Research Article

A Dutch Fanconi Anemia FANCC Founder Mutation in Canadian Manitoba Mennonites

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Fanconi anemia (FA) is a recessive DNA instability disorder associated with developmental abnormalities, bone marrow failure, and a predisposition to cancer. Based on their sensitivity to DNA cross-linking agents such as diepoxybutane (DEB) and mitomycin C (MMC), FA cells have been assigned to 15 complementation groups. Currently, 15 different complementation groups and their associated genes have been identified. Founder mutations have been found in several populations. The majority of Dutch FA patients belong to complementation group FA-A (65%) followed in frequency by FA-C (10%) and FA-G (10%) [4].

The incidence of FA is approximately 1 in 130,000 live births, with a carrier frequency of approximately 1 in 181 [5]. In some ethnic groups, however, the incidence is much higher due to genetic isolation and a founder effect. For example, founder mutations in the FANCA gene have been found in several populations including the South African Afrikaners, Spanish Gypsies, and Moroccan Israeli Jews [6–8]. Furthermore, sub-Saharan Blacks and Japanese carry founder mutations in the FANCG gene [9, 10]. In addition, FANCC c.456 + 4A > T (also known as IVS4 + 4A > T) is a previously identified founder mutation in the FANCC gene
in the Ashkenazi Jewish population [11, 12]. Remarkably, the 
**FANCC** c.456 + 4A > T mutation has a severe phenotype in 
Ashkenazi Jews, but a milder phenotype in Japanese FA 
patients, suggesting the presence of unidentified modifying 
facets [13]. The majority of Dutch FA patients belong to 
complementation group FA-C, with c.67delG (also known as 
322delG) being the predominant mutation ([14], personal 
communication H. Joenje). In this paper, we report 15 
patients of Dutch ancestry and a large Canadian Manti-

toba Mennonite kindred harbouring the **FANCC** mutation. The presence of the **FANCC** c.67delG mutation in this kindred together with the fact that the Mennonites 
arose in The Netherlands around 1550–1600 AD suggested 
a common founder for the Dutch and Mennonite c.67delG 
mutation. We demonstrate that the Dutch and Manitoba 
Mennonite **FANCC** c.67delG patients do, in fact, share the 
same haplotype surrounding this mutation, indicating a 
common genetic origin.

### 2. Materials and Methods

#### 2.1. Dutch Patients. All 15 patients with the **FANCC** c.67delG 
mutation lived in The Netherlands except VU449, VU654, 
and VU911 who lived in the United Kingdom, Northern 
France, and Canada, respectively and had Dutch grand 
and great grandparents. The FA diagnosis was based on 
clinical symptoms suggestive of FA, in combination with a 
positive result from a chromosomal breakage test using a 
standard DNA cross-linking agent. Classification as an FA-C 
patient was based on complementation studies or sequencing 
analysis.

Genomic DNA was isolated from fibroblasts, blood, or 
lymphoblastoid cell lines from previously diagnosed **FANCC** 
c.67delG patients using the Qiagen Blood mini kit (Qiagen, 
Venlo, The Netherlands).

#### 2.2. Canadian Manitoba Mennonite Family. The proband of 
this family was diagnosed with FA at the age of five years, 
when she presented with bone marrow failure. At birth, 
there was documented intrauterine growth retardation, joint 
contractures, and a ventricular septal defect. At the time 
of presentation, the proband was also noted to be of small 
stature and to have a triangular facies and multiple café-
au-lait macules. She died at the age of six years from com-

clications following allogeneic bone marrow transplantation 
from her HLA-identical sibling. A younger sibling (VU1454) 
was subsequently diagnosed with FA and was found to 
be homozygous for the **FANCC** c.67delG mutation. She 
had normal growth parameters at birth and no noted FA-

associated anomalies except for the development of café-au-
lait macules.

A field trip was conducted to the rural community in 
which this family lived, and family members were given an 
FA information session. Forty-five members of the extended 
family consented to participate in this study. Clinical his-
tories were obtained, and cheek swabs were collected for 
genotyping. Minors who provided assent or whose parents 
consented on their behalf were also included in the study.

#### 2.3. Genotype Analysis. Patients and family members were 
genotyped using fluorescently labelled microsatellite markers 
and single-nucleotide polymorphisms (SNPs) in an 8 Mb 
region surrounding the **FANCC** gene. Markers used were the 
CA repeat markers D9S1842, D9S1781, D9S197, D9S1689, 
D9S1816, D9S1809, D9S1851, D9S180, and D9S176. Amplifica-

tion of the CA repeat markers was performed with the 
GeneAmp PCR system 9700 (Applied Biosystems, Foster 
City, CA, USA). Samples were analyzed on ABI 3730 or 
ABI 310 DNA Analyzer (Applied Biosystems, Foster City, 
CA, USA). SNPs used were rs1331216, rs2277182, and 
rs1016013. Amplification of the SNPs was performed with the 
GeneAmp PCR system 9700, and the PCR products 
were purified using a SAP/EXO treatment (Amersham 
Biosciences, Uppsala, Sweden) according to manufacturer’s 
instructions. Sequencing was performed with the Big Dye 
Terminator v3.1 Cycle Sequencing kit (Applied Biosystems, 
Foster City, CA, USA). Samples were analyzed on an ABI 
3730 DNA Analyzer (Applied Biosystems, Foster City, CA, 
USA).

Genotyping of the Canadian patient and family members 
for the **FANCC** c.67delG mutation was performed using 
standard methods (GeneDx, Inc., Gaithersburg, MD, USA). 
In brief, an allele-specific assay was designed to detect the 
presence of the single base deletion, and all samples showing 
the heterozygous presence of the deleted G nucleotide were 
sequenced bidirectionally to confirm the findings.

### 3. Results

Eleven of the 15 FA-C patients of Dutch ancestry analyzed 
in this study were homozygous for the c.67delG mutation, 
and 4 were compound heterozygous, each with a different 
second mutation. Using polymorphic microsatellite markers 
and SNPs, the smallest common haplotype in the 26 
alleles harbouring the c.67delG mutation was determined 
to be 0.8 Mb, covering the region from rs1016013 until 
D9S1816 (Table 1(a)). A larger common haplotype of 2 Mb 
(D9S197-D9S1816) was found in 23 alleles. The 3 alleles 
responsible for the decrease of 1.2 Mb in the common hap-

lotype belonged to 3 sibs (VU1134, VU1135, and VU1136) 
homozygous for the c.67delG mutation. The presence of two 
partially differing haplotypes in these homozygous c.67delG 
patients was confirmed in the parents (results not shown).

The identical haplotype surrounding the c.67delG mutation 
indicates that all 15 FA patients have co-inherited this stretch 
of DNA from a common ancestor. The expected size of a 
co-inherited stretch of DNA can be estimated by the 
equation $200/(\text{number of meioses})$, which is based on the 
assumption that recombinants occurring in meioses from 
the first common founder on either side of the mutation are 
uniformly distributed over the interval of 0 to 100 Mb [15]. 
This indicates that the descent tree of the 15 FA patients, up 
to the common founder, given a shared common stretch of 
DNA of approximately 0.8 Mb, counts about 250 meioses. 
This corresponds to about 10–20 generations and a common 
founder living in the 16–18th centuries.

Genealogical investigations into the ancestors of these 
patients only retrieved 6 or 7 generations from the archives,
### Table 1: The haplotype associated with the FANCC c.67delG mutation determined in 15 patients of Dutch ancestry (Table 1(a)) and in the affected sib of the proband, the parents, and healthy sibs of the Mennonite kindred (Table 1(b)). In Table 1(a) simplified, deducted allele lengths are shown and in Table 1(b) the observed allele lengths are shown. For comparison, patient VU1135 is included in both tables. The dark grey boxes show the smallest common haplotype of 0.8 Mb. The light and dark grey box, together show the larger common haplotype of 2 Mb. The boxed areas indicate homozygosity for the relevant markers. At the top, the distances in Mb of the markers to the c.67delG mutation are indicated. Patients VU001 and VU002 are siblings as well as patients VU1134, VU1135, and VU1136.

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and therefore it was not possible to reveal the common ancestor. However, for patient VU166 and patient VU1131, a common ancestor couple was found living around 1800 AD, and consanguinity was shown for patients VU166, VU1134, VU1135, and VU1136 (Figure 1). Our genealogical investigations also showed that most of these 6th and 7th generation ancestors lived in 4 distinct areas in The Netherlands (Figure 2), further supporting the possibility of a single common ancestor.

Forty-five individuals in the Manitoba family were genotyped for the FANCC c.67delG mutation. Eighteen of the 45 (40%) participants were heterozygous for the FANCC c.67delG mutation, and no new homozygotes were identified. The medical histories collected from kindred members did not reveal any early-onset cancer, but did document several other disorders already known to be overrepresented in the Manitoba Mennonite population, including severe combined immunodeficiency (SCID) (C.R. Greenberg, unpublished observation) and hypertrophic cardiomyopathy (HCM) [16]. Consanguinity could not be shown in five generations of ancestors. Haplotype analysis was done on the affected sib, two unaffected sibs, and the parents of the proband; it revealed the same common haplotype as found in the Dutch FANCC c.67delG patients (Table 1(b)).

4. Discussion

This paper shows that c.67delG in FANCC is a founder mutation that has probably originated in The Netherlands.
Russia, and from there to other parts of the world, and many settled in western Canada during the 19th century [17]. It is therefore likely that the Manitoba Mennonite FA-C patients in this study were descended from the same common ancestor as the Dutch patients in this study. This founder must have lived more than 200 years ago, since genealogical investigation could not identify the common ancestor among the ancestors living after 1800 AD.

Even though the c.67delG mutation is generally thought to be a mild mutation probably due to FAC polypeptide isoforms retaining partial function leading to a mild disease phenotype [18], clinical variability can be seen. The affected Mannitoba Mennonite siblings showed apparent divergent phenotypes, but neither had skeletal abnormalities, a characteristic of the mild disease phenotype associated with the c.67delG mutation.

Based on the high degree of consanguinity, the presence of the Dutch founder mutation, and the geographic origin being The Netherlands, we suspect that the carrier frequency for this c.67delG mutation in the North American Mennonite population is higher than expected for a rare recessive trait. An unselected and unbiased survey would be required in order to determine the actual FA-C carrier frequency in this Mennonite population. Several genetic disorders are well known to be overrepresented in this population, but FA has not previously been included in this list. Both HCM and 17alpha-hydroxylase deficiency have previously been shown to be caused by Dutch founder mutations [19–21] among the Mennonites. Since present generations continue to marry according to traditional custom, we may see an increased frequency of FA-C patients in future generations. Therefore, Mennonite communities should be offered comprehensive genetic counselling and carrier testing for FA.

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**References**


