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Novel FANCI mutations in Fanconi anemia with VACTERL association.

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Abstract

Fanconi anemia (FA) is an inherited bone marrow failure syndrome caused by mutations in DNA repair genes; some of these patients may have features of the VACTERL association. Autosomal recessive mutations in FANCI are a rare cause of FA. We identified FANCI mutations by next generation sequencing in three patients in our FA cohort among several whose mutated gene was unknown. Four of the six mutations are novel and all mutations are likely deleterious to protein function. There are now 16 reported cases of FA due to FANCI of whom 7 have at least 3 features of the VACTERL association (44%). This suggests that the VACTERL association in patients with FA may be seen in patients with FANCI mutations more often than previously recognized.

Keywords

FANCI; Fanconi anemia; VACTERL association

INTRODUCTION

Fanconi anemia (FA) is a cancer-prone inherited bone marrow failure syndrome (IBMFS) caused by germline mutations in key components of the DNA damage response. Eighteen known FA subtypes account for about 95% of cases. Subtypes A, C, D1 (*BRCA2*), D2, E, F, G, I, J (*BRIP1*), L, M, N (*PALB2*), O (*RAD51C*), P (*SLX4*), Q (*ERCC4*), S (*BRCA1*), and T (*UBE2T*) are inherited in an autosomal recessive pattern [Kitao and Takata, 2011; Bogliolo et al., 2013; Hira et al., 2015; Sawyer et al., 2015]. *FANCB* is X-linked recessive. FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM comprise the FA core complex and interact with FANCD2 and FANCI, which then interact with FANCD1/BRCA2, FANCN/PALB2, FANCI/BRIP1/BACH1, FANCP/SLX4, and FANCO/RAD51C, as well as NBS1, BRCA1, and FAN1 to preserve genome integrity [Kitao and Takata, 2011]. Germline mutations in the genes encoding these proteins result in deficient DNA repair [Kitao and Takata, 2011]. The diagnostic test for FA is the detection of

increased chromosomal breakage in cells cultured with a clastogen, such as diepoxybutane (DEB) or mitomycin C (MMC) [Fargo et al., 2014].

In addition to progressive bone marrow failure (BMF) in childhood and an elevated risk of cancer, many patients with FA also have congenital malformations such as radial bone and thumb abnormalities, short stature, skin hyperpigmentation, and/or café au lait macules [Shimamura and Alter, 2010]. A subset of patients with FA has a constellation of features consistent with the VACTERL-H (vertebral anomalies, anal atresia, cardiac anomalies, tracheal-esophageal fistula, esophageal atresia, renal structural abnormalities, limb anomalies, and hydrocephalus) association [Solomon et al., 2010]. To date, the VACTERL association in FA has been reported in patients with mutations in *FANCA*, *FANCB*, *FANCC*, *FANCD1/BRCA2*, *FANCD2*, *FANCE*, *FANCF*, and *FANCG* [Alter and Rosenberg, 2013]; it appears to be present in other genotypes as recently reported in *FANCL* and described in this report [Vetro et al., 2015].

We report three unrelated patients with FA and the VACTERL phenotype due to previously unreported autosomal recessive *FANCI* mutations, and review the literature on the clinical features and mutations of 13 previously reported cases with *FANCI* mutations [Levitus et al., 2004; Dorsman et al., 2007; Sims et al., 2007; Scheckenbach et al., 2012].

METHODS

Patients

Families with FA and their relatives are participants in an IRB-approved longitudinal cohort study at the National Cancer Institute (NCI) entitled “Etiologic Investigation of Cancer Susceptibility in Inherited Bone Marrow Failure Syndromes” (www.marrowfailure.cancer.gov, NCI 02-C-0052, [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT00027274). Patients and their family members complete detailed family history and medical history questionnaires. All participants or their guardians provided written informed consent in accordance with Health and Human Services regulation 45 CFR 46. We conduct detailed medical record review, collect biospecimens, and perform thorough clinical evaluations of affected individuals and their relatives at the NIH Clinical Center [Alter et al., 2010]. All cases were confirmed by chromosomal breakage analysis using DEB and MMC [Fargo et al., 2014]. The three cases reported here are the only three with *FANCI* in our cohort of 141 patients with FA, of which 18 have the VACTERL association.

Sequence Analyses

We performed whole exome sequencing (WES) on two probands with FA (NCI-82-1 and NCI-309-1) and their healthy relatives at the NCI’s Cancer Genomics Research Laboratory as previously described ([Ballew et al., 2013; Kocak et al., 2014], respectively). Sequencing on the third proband (NCI-253-1) was performed with a custom Haploplex kit (Agilent Technologies, Inc., Santa Clara, CA), which was enriched for the coding regions of all known FA genes as described [Naipal et al., 2014]. Barcoded sequence libraries were sequenced on the Miseq using 150 bp paired-end protocol and Surecall version 2.0 software was used for the data analysis. All variants were filtered based on autosomal recessive

inheritance that included both homozygous and compound heterozygous states as well as rarity in publically available databases. We also specifically evaluated known FA-associated genes for variants in our patients. In silico evaluation of variants was performed with multiple algorithms and compared with known variants in the FA database (<http://www.rockefeller.edu/fanconi/>), Supplementary Table SI. Mutations in *FANCI* were validated using the SMRTbell Template Prep Kit and sequenced on a Pacific Biosciences RS according to the manufacturer's instructions, or through whole-gene sequencing as described [Chandrasekharappa et al., 2013]. The *FANCI* reference sequences used were NM_001113378.1 and NP_001106849.1.

RESULTS

Case NCI-82-1

Patient NCI-82-1 was noted to have multiple congenital anomalies at her birth at 38 weeks gestation to non-consanguineous parents of Northern European and American Indian ancestry (Table I). FA was suspected at birth and the diagnosis confirmed at 3 months of age due to elevated chromosomal breakage in the presence of clastogens.

NCI-82-1 was evaluated at NIH at age 5 9/12 years. At that time, she had marked short stature with height and weight below the 1st centile for age (height Z-score -5.24 and weight Z-score -4.9), microcephaly (head circumference 44 cm; 50th centile for an 8 months old), and a small triangular face ("Fanconi facies"). Her constellation of congenital anomalies was consistent with the VACTERL association (fused cervical vertebrae, atrial septal defect [ASD], ventricular septal defect [VSD], duodenal atresia, small kidneys, and absent thumbs). She also had many features seen in FA (Table I). At that time, she had mild thrombocytopenia with a platelet count of 120⁹/L. Her bone marrow was hypocellular (30%) with a 47,XX,+i(1)(q10)[2]/46,XX[48] clonal abnormality.

Her cytopenias progressed over time and she was treated with etanercept for 6 months at 8.5 years of age without a response. She underwent HLA-matched sibling donor hematopoietic stem cell transplantation (HSCT) at age 10.5 years with successful engraftment. Unfortunately, she developed acute and chronic graft versus host disease (GvHD) and died from multi-organ failure 11 months after HSCT.

Analysis of WES data for NCI-82-1 was performed under an autosomal recessive inheritance model that included homozygous or compound heterozygous variants. The proband NCI-82-1 had two mutations present in *FANCI*, one deletion (chr15:89857921_89857924delCTTT, c.3799_3802delCTTT [NM_001113378.1], p.Ser1268Argfs*5 [NP_001106849.1]) and one insertion (chr15:89858595_89858596insG, c.3899_3900insG, p.Asp1301Glyfs*3) (Fig. 1). The deletion and insertion both cause alterations in the reading frame that result in premature stop codons and the loss of 61 or 28 amino acids from the C-terminus, respectively. The unaffected sibling and one parent were both carriers of only the insertion. The other parent's DNA was not available but long range sequencing analysis confirmed that the two mutations affected separate alleles.

Case NCI-253-1

NCI-253-1 was a female with the VACTERL association and FA anomalies (Table I). She was born via C-section at 34 weeks gestation due to fetal distress to non-consanguineous parents of European and Hispanic ancestry. NCI-253-1 was diagnosed with FA at age 5 months based on elevated chromosome breakage. She was diagnosed with hypothyroidism at 2 years, 9 months of age.

She was evaluated at NIH at age 3 years. She had marked short stature (height Z-score -3.7 and weight Z-score -2.85 SD), microcephaly (head circumference 45 cm; 50th centile for 1 year old), and a small triangular face ("Fanconi facies"). Her congenital anomalies were also consistent with the VACTERL association (cervical vertebral anomaly, VSD, patent foramen ovale, horseshoe kidney, and absent thumb). Her blood counts were normal but her bone marrow was hypocellular (40%) with normal cytogenetics (46,XX[20]).

WES of NCI-253-1 identified compound heterozygous mutations in *FANCI*. There was one novel mutation p.Cys1014Tyr (c.3041G>A, chr15:89847129G>A) and one previously reported mutation (c.1461T>A, p.Tyr487X, chr15:89824480T>A) (Fig. 1). Targeted sequencing revealed that one parent carried the Cys1014Tyr mutation and the other carried the Tyr487X mutation.

Case NCI-309-1

Case NCI-309-1 was born to non-consanguineous parents of Asian, Hispanic, European, and Native American ancestry. She is one of fraternal twins conceived by in vitro fertilization. NCI-309-1 and her healthy brother were delivered by C-section at 32 weeks for fetal distress. At birth, she was noted to have bilateral hypoplastic thumbs, microcephaly, and congenital heart disease (ASD, VSD, and PDA, all of which closed spontaneously) (Table I). A chromosome breakage test performed soon after birth was consistent with FA. Evaluation of NCI-309-1 at 8 years of age revealed microcephaly, a small, triangular face ("Fanconi facies"), small eyes, small neck, narrow C5 vertebra, bilaterally hypoplastic thumbs, absent radial pulses, Chiari malformation, and a small pituitary gland with poorly visualized pituitary stalk. She had previously undergone a bilateral ureteric reimplantation for grade three vesicoureteral reflux. Several of these birth defects were consistent with VACTERL. She also had normal stature and normal hormone function. Mild neutropenia was present with an ANC $0.92 \times 10^9/L$. Her hemoglobin was 12.8 gm/dL, MCV 88.2 fL, platelets $257 \times 10^9/L$, and HbF 2.6%. A bone marrow biopsy revealed 20–50% cellularity with trilineage hematopoiesis and normal cytogenetics (46,XX[20]).

Analysis of WES data for the NCI-309 family was performed under an autosomal recessive inheritance model that included homozygous or compound heterozygous variants. The proband NCI-309-1 had two mutations present in *FANCI*, p.Ser347Pro (c.1039T>C, chr15:89817462T>C) and p.Gly401Glufs*3 (c.1201_1201delG, chr15:89820030_89820030delG) (Fig. 1). One parent carried the p.Ser347Pro mutation whereas the other parent carried the p.Gly401Glufs*3 mutation.

DISCUSSION

Autosomal recessive mutations in *FANCI* were first reported in 2007 and are a relatively rare subgroup of FA [Levitus et al., 2004; Dorsman et al., 2007; Sims et al., 2007; Shimamura and Alter, 2010; Scheckenbach et al., 2012; Chandrasekharappa et al., 2013]. Our identification of three previously uncharacterized individuals with FA caused by compound heterozygous mutations in *FANCI* brings the total of reported cases of FA due to *FANCI* mutations to 16.

We identified six *FANCI* mutations in three probands, two of which have been previously reported in FA (p.Tyr487X and p.Gly401Glufs*3). All six mutations are predicted to have deleterious effects on protein function. Four of the mutations result in premature termination codons (p.Tyr487X in NCI-253, p.Ser1268Argfs*5, and p.Asp1301Glyfs*3 in NCI-82, and Gly401Glufs*3 in NCI-309) (Fig. 1). While the transcripts encoding p.Tyr487X and p.Gly401Glufs*3 most likely undergo nonsense mediated decay, p.Ser1268Argfs*5 and p.Asp1301Glyfs*3 may result in a translated protein lacking an EDGE motif and a C-terminal arginine/lysine rich nuclear localization sequence. A previously described *FANCI* mutation (p.Arg1299X) that results in a similar truncation to p.Ser1268Argfs*3 and p.Asp1301Glyfs*5 exhibits reduced nuclear localization [Colnaghi et al., 2011]. The same report demonstrated that the EDGE motif contributes to resistance to DNA crosslinking [Colnaghi et al., 2011]. The two missense mutations, p.Ser347Pro and p.Cys1014Tyr, affect highly conserved positions and are located in the first helical domain and third solenoid domain, respectively (Fig. 1). They are quite distant from the *FANCI*-*FANCD2* interface, but are near amino acids important for DNA binding [Joo et al., 2011]. Cys1014 is in the armadillo repeat region [Smogorzewska et al., 2007], a structural domain that has been implicated in mediating protein-protein interactions (Fig. 1).

Notably, the three FA cases due to *FANCI* mutations reported here all had features consistent with the VACTERL association. Four of the 13 previously published cases of FA due to *FANCI* mutations reported enough clinical information to conclude that they, too, had the VACTERL association [Levitus et al., 2004; Dorsman et al., 2007; Sims et al., 2007; Scheckenbach et al., 2012]. Thus, 7 of the 16 cases of FA due to *FANCI* mutations (44%) have FA in the setting of the VACTERL association. This is significantly higher than the value of 5% for all FA complementation groups among 245 patients with FA ($P=0.00008$, binomial probability test) [Faivre et al., 2005]. In that report, which was prior to the discovery of *FANCI*, the VACTERL association appeared to occur primarily in individuals with the D1, E, and F complementation groups, and less commonly in those in A, C, and G. A subsequent systematic review of 2,245 cases of FA reported in the literature identified 108 cases with three or more features of the VACTERL association [Alter and Rosenberg, 2013]. Three of the 42 FA VACTERL cases with genetic data (7%) had *FANCI* mutations. Additionally, VACTERL features were more frequent than predicted in individuals with *FANCB*, *D1*, *D2*, *J*, *N*, and *O* in our previous report [Alter and Rosenberg, 2013].

The VACTERL association is identified by the finding of any three features among the seven or eight heterogeneous findings, and may be sporadic, or due to underlying genetic disorders such as FA. Those with FA usually have FA-specific anomalies that are not part of

VACTERL, such as microcephaly, microphthalmia, hearing loss, café au lait macules, and others [Shimamura and Alter, 2010]. We recently identified an FA-specific subset of VACTERL due to the combined presence of radial ray and renal structural anomalies which was present in all of the *FANCI* patients who met VACTERL criteria (Table I) [Alter and Rosenberg, 2013]. This is quite different from the usual cluster of vertebral defects, cardiac malformations, and renal anomalies, although those were found in our patients as well [Solomon et al., 2010]. The identification of patients with FA among those with VACTERL association has important prognostic, therapeutic, and reproductive implications, and warrants referral to hematologists and genetic counselors.

In summary, we have characterized three patients with FA and the VACTERL association caused by autosomal recessive mutations in *FANCI*. Data from these patients and limited data from cases reported by others suggest that mutations in *FANCI* may be added to the FA genotypes in which the VACTERL association is unusually frequent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Schematic of the *FANCI* gene and location of reported mutations. The downward pointing arrows on the top of the schematic represent the location of mutations reported in the literature. The upward pointing arrows at the bottom of the schematic represent the locations of the mutations in the three new patients reported here. Red arrows indicate premature stop codons (nonsense or frameshift mutations). Blue arrows represent missense mutations. Purple arrows represent in-frame deletions. The top schematic shows the structural domains of FANCI, while the bottom schematic shows the relative positions of the FANCI functional domains (leucine zipper [green], ARM repeats [yellow], and EDGE motif [orange]).

Table 1.
Clinical Features of 16 Patients With Fanconi Anemia Due to *FANCI* Mutations

Patient ID, sex, (reference)	VACTERL features	FA features	Hematologic findings, age	Status	<i>FANCI</i> mutation(s)
EUFA592, F, Dorsman et al. [2007]; Levitus et al. [2004]	Thumb/radius, kidney, cardiac	Growth retardation	BMF, 2.5 yrs	Died at 6.5 yrs from aplastic anemia	p.Met1?, homozygous
BD952, F, sibling of 1428, Dorsman et al [2007]; Levitus et al [2004]	None reported	Growth retardation	BMF, 8 yrs	Died at 23 yrs	p.Arg1285Gln, homozygous
1428, M, sibling BD952, Dorsman et al. [2007]	None reported	Growth retardation	BMF, 7.3 yrs	Died at 15 yrs	p.Arg1285Gln, homozygous
EUFA695, M Dorsman et al. [2007]	None reported	NR	NR	NR	p.Arg964_Gln1002del and p.Gly422Arg
EUFA816, M, sibling of EUFA480, Dorsman et al. [2007]; Levitus et al. [2004]	None reported	Growth retardation	BMF, 6 yrs	Died at 12 yrs, after HSCT	p.Arg1285X and p.Glu1117fs
EUFA480, M, sibling of EUFA816, Dorsman et al. [2007]; Sims et al. [2007]	None reported	Growth retardation	BMF, 4.8 yrs	HSCT at 8.5 yrs, alive at 24 yrs	p.Arg1285X and p.Glu1117fs
EUFA961, M, Dorsman et al. [2007]; Levitus et al. [2004]	Thumb/radius, kidney, cardiac	Growth retardation	BMF, 8 yrs	Died at age 21 yrs after HSCT	p.Glu1117fs and p.His858_Arg879del
EUFA1399, M, Dorsman et al. [2007]	Thumb/radius, kidney, cardiac	Growth retardation	BMF, 1 yr	Alive at 30.5 yrs	p.Arg1299X, homozygous
F010191, NR, [Sims et al. [2007]	Thumb/radius	Growth retardation, microphthalmia, hearing loss	Anemia, 1 yr, transfusion dependent	Alive at 31 yrs	p.Arg614X and p.Arg1299X
F010095, NR, Sims et al. [2007]	Thumb, kidney	Growth retardation, microphthalmia, multiple congenital malformations including hearing loss	BMF, 6 yrs	Died at 21 yrs during HSCT	p.His858Tyr and His1146LLeufsX12
IFAR663, Sims et al. [2007]	Thumb, kidney, cardiac	Growth retardation, microphthalmia, multiple congenital malformations including brain, and hearing loss	HSCT at 6 years	Alive at 10 yrs	p.Glu837X and p.Asp1301GlyfsX3
Case 6, F, Scheckenbach et al. [2012]	None reported	None	Anemia and thrombocytopenia, treated with danazol starting at age 12 for at least 3 yrs	Alive at 15 yrs	p.Arg1285Gly, homozygous
FA14, NR, Chandrasekharappa et al. [2013]		NR	NR	NR	p.Gly422Arg and intron 16 variant (c.1583+142C>T)
NCI-82-1, F, Current report	Bilateral absent thumbs, short right radius, fusion of C5-C6 vertebral bodies, ASD, VSD, duodenal atresia, small kidneys	Fanconi facies, short stature, microphthalmia, microcephaly, hearing impaired, right ear canal atresia, septo-optic dysplasia, small pituitary, absent septum pellucidum, café au lait macules, normal vision, pale optic disk, hypoplastic optic nerves, central hypothyroid, GH deficiency, mild	Diagnosed at birth, severe BMF, HSCT at 10.5 yrs	Died at 11.5 yrs, from HSCT complications	p.Ser1268Argfs*5 and p.Asp1301Glyfs*3

Patient ID, sex, (reference)	VACTERL features	FA features	Hematologic findings, age	Status	FANCI mutation(s)
NCI-253-1, F, Current report	Abnormal cervical vertebra, dangling left thumb, VSD, PFO, horseshoe kidney	Premature with intrauterine growth retardation. Triangular facies, short stature, microcephaly, microphthalmia, narrow ear canals, abnormal middle ear bones, colpocephaly, abnormal corpus callosum, developmental delay, café au lait macules, myopia, astigmatism, normal optic disks, primary hypothyroidism, mild developmental delay. GH not measured. Mother age 32 yrs at birth.	Diagnosed at 5 mo. At age 3 yrs: normal white blood count, hemoglobin, and platelets. HbF 6.3%, bone marrow cellularity 40% at 5 yrs	Alive at 6 yrs	p.Tyr487X and p.Cys1014Tyr
NCI-309-1, F, Current report	Hypoplastic thumbs, short neck with narrow C5 vertebra, VSD, ASD, PDA, grade 3 vesicoureteral reflux requiring ureter re-implantation	Short left first metacarpal, microcephaly, microphthalmia, triangular facies, chiari malformation, small anterior pituitary gland with poorly visible stalk, mild bilateral conductive hearing loss; normal optic discs, optic nerves, and vision. Normal endocrine function, normal development. Mother age 32 yrs at birth.	Diagnosed at birth. At age 8 yrs: mild neutropenia, normal hemoglobin and platelets. Bone marrow cellularity 20–50%	Alive at 9 yrs	p.Ser347Pro and p.Gly401Gluufs

F, female; M, male; NR, not reported; yrs, years of age; mo, months; BMF, bone marrow failure; HSCT, hematopoietic stem cell transplantation; CBC, complete blood count; HbF, hemoglobin F; ASD, atrial septal defect; VSD, ventricular septal defect; PFO, patent foramen ovale; GH, growth hormone. Patient characteristics and identifiers (ID) are derived from the referenced publications. Mutation nomenclature is written as reported in each publication. The data may not be directly comparable because of variability between centers and data reported in each publication. *VACTERL* denotes an inference of the VACTERL association based on information reported in the published report.

^aDuodenal atresia is considered to be part of the VACTERL association by some reports [Solomon et al., 2010].