University of Campinas, according to conventional methods (Rosendorff and Bernstein, 1988; Auerbach *et al.*, 1989).

Molecular Analysis of *FANCA* and *FANCC* genes

Genomic DNA was obtained from peripheral blood of patients enrolled in the study using the salt/chloroform method (Müllenbach *et al.*, 1989). *FANCA* and *FANCC* mutations were analysed by polymerase chain reaction (PCR) followed by restriction site assays.

FANCA and *FANCC* exonic sequences of interest were amplified by PCR using primers described by Levran *et al*. (1997) and Gibson *et al*. (1996). PCR was carried out in 25 µL reactions with 250 ng of genomic DNA, 10 ng/µL of each primer, 0.5 mM of each dNTP, and 1.5 units of Taq polymerase in a buffer containing 6.7 mM $MgCl_2$. After initial denaturation at 94 °C for 5 min, samples were amplified for 30 denaturation cycles at 94 °C for 1 min, annealing at 51-60 °C, and extension at 72 °C for 1 min, followed by a final 5 min extension at 72 °C.

PCR products were then digested with 5-10 units of the appropriate restriction enzyme for a minimum of 2 h at 37 °C (50C for Bcl I), according to previously described techniques (Gibson *et al*., 1996; Levran *et al*., 1997) and analysed on horizontal 7% polyacrylamide gel.

The investigated gene mutations, restriction enzymes, and sizes of the normal and mutant gene fragments obtained from PCR and restriction site assays performed in the study are presented in Table 1.

Results

The clinical and laboratory features of 22 FA patients enrolled in the study are presented in Table 2. Their mean age ± SD was 14.0 ± 7.8 years (range: 2-33 years); 10 patients were male and 12 female, 14 were white and 8 black. Sixteen patients presented congenital abnormalities such as microphthalmia (8 cases), microcephaly (4 cases), abnormalities of the thumbs (5 cases), *café-au-lait* spots (4 cases), hyperpigmentation (4 cases), short stature (2 cases), genital abnormalities (1 case), and renal aplasia (1 case). Short stature was the only physical abnormality identified in *FANCA* patients. Variable degrees of peripheral cytopenia and positive DEB test were found in all patients enrolled in the study. Cases 1, 2, 16 and 22 are children of consanguineous parents (18%).

FA was attributed to Δ3788-3790 mutation of the *FANCA* gene in 6 out of 22 (27.3%) patients. The gene abnormality was present in 18.2% of FA alleles. Mutations of the *FANCC* gene were found in 14 out of 22 (63.6%) patients, with the following prevalence: 15.9% for IVS4+4A → T, 11.4% for ΔG322, 9.1% for W22X, 2.3% for Q13X, 2.3% for L554P, and 2.3% for R548X on FA alleles. The analysed mutations were not found in 2 out of 22 (9.1%) patients enrolled in the study. Figure 1 shows the analysis for IVS4+4A → T mutation.

Table 1 - Fragments observed after digestion with respective restriction enzymes for the distinct analysed mutations in Fanconi anaemia patients.

Mutation	Gene	Restriction enzyme	Result of PCR	Normal fragments	Mutant fragments
Δ3788-3790	*FANCA*	MboII	160 bp	130 + 30	160
IVS4+4A → T	*FANCC*	Sca I	131 bp	108 + 23	131
ΔG322	*FANCC*	Bsp1286 I	151 bp	129 + 22	152
W22X	*FANCC*	FoK I	221 bp	204 + 17	187 + 17 + 17
Q13X	*FANCC*	Bcl I	250 bp	227 + 23	250
L554P	*FANCC*	Bbv I	364 bp	260 + 104	364
R548X	*FANCC*	Ava I	364 bp	231 + 133	364
L496R	*FANCC*	Hha I	303 bp	303	218 + 85
R185X	*FANCC*	Nla III	122 bp	105 + 17	74 + 31 + 17

PCR, polymerase chain reaction; bp, base pairs.

Table 2 - Clinical and molecular features of 22 patients with Fanconi anaemia.

Case	Age (years)	Gender	Race	Abnormal gene	Genotype
1	28	Female	White	*FANCA*	Δ3788-3790 / Δ3788-3790
2	23	Female	Black	*FANCA*	Δ3788-3790 / Δ3788-3790
3	8	Male	White	*FANCA*	Δ3788-3790 / NI
4	6	Male	White	FANCA	Δ3788-3790 / NI
5	15	Female	White	*FANCA*	Δ3788-3790 / NI
6	10	Female	White	*FANCA*	Δ3788-3790 / NI
7	18	Male	White	*FANCC*	IVS4 + 4 A → T / ΔG322
8	10	Female	White	*FANCC*	IVS4 + 4 A → T / ΔG322
9	12	Male	White	*FANCC*	IVS4 + 4 A → T / ΔG322
10	8	Male	White	*FANCC*	IVS4 + 4 A → T / NI
11	18	Male	Black	*FANCC*	IVS4 + 4 A → T / NI
12	15	Female	Black	*FANCC*	IVS4 + 4 A → T / NI
13	20	Female	Black	*FANCC*	IVS4 + 4 A → T / NI
14	18	Female	Black	*FANCC*	ΔG322 / NI
15	14	Male	White	FANCC	ΔG322 / W22X
16	14	Male	White	*FANCC*	W22X/W22X
17	2	Male	White	*FANCC*	W22X/ NI
18	33	Female	White	FANCC	Q13X / NI
19	19	Female	Black	*FANCC*	L554P / NI
20	5	Male	Black	*FANCC*	R548X/ NI
21	10	Female	White	NI	NI / NI
22	3	Female	Black	NI	NI / NI

NI, not identified.

Two pre-symptomatic patients with FA were identified in our familial studies (Cases 1 and 2).

Discussion

We have screened the Δ3788-3790 mutation of the *FANCA* and eight mutations (IVS4+4 A → T, ΔG322, W22X, Q13X, L554P, R548X, L496R, and R185X) of the *FANCC* genes in an unselected group of Brazilian patients with confirmed FA diagnosis.

The median age of the studied group, 14 years old, was higher than those obtained in previous reports, which was 7 years old (McMullin *et al*., 1991; Auerbach and Allen, 1994; Butturini *et al*., 1994), and may be attributed to the difficulties in achieving a reference service for FA diagnosis in the country. The congenital abnormalities were

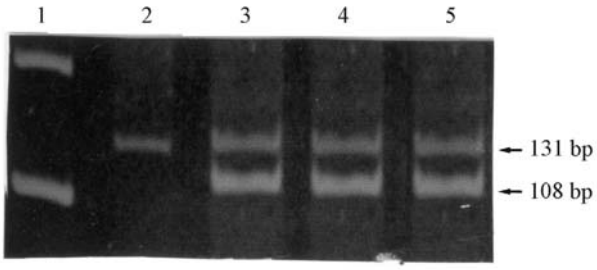

Figure 1 - Polymerase chain reaction and restriction site assays for detection of IVS4+4A → T mutation of the *FANCC* gene in Fanconi anaemia. Ethidium-bromide stained 7% polyacrylamide gel showing fragments of 131 bp and 108 bp corresponding to the mutant and normal alleles, respectively. Lane 1 shows the DNA size marker leader 100 bp. Lane 2 shows the result from an individual with homozygous IVS4+4A → T mutation used as control, and lanes 3 to 5 show the results from heterozygous individuals.

more frequent and severe in FA determined by *FANCC* gene mutations, particularly in cases with IVS4+4 A → T mutations, in accordance with previous reports (Faivre *et al*., 2000).

Interestingly, the disease was found in 8 (36.4%) patients of African origin in our group, in disagreement with the reports of Rosendorff *et al*. (1987) and MacDougall *et al*. (1990), in which the disease was rare in this race.

Mutations in the *FANCC* and *FANCA* genes accounted for approximately two-thirds and one-third of our cases. The disease was not determined by the tested mutations in only 9.1% of analysed cases. Therefore, *FANCC* gene mutations were the most prevalent in our group of patients (14 patients), in disagreement with previous reports that show to a higher prevalence of *FANCA* mutations in the majority of populations (Tischkowitz and Hodgson, 2003).

Levran *et al*. (1997) and Auerbach *et al*. (2003) described the Δ3788-3790 and IVS8-2A > G as the most common Brazilian mutations of *FANCA* and *FANCC* genes. As far as we know, both studies included Brazilian patients from a single bone marrow transplantation service, and may have included predominantly patients with the most severe disease forms. In our sample there were both patients with slight and severe haematological manifestations. As we did not select patients for study, it is possible that mutations of the *FANCC* gene represent a particular characteristic of the Brazilian population.

The most prevalent mutation of *FANCA* gene in our group was Δ3788-3790, in accordance with the report by Levran *et al*. (1997). The second most common mutation was the IVS4+4 A → T of the *FANCC* gene (Yamashita *et al.*, 1996; Gillio *et al.*, 1997; Tamary *et al.*, 2003).

In addition, the molecular analysis performed in our study was also important for early diagnosis of the disease, identification of pre-symptomatic and unaffected siblings with FA, as well as genetic counselling for the family.

Another fact that draws our attention is the high number of compound heterozygotes among FA patients. Since FA is considered a rare disease, a high rate of consanguineous parents and a larger number of homozygotes was expected, but not found in study. Our data suggest that FA may not be as rare as thought and taking into account its variable expressivity, many cases may be undiagnosed.

In conclusion, these results present preliminary evidence that *FANCA* and *FANCC* gene mutations are the most prevalent mutations among Brazilian FA patients. However, a large study concerning the molecular analysis of the Brazilian FA patients from different areas of the country should be carried out to clarify this issue.

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