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ORIGINAL PAPER

Phenotypes of adults with Fanconi anaemia

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Summary
The long-term outcomes of adults with Fanconi anaemia (FA) have improved with advances in haematopoietic stem cell transplantation (HSCT) and more detailed follow-up and screening guidelines. The phenotype of those who survive to adulthood may differ from the typical presentation of FA. We collected retrospective clinical data on adults with FA who received their care at the Cincinnati Children's Hospital Medical Center. In our final cohort of 52 patients, there were 29 females and 23 males, with median (range) age of 21 (18–37) years. Overall, 42 patients (81%) were alive at last follow-up. In all, 36 adults (69%) had undergone HSCT, including eight who had developed myelodysplasia or acute myeloid leukaemia. Eight (15%) developed squamous cell carcinoma. Endocrine complications were common, including hypothyroidism (42%), diabetes (10%), low body mass index (31%) and low bone mineral density (51%). The majority of adults with FA were employed (52%) or full-time students (13%). A significant subset of patients with FA are surviving into adulthood without requiring HSCT. Endocrine abnormalities and the development of solid tumours complicate adulthood. With improved survival outcomes following HSCT and more aggressive malignancy screening protocols, ongoing longitudinal analysis will be important to further characterise this cohort and the phenotype of untransplanted adults with FA.

KEYWORDS
bone marrow failure, Fanconi anaemia, squamous cell carcinoma

INTRODUCTION

Fanconi anaemia (FA) is a chromosome breakage syndrome characterised by bone marrow failure, congenital anomalies, and predisposition to both haematological malignancies and squamous cell carcinoma (SCC).[1] The majority of those diagnosed with FA will undergo haematopoietic stem cell transplantation (HSCT) due to either marrow aplasia or haematological malignancy, although this does not reduce subsequent risks of SCCs.[2] Long-term outcomes for people with FA have improved with advances in HSCT, as well as more detailed guidelines for follow-up and screening. Given the rarity of the syndrome, descriptions of the phenotype of adults with FA are limited to small reports from registries.[3,4]

We describe the long-term outcomes of 52 adults with FA who received care at our FA comprehensive care centre. Our objectives were to characterise the overall survival and outcomes of patients with FA surviving to adulthood.

METHODS

We performed a retrospective chart review of 148 patients with FA who were aged >18 years at last follow-up. To ensure that we had the most updated long-term follow-up data, patients were only included in our final cohort if they had been seen in clinic within 6 years of data collection, or if they had died after reaching their 18th birthday. For the final cohort of

52 adults with FA, we extracted clinical data relevant to disease phenotype, treatments and outcomes. Diagnosis of FA was made by positive diepoxybutane (DEB)-induced chromosomal breakage or genetic mutation testing. Osteoporosis was defined as dual-energy X-ray absorptiometry (DEXA) scans z score ≤−3, while osteopenia was defined as z score between −2 and −3. Approval for this retrospective review was obtained from the Cincinnati Children's Hospital Medical Center Institutional Review Board. Proportions were compared using Fisher's exact test and continuous variables were compared using Mann–Whitney *U*-test using GraphPad Prism 9.

RESULTS

Demographics

A total of 52 adults with FA were included in our final cohort (Table 1). There were 29 females and 23 males, with a median (range) age of 21 (18–37) years at last follow-up. In all, 11 patients died. Three sibling pairs were included. The median (range) time since last follow-up for the remaining 41 patients was 1 (<1–6) years. In all, 41 of the 52 patients with FA had known FA complementation groups: 28 were in Group A (68%) and three in Group C. Two patients each had mutations in complementation groups D2, G, I, and L, and one each in groups B, F and T (Table 2). Overall, 10 additional patients had unknown genotypes.

TABLE 1 Demographics and patient characteristics

Characteristic	*N* (%)
Age, years	
18–19	15 (29)
20–29	33 (63)
30–39	4 (8)
Female	29 (56)
Alive	42 (81)
Typed	40 (77)
FANCA	26 (65)
FANCC	3 (8)
Other	11 (27)
Revertant	2 (4)
Identified congenital anomaly(ies)	29 (56)
Bone marrow transplant recipient	36 (69)
Androgen therapy	10 (19)
Cancers	19 (37)
MDS/AML	10 (53)
Squamous cell carcinoma	8 (42)
Other	2 (11)
Highest education	
High School	23 (44)
College	21 (40)
Graduate School	2 (4)

Abbreviations: AML, acute myeloid leukaemia; FANCA, Fanconi anaemia complementation Group A; FANCC, Fanconi anaemia complementation Group C; MDS, myelodysplastic syndrome.

Congenital anomalies

The most common congenital anomalies were detected in the skeletal system and skin in 29 patients. In all, 17 adults had skeletal anomalies, mostly related to the thumb, and 17 had skin abnormalities, most commonly pigmentation anomalies including café-au-lait macules. In all, 12 patients had short stature, and nine had ear anomalies. A total of seven patients had renal anomalies, of which only two had low glomerular filtration rates (14 and 42 ml/min/1.73 m^2), which did not impact either patient's quality of life. The patients also had congenital anomalies in the heart (5), nose/throat (5), eyes (4), central nervous system (4), gastrointestinal tract (3), and genitourinary tract (2). Overall, 23 patients had no congenital anomalies. There were no differences in sex and distribution of anomalies.

Haematology and HSCT

Overall, 16 of the 52 adults with FA had not undergone HSCT. Of these, five (31%) had mild bone marrow failure, three (19%) had moderate bone marrow failure, and eight (50%) had normal blood counts without cytopenias. In all, 12 of the 16 patients who had not undergone HSCT, including five of the eight who do not have evidence of bone marrow failure, had FA complementation Group A (*FANCA*) mutations. Only 10 (19%) of the 52 patients, including six who eventually underwent HSCT, had prior documented androgen exposure. Two patients with moderate bone marrow failure had prior androgen exposure, two with mild bone marrow failure had androgen exposure, one current and one in the past, and six with normal blood counts had prior androgen exposure. None of the patients currently required transfusion support.

Overall, 36 patients with FA in our cohort had undergone HSCT (Table S1). In all, 16 of 28 patients with *FANCA* mutations had undergone HSCT (57.1%), compared to 20 of 24 with other or unknown mutations (83%, $p = 0.070$). There were three pairs of siblings in our cohort, all with complementation Group A: in one pair, both siblings required HSCT, in another, neither had required HSCT, while in the final pair, one sibling had undergone HSCT but the other had not required HSCT. Indications for HSCT included aplastic anaemia (27 patients) and the development of clonal disease (seven, myelodysplastic syndrome [MDS]; one, acute myeloid leukaemia [AML]). Two patients developed refractory anaemia with excess blasts and monosomy 7, and five had concerning evolving cytogenetic abnormalities without overt dysplasia, including monosomy 7, deletion 7q, and trisomy 1q or 3q. The patient with AML had MDS-related changes, including deletion 7q31, trisomy 1q25, and

TABLE 2 Known mutations of adults with Fanconi anaemia

Number	FA gene	Mutation allele 1	Mutation allele 2
8	A	Unavailable	Unavailable
2	A	c.2851C>T(p.R951W)	c.2851C>T(p.R951W)
1	A	c.3788_3790delTCT(p.F1263del)	c.3788_3790delTCT(p.F1263del)
1	A	c.2152-?_2778+?del(ex24_28)	Unavailable
1	A	c.1827-1G>A	c.2852G>A(p.R951Q)
1	A	c.3788_3790delTCT	IVS22-1G>T
1	A	c.3391A>G	c.1480C>G(p.L494V)
1	A	c.987_990delTCAC	c.987_990delTCAC
1	A	c.190-2A>T	c.1115_1118delTTGG(p.V372fs)
1	A	c.337_338delTC	Unavailable
1	A	1734_1739 del 6 (Y578X)	3788_3790 del TCT (F1263del)
1	A	c.3788_3790delTCT	Unknown
1	A	c.3391A>G	c.3408+1G>A
1	A	c.4198C>T	c.1340C>G
1	A	c.2T>C	c.1827-1G>A
1	A	c.1627–?_2316+?del (ex18_25)	c.3163C>T (Arg1055Trp)
1	A	c.2T>C	c.2233_2234insT
1	A	entire allele (ex 1–43 deleted) c.-42-?-4368+?del)	C.2852G>A
1	A	c.2852G>A	deletion
1	A	c.42-?_4368+?del (ex1_43)	c.2853-?_4368+?del (ex30_43)
1	B	c.2249_2252delGAAG(p.G750fs)	c.2249G>T(p.G750V)
1	C	c.320G>A	c.1672C>T
1	C	R 548X	R 548X
1	C	Unavailable	Unavailable
1	D2	c.2715+1G>A	c.2976+5G>A (p.?)
1	D2	c.2660delA	c.1948-6C>A
1	F	c.484_485delCT	c.484_485delCT
1	G	c.307+1G>C	c.307+1G>C
1	G	c.1008_1009insA (p.P337fs)	Unavailable
1	I	c.3058+1G>A	c.3604G>C
1	I	c.1264G>A p.Gly422Arg	Unavailable
1	L	c.1007_1009delTAT (exon 12)	c.1095_1098dupAATT (exon 14)
1	L	Unavailable	Unavailable
1	T	Unavailable	Unavailable
10	Unknown	Unknown	Unknown

Abbreviation: FA, Fanconi anaemia.

trisomy 3q27. Details of HSCT were available for the 30 patients who were transplanted at our centre: six (20%) received transplants from matched siblings, two received haploidentical transplant from parents (7%) and 22 received unrelated donor transplants (73%). The median (range) age at transplant for patients with bone marrow failure was 10.5 (4.2–24.9) years. Patients received transplants for MDS/AML at a median (range) age of 15.4 (8.0–27.9) years ($p = 0.12$). Five patients developed acute graft-versus-host disease (GVHD), and four developed chronic GVHD, all of whom received their transplants before 2011. Overall, 10 of the 30 patients died. Three died before 2011: one with acute respiratory distress syndrome (ARDS) after transplant, one with progressive MDS, and one with SCC. Seven died after 2011: one with post-transplant lymphoproliferative disease, two with infection, and four with SCC.

Oncological complications

Five patients in our study had undergone HSCT as a child (median [range] age 13.5 [8–16.4] years) due to MDS or AML related to FA. Three additional patients received HSCT as adults for a haematological malignancy (median [range] age

18.9 [18.5–27.9] years). Two patients developed solid tumours by the age of 20 years, six more by the age of 30 years, and two more by the age of 40 years, including seven who had previously undergone HSCT. Three patients of the 16 (19%) who had not required HSCT developed solid tumours. Eight patients developed SCC, of whom six had previously undergone HSCT at a median (range) of 15 (8.5–27) years prior. All six patients had received irradiation as part of their transplantation conditioning, and one had experienced acute oral and gastrointestinal GVHD. Four of the eight patients with SCC had *FANCA* mutations. SCC sites included oral, pulmonary and genitourinary. The median (range) age at diagnosis of a SCC was 25 (19–40) years. Treatment of SCC in these patients included resection, radiation, cetuximab, and more recently, immune therapy with the programmed cell death-protein 1 (PD-1) inhibitor pembrolizumab. Two patients with SCC are still alive. The median (range) survival after diagnosis of SCC was 1.6 (0.2–4.8) years. Two additional patients developed non-SCC malignancies: one, who had previous androgen exposure, developed hepatocellular carcinoma at the age of 27 years, treated with resection only; and one developed papillary thyroid cancer at the age of 18 years, treated with total thyroidectomy and iodine 131 ablation. Both these patients with non-SCC cancers remain alive.

Endocrine complications

Hypothyroidism is common in adult patients with FA (Table 3). In all, 21 patients developed hypothyroidism requiring thyroid hormone supplementation, including 16 who had undergone HSCT. In all, 12 of these patients developed hypothyroidism after HSCT, while four had known hypothyroidism prior to transplant. The pre-transplant thyroid status of two currently hypothyroid patients transplanted elsewhere was unclear.

Three of the 29 women in our cohort have been diagnosed with primary ovarian failure. Two of these three women had undergone HSCT previously, prior to puberty. Two females, neither of whom had undergone HSCT, had biological children. The fertility of men in this cohort was not routinely tested and none were known to have fathered children.

TABLE 3 Endocrine complications in adults with Fanconi anaemia

Complication	*N* (%)
Hypothyroidism	22 (42)
Primary ovarian failure	3/29 women (10)
Diabetes	5 (10)
Type 1	3 (60)
Type 2	2 (40)
Underweight	16 (31)
Impaired bone mineral density	19/37 with DEXA scans[a]
Osteopenia	11 (58)
Osteoporosis	8 (42)

Abbreviation: DEXA, dual-energy X-ray absorptiometry.
[a]Only 37 of our cohort of 52 adults had DEXA scan data.

Overall, 6% of the patients in our cohort had developed diabetes. One adult had Type 1 diabetes, diagnosed at the age of 14 years, and two had Type 2 diabetes, diagnosed at the ages of 11 and 24 years. Four of those five patients had other concurrent endocrine abnormalities, including primary ovarian failure, growth hormone deficiency, hyperparathyroidism and adrenal insufficiency, and all five had previously undergone HSCT.

The majority of adults with FA have below average or normal body mass index (BMI). In all, 16 patients had a BMI <18 kg/m^2 and were underweight, while 26 had a normal BMI. Only four patients were considered overweight and one obese. The median BMI of our cohort was 19.8 kg/m^2. The median BMI of patients who had undergone HSCT was not significantly different from that of untransplanted patients (19.0 vs. 20.0 kg/m^2, $p = 0.62$).

Bone mineral density is impaired in adults with FA. Of 37 patients who had DEXA scans, 11 had scores indicative of osteopenia, while eight had scores indicative of osteoporosis. The median (range) z score was −1.3 (−4.5 to 2.98). In the subgroup analysis, the median (range) DEXA scan z score of patients who were hypothyroid was −1 (−4.5 to 2.98), compared to −1.3 (−4.4 to 1.7) for euthyroid patients ($p = 0.84$). Six of the 16 (37.5%) patients with hypothyroidism had a z score of <−2.0, compared to five of 15 (33.3%) euthyroid patients. Two of 11 patients (18.1%) who had not undergone HSCT had a z score of <−2.0, compared to nine of 34 HSCT recipients (37.5%; $p = 0.44$, Fisher's exact test).

Renal complications

Chronic kidney disease is unusual in adults with FA. In this cohort, nuclear glomerular filtration rate (GFR) calculations were rarely performed, and so kidney function was determined by GFR calculations via cystatin C measurements in 37 patients.[5] Although two patients had congenital renal anomalies associated with low GFR, only four additional (8%) patients had kidney disease. The median (range) GFR of the 37 adults with FA was 125 (14–484) ml/min/1.73 m^2 (normal range 80–120 ml/min/1.73 m^2).

Pulmonary function

The median (range) forced expiratory volume (FEV1)% reference of 27 patients was 76% (51%–111%). The median (range) diffusing lung capacity for carbon monoxide (DLCO)% reference is 75% (74%–98%).

Education, work, and social characteristics

Overall, 45 (87%) of the adults in the cohort had graduated from high school and 25 had received or completed schooling

beyond high school. Seven patients were full-time students, including two in graduate school. In all, 27 were employed in fields such as nursing, sales, food service, trade jobs or office work. A total of 22 patients were living independently, and seven of the 19 patients in our cohort who were not living independently were in school.

Survival

Overall, 41 patients were alive at last follow-up. Six adults had died from SCC, two from haematological malignancy, two from infection, and one from ARDS post-HSCT. All but one of the deceased patients had undergone HSCT. Two remaining adults diagnosed with and treated for SCC were alive at 2 and 2.5 years following their initial diagnoses.

DISCUSSION

Patients with FA are now increasingly surviving into adulthood. Data regarding adult phenotypes in rare diseases like FA are scarce (Table 4), and the complex clinical care needed may be separated between paediatric and adult providers resulting in gaps in the clinical expertise to care for these patients into adulthood. This large cohort provides insight into the complications of patients with FA with age and may help inform care.

While androgen therapy has long been known to result in some transient improvement in cytopenias, long-term data demonstrates that most patients discontinue therapy due to intolerable side-effects, or progression or transformation of their bone marrow.[6] Thus, bone marrow transplant remains a needed therapy for many patients with FA, including 36 adults in this cohort, for either bone marrow failure or clonal disorders. Our cohort of transplanted patients, of whom 20 of 36 (55.5%) were non-FANCA, may reflect studies that have demonstrated an increased risk of bone marrow failure in patients with FANCC and FANCG as compared to FANCA,[3] or differences in background ethnicity. Although only three pairs of siblings were included, two of the three pairs had congruent outcomes, consistent with a larger cohort of families.[7]

As families of children with FA have described their experience waiting for the next complications to manifest as 'waiting for the next shoe to drop',[8] it is of interest that many adults with FA do not require bone marrow transplants, confirming earlier findings.[9,10] Moreover, some patients are not discovered to have FA until adulthood.[11] Continued long-term follow-up will be crucial to better understand the phenotype and prognosis of untransplanted adults with FA and how they may differ from those undergoing transplantation. These data indicate that it is inappropriate to transplant patients who have not yet developed severe bone marrow failure. Evaluating such long-term data will inform screening guidelines for adults with FA as they age and how these may need to be adjusted depending on individual's treatment or transplant exposures.

As expected from long-term registry data, where the cumulative incidence of solid tumours at the age of 20 years was 15%, many patients in our cohort developed SCCs or other solid tumours.[4,12] The cumulative incidence of solid tumours was only 4.4% by the age of 20 years in our cohort, but did reach 16.7% by the age of 23 years, as 60% of adults in our cohort who developed a solid tumour were diagnosed in their 20's. More long-term data are necessary to determine if the decreased radiation exposure for many of our patients transplanted in the recent era without the use of radiation contributes to a lower incidence or a delayed development of SCCs. Unfortunately, outcomes for patients with head and neck SCCs remain disappointing, although there is hope that newer immunomodulating therapy, rather than traditional radiation or chemotherapy, will improve outcomes.[13] In addition, alternative mechanisms such as targeting the oral microbiome are promising for prevention or treatment of oral SCCs.[14] In our cohort, one adult previously treated with androgens developed hepatocellular carcinoma, which has been reported in numerous single case reports in patients with FA, although liver adenomas associated with androgen therapy are more common.[15]

Patients with FA have a well-described endocrine phenotype, with up to 79% of children and adults having features commonly including short stature, glucose intolerance, hypothyroidism, and hypogonadism.[16,17] Bone mineral density in children with FA after HSCT is comparable to children with cancer who underwent HSCT,[18] although less is known about

TABLE 4 Comparison of published cohorts of Fanconi Anaemia patients including adults

	Rosenberg et al., 2008[3]	Risitano et al., 2016[4]	Steinberg-Shemer et al., 2020[10]	Wang et al., 2022 (present study)
Number of patients	181 total, 90 aged >16 years	180 total, 135 aged >18 years	111	52 aged >18 years
Age, years, median (range)	NR	NR	NR (0.1–49)	21 (18–37)
Underwent HSCT, *n* (%)	62 (34)	102 (57)	59 (53)	36 (69)
Bone marrow failure, *n* (%)	66 (36)	172 (96)	91 (82)	35 (67)
MDS/AML, *n* (%)	14 (7.7)	13 (8)	15 (14)	8 (15)
Solid tumours, *n* (%)	10 (5.5)	20 (11)	10 (9)	10 (19)
Alive, *n* (%)	NR	94 (52)	65 (59)	41 (79)

Abbreviations: AML, acute myeloid leukaemia; HSCT, haematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; NR, not reported.

bone mineral density prior to or without HSCT. Risk factors for lower bone mineral density after HSCT included lower BMI z score and percentage fat mass, similar to risk factors for the general population, although likely more common in patients with FA, of whom 22%–38% have low BMIs.[17] In our cohort of adults, 31% had a low BMI, and over half of the patients who underwent DEXA scans had impaired bone mineral density, including patients who had not undergone HSCT. Our study also reinforces that patients with FA have insulin resistance and are at greater risk of diabetes mellitus, despite having on average lower BMIs.[16,17,19] Given their prevalence, early detection and treatment of endocrine and oncological complications of FA form the basis of annual screening guidelines for children and young adults with FA.

The limitation of our study is that it is a single institution retrospective study that relies on chart review and sometimes incomplete records. Nevertheless, we believe it presents real-world insight into living as an adult with FA.

Perhaps the most encouraging finding of our study is that patients with FA are not only surviving into adulthood, but more importantly, living active and productive lives as adults. Moreover, in a proportion of adults, this has been possible without HSCT. A sobering 21% of adults with FA died after their 18th birthdays, the majority from SCC, highlighting an urgent need for new and more effective chemoprevention and treatment options. Our comprehensive data from 52 adults with FA can inform adult clinicians and families regarding clinical care and decision making, as well as help refine and develop future screening approaches.

AUTHOR CONTRIBUTIONS

YunZu Michele Wang, Michaela Loveless, Erica Miller and Kasiani C. Myers collected data and designed the research; Adam S. Nelson, Parinda A. Mehta, Kasiani C. Myers and Stella M. Davies planned treatment strategies for the patients; YunZu Michele Wang and Kasiani C. Myers wrote the paper; all authors critically reviewed the manuscript.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PATIENT CONSENT STATEMENT

Not applicable (retrospective review).

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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