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Fanconi anemia in Ashkenazi Jews

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Abstract

Fanconi anemia (FA) should be included among the genetic diseases that occur at high frequency in the Ashkenazi Jewish population. FA exhibits extensive genetic heterogeneity; there are currently 11 complementation groups reported, and 8 (i.e., *FANCA*, *FANCC*, *FANCD1/BRCA2*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, and *FANCL*) genes have been isolated. While patients may be from widely diverse ethnic groups, a single mutation in complementation group FA-C, c.711 + 4A > T (commonly known as IVS4 + 4A > T prior to current nomenclature rules) is unique to FA patients of Ashkenazi Jewish ancestry, and has a carrier frequency of greater than 1/100 in this population. In addition, a mutation (c.65G > A) in *FANCA* (FA-A is the most common complementation group in non-Jewish patients) and the mutation c.6174delT in *FANCD1/BRCA2* are also unique to the Ashkenazi Jewish population. Therefore, the study of Fanconi anemia can lend insight into the types of cancer-predisposing genetic diseases specific to the Ashkenazi.

Introduction

There are a number of genetic diseases that occur at high frequency in the Ashkenazi Jewish population, including Tay–Sachs, Gaucher, and Canavan syndromes. Fanconi anemia (FA, OMIM #227650) should also be included in this category because a single mutation c.711 + 4A > T (IVS4 + 4A > T; refseq NM_000136.1) in complementation group FA-C (OMIM #227645) is unique to FA patients with Ashkenazi Jewish ancestry, and has a carrier frequency of greater than 1 in 100 in this population [1]. In addition, a mutation (c.65G > A) in FA group FA-A (OMIM #607139) [2] and the mutation (BRCA2*6174delT) in FA-D1/BRCA2 (OMIM #605724) [3] are also unique to the Jewish population. Therefore, the study of FA can lend insight into the types of cancer-predisposing genetic diseases specific to the Ashkenazi.

FA is a rare autosomal recessive disorder characterized by progressive pancytopenia, diverse congenital abnormalities, and a predisposition to both hematologic and solid tumors [4–9]. Clinical diagnosis of FA is confirmed by study of chromosomal breakage induced by diepoxybutane (DEB) or other crosslinking agents, which provides a unique cellular marker for diagnosis of the disorder (Figure 1) [10, 11]. The DEB test can be used to identify the pre-anemic patients as well as the patients with aplastic anemia or leukemia who may or may not have the physical stigmata associated with FA.

Congenital malformations vary from patient to patient, and may affect skeletal morphogenesis as well as any of the major organ systems (Figure 2). Clinical variability is both interfamilial and intrafamilial; different congenital malformations can be found among siblings or even between monozygotic twins. FA affects all races and ethnic groups and has an estimated carrier frequency of 1 in 300, although the true gene frequency may be higher due to misdiagnosis prior to the use of DEB testing. The frequency of FA varies among ethnic groups and is particularly high in the Ashkenazi Jewish population [1, 12].

The clinical heterogeneity found in FA patients may be explained in part by genetic heterogeneity. So far 11 complementation groups have been identified [13–18], and 8 (i.e., *FANCA*, *FANCC*, *FANCD1*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, and *FANCL*) FA genes have been isolated. FA-A is the major group among non-Jewish individuals, and accounts for approximately 65% of FA cases. Studies of the first cloned FA gene, *FANCC*, revealed that clinical variability may also be

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Figure 1. A metaphase spread prepared after DEB treatment of PHA-stimulated cultured peripheral blood lymphocytes from a patient affected with FA. At this concentration of DEB (0.01 μg/ml) unaffected cells do not exhibit significant chromosomal breakage while FA cells show multiple chromatid breaks and exchanges.

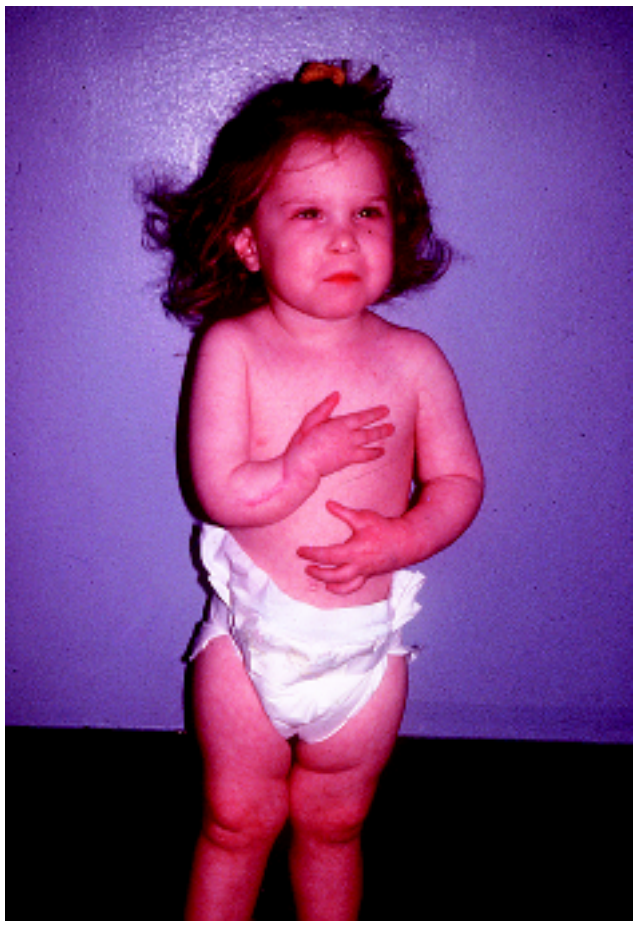

Figure 2. A two-year-old male of Ashkenazi Jewish ancestry who demonstrates physical features associated with FA. The photograph was taken post-surgery on his hands. Prior to surgery, the right hand exhibited a hypoplastic radius and absent thumb, while the left hand had a hypoplastic thumb. The patient exhibits growth retardation, dysmorphic facial features, microphthalmia, microcephaly and café-au-lait spots; he also has a kidney abnormality, undescended testes and a small penis. This patient is homozygous for the c.711 + 4A > T mutation in FA-C, and his phenotype is typical of patients with this genotype (From Auerbach et al. 2002 by permission.)

related to mutations in different parts of the FA gene [8, 17, 18]. Cellular studies have revealed possible roles of FA gene products in DNA repair, cell cycle regulation and apoptosis, but the precise function of these proteins remains to be elucidated [19, 20].

Fanconi anemia complementation group FA-C

While FA-A is the most prevalent FA complementation group overall, accounting for 60 to 65% of all FA cases, FA-C accounts for 10 to 15% of cases in the United States, and is the most common FA group among Ashkenazi Jews. *FANCC*, the gene mutated in group FA-C, was isolated by functional cloning and was localized to chromosome 9q22.3 by *in situ* hybridization [21, 22]. *FANCC* is comprised of 3 non-coding 5′ exons (exons −1, −1a and −1b) and 14 coding exons which give rise to various cDNAs, each containing an alternative 3′ UTR terminated by a consensus polyadenylation signal [23]. The significance of these various UTRs is unknown but they are thought to play a role in the regulation of expression. *FANCC* encodes a predicted protein of 558 amino acids with an estimated weight of 63 kD. The protein is highly hydrophobic which renders biochemical studies difficult. At the DNA sequence level as well as at the protein level, no homologies have been found to known genes, proteins or domains that could serve as clues to its biological role. A variety of mutations and polymorphisms have been described in the *FANCC* gene [18, 24–27]. The most common mutation in *FANCC*, c.711 + 4A > T, is the only *FANCC* mutation found in Ashkenazi Jewish FA patients and their families [23]; this mutation has not been found in any affected individual of non-Jewish ancestry [1]. The carrier frequency of the c.711 + 4A > T mutation was found to be 1 in 89 (1.1%; 95% confidence interval 0.79 to 1.56%) in an Ashkenazi Jewish population, while no carriers were identified in an Iraqi Jewish population, which represents the original gene pool of the Jews expelled from Babylon 2500 years ago [1]. A founder effect is the most likely explanation for the existence of a single mutation accounting for all *FANCC* chromosomes

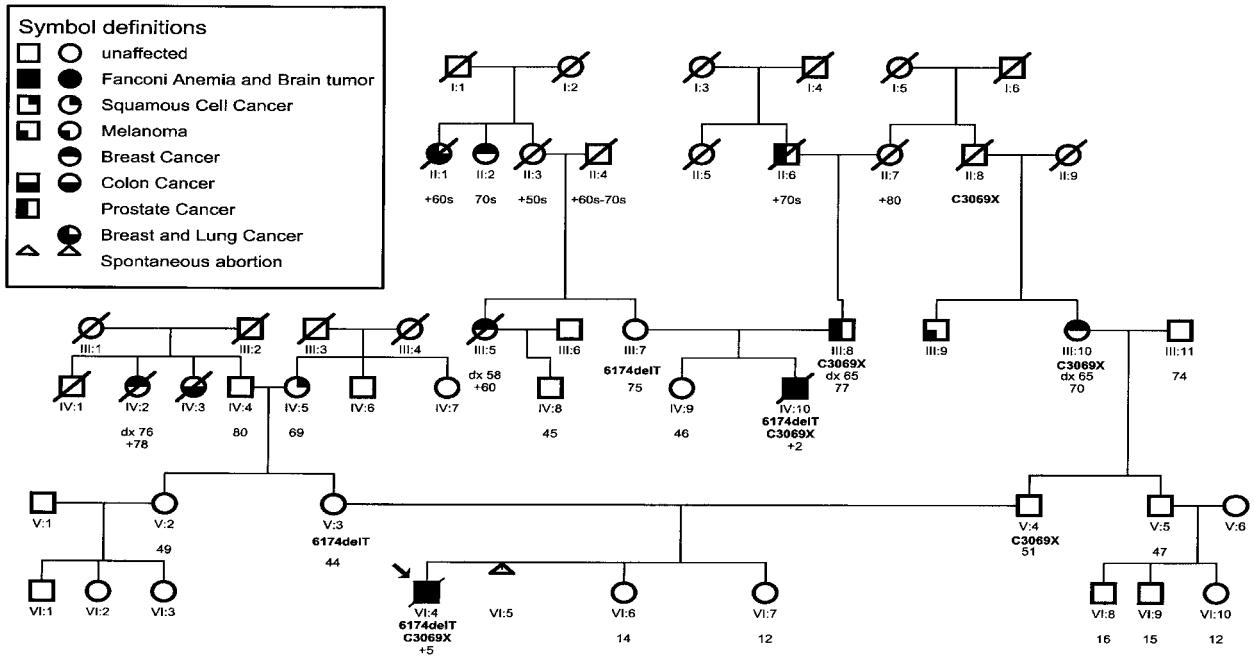

Figure 3. Pedigree of a BRCA2 FA kindred. The proband (*arrow*) was a child affected with FA. The numbers under the symbols refer to age at diagnosis if preceded by a 'dx', age at death if preceded by a '+', and current age in years if the number has no additional symbol. 'C3069X' under the symbol indicates that the patient was a carrier of the BRCA2*C3069X mutation, and '6174delT' indicates that the patient carried the BRCA2*6174delT mutation. Diagnoses of cancer were confirmed by review of pathology report for patients III:10 and IV:5, and by postmortem exam in IV:10. No autopsy was performed to confirm radiologic diagnosis of the brain tumor in patient VI:4. Other cancer diagnoses were by family report. An additional individual, the sister of III:2, also had breast cancer (not shown on pedigree) (From Offit et al. 2003 by permission of Oxford University Press.)

of Ashkenazi origin. The expected linkage disequilibrium was found between the c.711 + 4A > T mutation and an EcoRI RFLP in intron 11 of FA-C; 100% of affected chromosomes in homozygous c.711 + 4A > T probands carry allele 1 of the RFLP, while the allele frequencies in normal Ashkenazi chromosomes are 69% for allele 1 and 31% for allele 2 [12]. Conversely, analysis of the polymorphic marker D9S151, approximately 3.9 cM proximal to *FANCC*, finds no significant linkage disequilibrium with the c.711 + 4A > T mutation.

Fanconi anemia complementation group FA-A

FANCA, localized to chromosome 16q24.3, was cloned in 1996 by both functional complementation and positional cloning [28–29]. The 5.5-Kb cDNA that was isolated independently by each of these approaches contained a predicted ORF of 4683 nucleotides encoding a protein of 162 kD. The predicted FANCA polypeptide has no homology to known FA proteins. Most FA patients with Ashkenazi ancestry on only one side of their family are not in group FA-C, as *FANCC* mutations are rare in other ethnic groups. Since FA-A is the most common group overall, patients of mixed Ashkenazi and other ancestry are often in FA-A. A specific mutation (c.65G > A in exon 1) in *FANCA* in Ashkenazi Jews has been identified [2]. However, due to the rarity of this mutation in the general population routine screening of this mutation is not required.

Fanconi anemia complementation group FA-D1 (*BRCA2*)

Howlett et al. [30] reported that germline mutations in the breast cancer susceptibility gene *BRCA2* are associated with the FA-D1 complementation group. Biallelic mutations in *BRCA2* have now been shown to be associated with high rates of brain tumors, Wilms tumors and early onset leukemia (acute myeloid leukemia, AML and acute lymphoblastic leukemia, ALL) [31–33]. Another recent analysis of four kindreds affected with FA revealed the presence of germline *BRCA2* mutations. One kindred from this study, of Ashkenzai Jewish ancestry, had five members who were diagnosed with breast cancer and two cousins who were BRCA2*6174delT/C3069X compound heterozygotes and had FA and brain tumors (Figure 3). Kindred 2 in this study consisted of a mixed Ashkenazi Jewish and Lithuanian Catholic ancestry with no family history of breast cancer and included a girl with FA who was diagnosed with a medulloblastoma at age 4.5 years. The proband in this kindred carried the BRCA2*6174delT mutation as well as the BRCA2*886delGT [33]. The carrier frequency of the breast and ovarian cancer-predisposing mutation BRCA2*6174delT is approximately 1 in 100 among individuals of Ashkenazi Jewish heritage [34]. These findings provide rationale for offering genetic counseling to individuals who carry a germline *BRCA2* mutation and who plan to have children with a partner of Ashkenazi Jewish descent. Among Ashkenazi Jewish kindreds, numerous BRCA2

protein-truncating alleles, including BRCA2*9325insA, have been reported in the 3′ region surrounding nucleotide 9435 [35–37]. For example, the BRCA*886delGT allelle detected in the maternal lineage of kindred 2 has been observed 12 times in the Breast Cancer Information Core database [35]. Thus, although the probability of an Ashkenazi Jewish carrier of the BRCA2*6174delT mutation having offspring with a carrier of another *BRCA2* mutation is quite low, the possibility of such a couple having an offspring with FA is documented. In addition, for individuals known to carry *BRCA2* mutations, particularly mutations that result in a carboxyl-terminal protein truncation, the 1% probability of the spouse (if of Ashkenazi Jewish descent) carrying a BRCA2*6174delT mutation [34] and the potential 25% risk of having an offspring with FA suggest that genetic counseling in this setting may be indicated.

Clinical features of Fanconi anemia

The clinical features described here are based on periodic reviews of data from the International Fanconi Anemia Registry (IFAR), established at The Rockefeller University in 1982 to collect clinical, genetic, and hematologic information from a large number of FA patients. There are over 900 patients in the IFAR with a diagnosis of FA confirmed in North America. Large numbers of subjects and long term follow-up make this database unique. The primary source of case material for the IFAR is physician reporting. FA is associated with abnormal growth parameters both prenatally and postnatally. Short stature is a well recognized feature of the syndrome; the mean stature of FA patients in the IFAR is near the 5th percentile. Weight and head circumference are also often $\leq$ 5th percentile. Some children with FA have sub-normal response to growth hormone stimulation and/or overt or compensated hypothyroidism which may further compromise their growth. A number of FA patients also exhibit impaired glucose tolerance, post-glucose hyperinsulenemia, or diabetes. Members of complementation group FA-C, however, have worse height and a greater tendency towards primary hypothyroidism, but a better insulin/glucose profile, than FA patients overall. Those subjects homozygous for the AJ c.711 + 4A > T donor splice site mutation of FA-C appear to be a more exaggerated subset, with the same qualitative problems, but with quantitative differences [38]. We suggest endocrine evaluation in all FA children, since correction of growth hormone or thyroid hormone deficiency may improve final height outcome.

A review of congenital malformations associated with FA indicated that the FA phenotype is even more variable than previously recognized. Gastrointestinal, central nervous system and skeletal malformations in FA patients, previously not included as part of the FA phenotype, were observed [6]. Most FA patients with congenital malformations are not diagnosed until after the onset of hematologic abnormalities; delayed diagnosis might be due to lack of physician awareness of the phenotypic spectrum of FA. From a developmental standpoint, it is interesting that radial ray abnormalities in FA patients can be bilateral or unilateral. Even patients with bilateral abnormalities usually exhibit asymmetry, with limbs having different specific anomalies.

Approximately one-third of FA patients do not manifest congenital malformations [6]. These patients frequently have alterations in growth similar to FA patients who manifest birth defects. Other very common findings in these patients are skin pigmentation abnormalities and/or microphthalmia. Increased awareness of the facial anomalies as well as the complete spectrum of minor malformations seen in these patients should enable an earlier diagnosis to be made among patients without major congenital anomalies [7].

Based on patient outcome data as reported to the IFAR, the cumulative incidence of bone marrow (BM) failure by age 40 years is 90% with median time to onset of 7 years. Initial hematologic findings were diverse; thrombocytopenia associated with an elevated HbF and macrocytosis usually proceeded the onset of anemia or neutropenia. In some cases, patients presented with myelodysplastic syndrome (MDS) or AML, without prior diagnosis of aplastic anemia. Thrombocytopenia and pancytopenia were often associated with decreased BM cellularity. In contrast, the cumulative incidence of hematologic malignancy, defined as the onset of acute leukemia or MDS, by 40 years of age is 33% with no signficant difference between the FA complementation groups A, C, G. These data indicate an extraordinarily high risk of BM failure and AML in persons with FA, and underscore potential use of FA as a model of BM failure and leukemia development [8].

Genotype–phenotype correlations

In a study of genotype–phenotype correlations in FA-C patients in the IFAR, Gillio et al. [18] showed that the *FANCC* genotype affects clinical outcome, and allows division of the patients into three groups: (1) patients with the c.711 + 4A > T mutation (n = 26); (2) patients with at least one exon 14 mutation (p.R548X or p.L554P) (n = 16); and (3) patients with at least one exon 1 mutation (c.322delG or p.Q13X) and no known exon 14 mutation (n = 17) [7, 8]. c.711 + 4A > T and exon 14 subgroups are associated with a severe phenotype manifested by multiple major congenital malformations (Figure 2), early onset of hematologic disease and poorer survival compared to exon 1 patients and to the non-FA-C IFAR population. All c.711 + 4A > T patients have characteristic facial features, exhibiting microphthalmia and elfin-like facies (Figure 4). Of the 59 FA-C patients, 16 (27%) have

Figure 4. Four unrelated FA patients exhibiting typical facial features of patients with the c.711 +4A > T mutation in *FANCC*. These patients are of Ashkenazi Jewish ancestry and are homozygous for the c.711 + 4A > T mutation. (Photos published by permission.)

developed AML; the incidence of leukemia in each of the FA-C subgroups ranges from 19 to 37%. The median age at diagnosis of leukemia in the c.711 + 4A > T subgroup is 15.9 years. Twelve of the twenty-six c.711 + 4A > T patients have expired; leukemia was the cause of death in five of them. These findings were confirmed by a more recent analysis of the IFAR data from a 20-year perspective [8].

A recent clinical study by Wagner et al. [31], demonstrated that biallelic mutations in *BRCA2* result in the classic FA phenotype (Figure 5), including short stature, failure to thrive and hypersensitivity to DEB. However, these patients had a significant risk of acute leukemia at a very early age, compared to other FA patients (Figure 6). FA-D1 patients are also at high risk for medulloblastomas and Wilms tumors, compared to other FA patients. In addition, these patients had a family history of breast cancer typical of known *BRCA2* kindreds. BRCA-related cancers do not appear to be very high in FA families from complementation groups other than FA-D2 (Auerbach, unpublished data). Thus, the FA-D1 patients appear to have a unique phenotype.

Management and therapy

Allogenic hematopoietic cell transplantation using stem cells from the BM or umbilical cord blood currently offers the only proven treatment with the potential possibility for a cure for correcting the BM failure in FA patients as well as a possible cure or prevention of leukemia. Non-transplantation treatment strategies including androgen therapy and hematopoietic growth factors (G-CSF) provide transient improvement in the peripheral blood counts, but have several long-term complications including hirsutism and benign liver adenomas.

Early experience with BM transplantation for FA showed a poor outcome that was primarily due to regimen-related toxicity. The recent use of a specially designed pretransplant conditioning protocol that considers the hypersensitivity of FA cells to DNA-cross-linking agents, greatly improved the results of transplantation in patients with an unaffected HLA-identical sibling transplant as a donor [39]. Unfortunately, only 30 to 40% of the patients in need of therapy have an HLA-matched family donor. Experience has

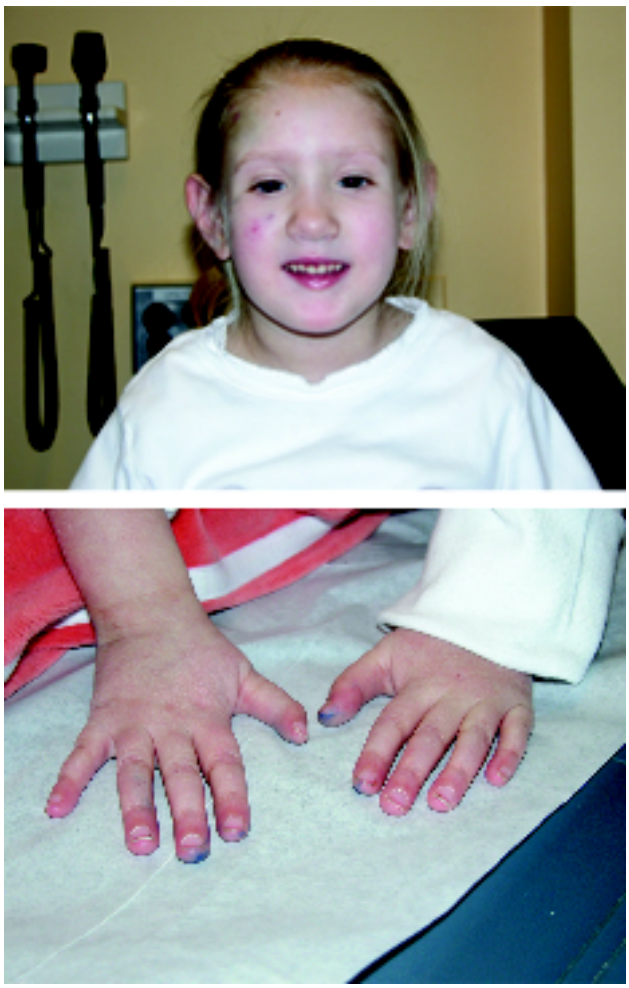

Figure 5. A five and a half-year-old female FA patient with biallelic mutations in *BRCA2*. She had a birth weight of 5 lbs 8 oz at 40 weeks gestation. The patient exhibited failure-to-thrive requiring G-feeding tube, café-au-lait spots, hypoplastic thumb, acute stress disorder (ASD), and required bilateral ureteral reimplantation. Also exhibited were mid-facial hypoplasia, microcephaly, ear anomalies, 5th finger clinodactyly and 2–3 toe syndactyly. At five and a half years she presented with rapidly evolving AML; bone marrow ISCN: 46,XX,der(5)t(1;5)t(8;21) [13]/46,XX,t(1;7) [5].

indicated that many families will pursue future pregnancies in hopes of having a nonaffected HLA-matched sibling to provide a source of hematopoietic stem cells for transplantation [40, 41]. Therefore, for couples with a child with FA, counseling must include a discussion of pre-implantation genetic diagnosis (PGD) of unaffected HLA-matched embryos [39, 42]. Embryos that are disease-free and HLA identical (if appropriate) are identified via this technique and implanted into the mother's uterus [43].

In addition, all patients with FA should be followed routinely by a hematologist, even prior to the onset of BM failure. Patients must have BM examinations annually to better understand the natural history of this disease and the significance of cytogenetic clonal abnormalities. These marrow examinations should be more frequent after the onset of marrow failure and/or the development of clonal hematopoiesis. Moreover, the hematologist must be aware of the importance of family genetic counseling, the availability of prenatal diagnosis and PGD. However, the hematologist must also be aware that the availability of predictive testing has led to complex ethical issues [44].

Conclusion

Fanconi anemia is categorized in the group of genetic diseases that affect the Ashkenazi Jewish population. The carrier frequency of FA is particularly high in this population, with an estimated carrier frequency of 1 in 89 for the c.711 + 4A > T mutation in *FANCC*. This mutation should be included in the battery of tests routinely provided to the Jewish population. In addition, biallelic *BRCA2* mutations can also lead to Fanconi anemia-like syndromes with high rates of brain tumors, Wilms tumors and early onset leukemia (AML and ALL). Therefore, genetic counseling should be offered to individuals who carry germline *BRCA2*

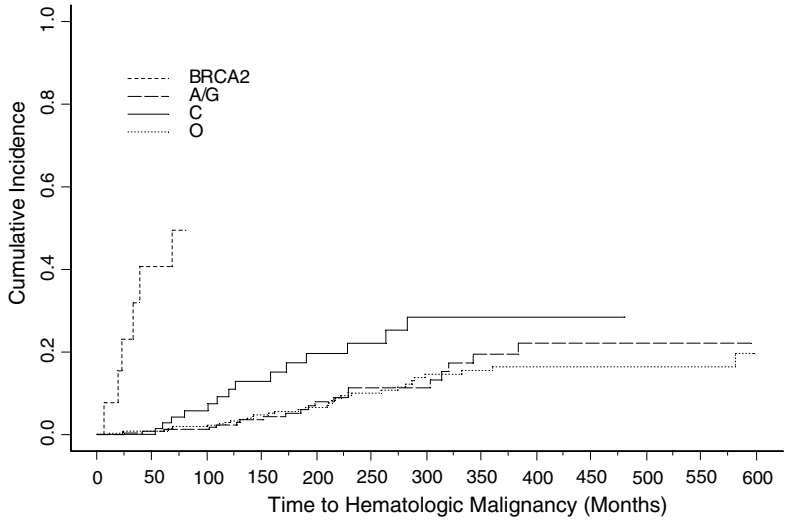

Figure 6. Cumulative incidence of hematologic malignancy among *BRCA2* mutation carriers (14 patients) *versus* group FA-C *versus* all other complementation groups (746 patients).

mutations and who plan to have children with a partner of Ashkenazi Jewish descent.

Acknowledgements

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