SHORT COMMUNICATION

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Phenotypic Variability and Cutaneous Features in 2 Siblings with Fanconi Anaemia and FANCA Mutation

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Fanconi anaemia (FA) is a rare phenotypically variable chromosomal breakage disorder that is considered the commonest inherited bone marrow failure (BMF) syndrome (1–3). The DNA repair abnormality typically results from recessive mutations in over 22 FANC genes (*FANCA-FANCW*) resulting in a multitude of congenital abnormalities, cutaneous changes, solid tumours, including squamous cell carcinomas (SCC) of the head and neck, as well as progressive BMF. Almost two-thirds of mutations occur in *FANCA*. Patients are usually diagnosed within the first decade of life (median of 7 years) with haematological abnormalities including myelodysplastic syndrome, acute myeloid leukaemia, and BMF (4). The phenotype, however, is highly variable, ranging from minimal symptoms to BMF and early death (5). Congenital abnormalities are common, grouped typically as VACTERL-H (Vertebral, Anal, Cardiac, Tracheo-esophageal fistula, Esophageal atresia, Renal, upper Limb and Hydrocephalus) or less commonly PHENOS (skin Pigmentation, small Head, small Eyes, Nervous system, Otology, Short stature) (1, 3–6). Cutaneous manifestations are one of the clinical hallmarks of FA and present mainly as skin pigmentation such as freckling or café-au-lait spots (7). Patients also have a 700-fold increased risk of developing SCC of the head and neck and have deleterious radiosensitivity (8, 9). Attempts have been made to correlate phenotypic severity with mutation type within the various complementation groups and the affected FANC protein domains. Yet, solid genotype–phenotype correlation remains elusive as many identical mutations within the same complementation group manifest differently, even among monozygotic twins. This could result from various modulating factors including dietary, environmental and epigenetic factors, as well as potential revertant mosaicism described frequently in FA (1, 3, 10).

CASE REPORT

A 35-year-old male presented with 2 rapidly enlarging and ulcerative nodules on the lower lip and left cheek (**Fig. 1**). His medical history was notable for Sertoli cell-only syndrome resulting in infertility, gout, primary hypothyroidism, and generalized anxiety disorder. He was a non-smoker and had an indoor job with little sun exposure. His parents were consanguineous. Physical examination revealed short stature, a fair complexion, solar damage with significant facial telangiectasia, as well as facial and arm freckling. An ill-defined hyperpigmented patch was identified on the left forearm (**Fig. 2**a). Histopathological analysis confirmed a diagnosis of moderately differentiated SCC of the lip and basal cell carcinoma (BCC) of the cheek that were subsequently fully excised.

Further questioning identified a younger sister diagnosed with FA at the age of 24 followed by bone marrow transplantation a year later. She was known to have a pelvic kidney. Examination identified short stature, micrognathia, facial freckling, a profusion of guttate hypopigmented macules distributed over the trunk (Fig. 2b), and an ill-defined hyperpigmented patch on her back (Fig. 2c). She, akin to her sibling, presented without any evidence of palmoplantar keratoderma or limb abnormalities.

Further tests undertaken for the brother to investigate FA revealed a normal complete blood count (haemoglobin 13.3g/dL, white blood cells 4.53 x 10^9/L, and platelets 279 x 10^9/L). Chromosomal instability studies were consistent with chromosomal breakage (Fig. 2d). PHA-mitogen stimulated lymphocyte culture, stressed

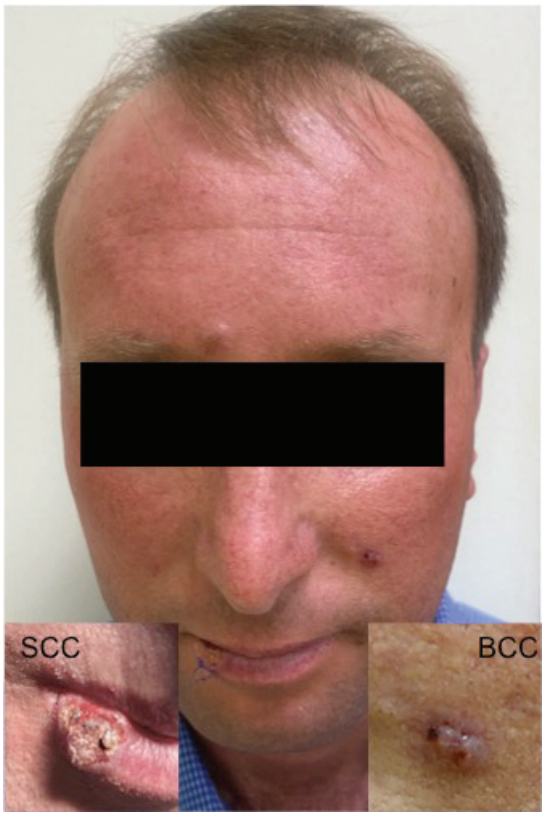

Fig. 1. Clinical facial features of the index case with Fanconi anaemia. There is evidence of fair complexion and solar damage with significant facial telangiectasia. The squamous cell carcinoma is noted on the lower lip. The basal cell carcinoma is noted on the left cheek.

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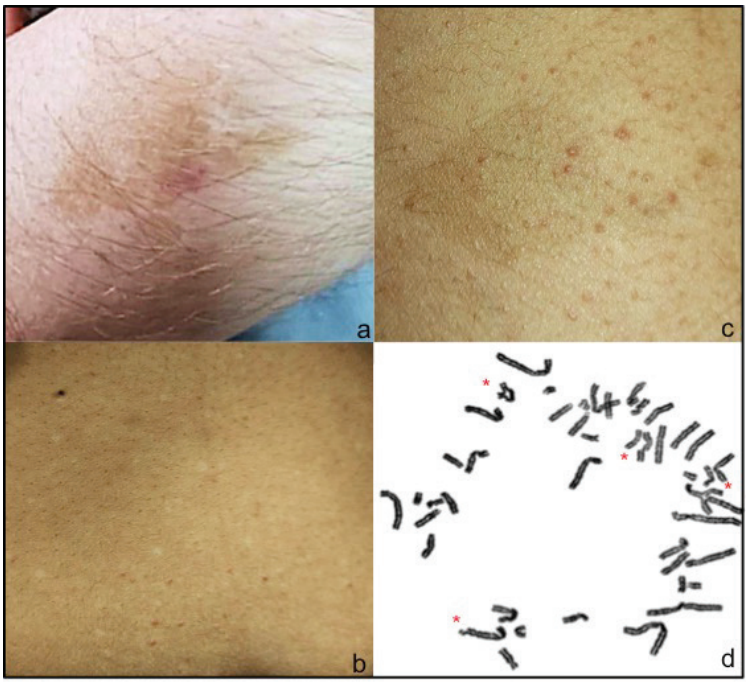

Fig. 2. Cutaneous features and chromosomal instability studies identified in 2 siblings with Fanconi anaemia. (a) An ill-defined hyperpigmented patch identified on the left forearm of the brother. (b) Guttate hypopigmented macules distributed over the trunk of the sister and (c) an ill-defined hyperpigmented patch on her back. (d) Chromosomal instability studies showing chromosomal breakage (red asterisk*).

with Mitomycin C, indicated 5.24 spontaneous breaks per cell in the patient, compared with 0.1 breaks per cell in the control, with a positive result for FA defined as > 1.0 breaks per cell.

Whole-exome sequencing identified a pathogenic homozygous nonsense mutation c.2557C > T (p.Arg853Ter) in exon 27 of *FANCA* (NM_000135.4). This variant introduces a premature stop codon that is expected to lead to either a truncated or absent protein due to undergoing degradation via nonsense-mediated decay.

Further screening tests for malignancies and congenital anomalies identified myopia, plus multiple non-specific small submandibular and deep cervical lymph nodes on neck ultrasound. An echocardiogram was unremarkable. Abdominal ultrasound identified a pelvic kidney. A colonoscopy and chest/abdomen/pelvis computed tomography were normal.

DISCUSSION

Genotype–phenotype correlation has both prognostic and therapeutic implications in FA, yet a clear correlation remains elusive. High discordance rates are present in FA, as multiple studies have shown significant phenotypic heterogeneity among siblings with identical *FANC* mutations. Kimble et al. screened 216 families in the International Fanconi Anaemia Registry (IFAR) for *FANCA* mutations and identified distinct mutations in 152 out of 159 FA families, reflecting significant genetic heterogeneity (4). In another study, 20–40% of *FANCA* mutations were found to represent large deletions that extend beyond the boundaries of *FANCA* adding to the challenges of clear genotype identification (11).

With regard to phenotypic heterogeneity, a report by Jung et al. studied 25 siblings with FA and showed discordance in nearly all constitutional features but a similar haematological progression course (2). Other studies have shown the probands to have a more severe phenotype compared with affected siblings, leading to recommendations for screen of all siblings as some might have minimal undetected phenotypic alterations (1, 3, 12). Cutaneous features can aid in this screening; however, there exists a diversity of cutaneous manifestations. Very few reports specifically address cutaneous features in FA (7). The most detailed cutaneous study, by Ruggiero et al., studied 93 patients with FA and identified at least 1 pigmentary alteration in almost all patients that appeared before the teenage years. Café-au-lait macules (CALM) were the commonest finding in 92.5%, the number and size of which was highly variable. These were also faint with ill-defined edges giving them a "shadowy spot" appearance (7). Other findings included hypopigmented macules, skin-fold freckle-like macules that developed during or after puberty, and extensive photo-exposed freckling. Two features were found to be unique in FA: concurrent hypo- and hyperpigmented pigment macules, as well as hypopigmented skin-fold freckle-like macules that might help differentiate FA from other pigmentary syndromes (7). This is consistent with the physical findings described in this report: both siblings had faint CALMs and photo-exposed freckling while the sister had significant hypopigmented macules.

Diagnosis is often delayed until patients become symptomatic or develop cancer (7, 12). It was shown that 25% of patients develop malignancy prior to the diagnosis of FA (9). Therefore, early diagnosis is crucial for early screening and studies have shown that pigmentary changes in FA can be identified as early as 1 year of age, emphasizing the role of dermatologists in early recognition (7).

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The identified homozygous nonsense mutations (Arg-853Ter) leading to protein truncation would usually be expected to result in severe disease. However, the sister developed BMF in her third decade, while the brother developed SCC in his fourth decade. This is later than would be expected for the average FA patient as usually BMF presents in 70% of cases in the first decade of life and SCC in the second or third decades. One explanation would be the presence of revertant mosaicism, a common phenomenon in FA (1, 10). Also of interest is that both siblings had aged skin, particularly in photo-exposed areas, with significant facial freckling, as well as BCC and SCC in the brother. This premature ageing phenotype in FA has been explained by genetic instability, sensitivity to reactive oxygen species, and impaired cellular proliferation with eventual carcinogenesis (3).

Therefore, the occurrence of skin cancers in younger patients with premature signs of cutaneous ageing should alert dermatologists to the possibility of underlying DNA instability disorders. This report highlights cutaneous features associated with FA with the intent to equip healthcare professionals with a pattern of recognition that will assist in screening for FA.

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