bjh short report

Comparison of the clinical phenotype and haematological course of siblings with Fanconi anaemia

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Summary

Fanconi anaemia (FA) is a genetic disorder due to mutations in any of the 22 *FANC* genes (*FANCA–FANCW*) and has high phenotypic variation. Siblings may have similar clinical outcome because they share the same variants; however, such association has not been reported. We present the detailed phenotype and clinical course of 25 sibling sets with FA from two institutions. Haematological progression significantly correlated between siblings, which was confirmed in an additional 55 sibling pairs from the International Fanconi Anemia Registry. Constitutional abnormalities were not concordant, except for a moderate degree of concordance in kidney abnormalities and microcephaly.

Keywords: Fanconi anemia, sibling, prognosis, bone marrow failure, MDS, AML.

Fanconi anaemia (FA) is the most common inherited bone marrow failure syndrome.[1,2] Patients with FA often present with congenital anomalies and up to 70% of patients develop bone marrow failure (BMF) during the first decade of life, with high risk of progression to myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML).[3,4] Patients also have a high incidence of solid tumours, especially head and neck squamous cell carcinoma.[5,6]

There are 22 known genes that cause FA, most of which exhibit autosomal recessive inheritance pattern, except *FANCB*, which is X-linked recessive[7] and *RAD51/FANCR*, which shows a dominant negative cellular effect.[8,9] In case of autosomal recessive inheritance, a sibling has a 25% chance of being affected. As siblings share the same disease-causing variants, it may be expected that a clinical outcome of an affected sibling could be predicted based on that of a

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proband. Not only is this important information that the parents and family are seeking to allay their anxiety related to the unknown, but in fact it may have implications in treatment decisions for the sibling. However, the published sibling reports suggest that there can be a high degree of discordance.[10,11] To date, there has been no systematic evaluation of a large sibling cohort with FA as to whether they have a similar or different clinical course. Here, we show that siblings with FA generally have a similar haematological clinical course as compared to their affected probands.

Patients and methods

Study participants

We performed a retrospective review of medical records of available FA probands and their affected siblings treated at Memorial Sloan Kettering Cancer Center — MSK Kids (n = 9 families) and Cincinnati Children's Hospital Medical Center (n = 16 families) between April 1990 and June 2018. Longitudinal and detailed clinical information was available for this discovery cohort. We collected the onset of neutropenia [absolute neutrophil count (ANC) < 1 000/μl], anaemia [haemoglobin (Hb) <100 g/l], thrombocytopenia (platelets < 100 000/μl), MDS or AML, time to haematopoietic stem cell transplantation (HSCT), the presence of any congenital anomalies, radial, thumb or other skeletal abnormalities, kidney or cardiac abnormalities, microcephaly, low birth weight, tracheo-oesophageal fistula, anal atresia, short stature, growth retardation and learning disability. We then assessed onset of haematological manifestations in an additional 55 sibling pairs from the International Fanconi Anemia Registry (IFAR) as a validation cohort. The IFAR defines onset of haematological manifestations as at least one of the following: ANC < 1 000/μl, Hb < 100 g/l, platelets <100 000/μl, or development of MDS or AML. The Institutional Review Boards of each institution approved to perform retrospective chart review and exchange deidentified clinical data for this study. The median age of onset of haematological manifestations of the non-sibling cohort was calculated from 604 subjects from the IFAR who did not have siblings.

Statistical analyses

The Spearman rank correlation coefficient was computed to assess correlation between sibling pair's clinical manifestations for the discovery cohort. If there were multiple siblings in one family, a proband and the oldest affected sibling were used among available subjects for this analysis. We also calculated Cohen's kappa coefficient to determine whether a presence or absence of a particular clinical event was likely to occur in both siblings. For this analysis, we used both a proband *versus* an older sibling and a proband *versus* a younger sibling pair in cases of triple sibling members. To assess the correlation of onset of haematological manifestations in the validation cohort, the Spearman's rank correlation was calculated on a total of 55 sibling pairs (excluding sibling pairs with somatic mosaicism or incomplete data). The discovery cohort and validation cohort are mutually exclusive. We excluded known mosaics from the correlation analysis for haematological outcomes.

Results

Demographic characteristics of the discovery cohort are described in Table SI. In the discovery cohort, we examined whether a specific factor or clinical outcome, such as congenital anomaly or development of MDS/AML, was likely to appear in the same sibling pairs or not, by calculating

Table I. Cohen's kappa coefficient test for clinical outcome between sibling pairs [total 28 pairs of siblings from 25 families (MSKCC-CCHMC cohort].

Variable	Kappa	95% confidence interval	Level of agreement	Frequency of event (%)
Any congenital anomalies	0·14	−0·15, 0·43	None	73·58
Radial abnormalities	0·16	−0·24, 0·56	None	13·21
Thumb abnormalities	0·32	−0·03, 0·67	Minimal	37·74
Other skeletal abnormalities	0·51	0·03, 0·99	Weak	11·32
Kidney abnormalities	0·65	0·34, 0·96	Moderate	28·3
Cardiac abnormalities	0·35	−0·08, 0·78	Minimal	15·09
Microcephaly	0·76	0·44, 1·00	Moderate	16·98
Low birth weight	0·48	0·12, 0·83	Weak	26·42
Tracheo-oesophageal fistula	0·46	−0·17, 1·00	Weak	7·55
Anal atresia	0·34	−0·23, 0·92	Minimal	9·43
Short stature	0·23	−0·11, 0·57	Minimal	43·4
Growth retardation	0·44	0·09, 0·80	Weak	22·64
Learning disability	0·47	−0·13, 1·00	Weak	5·77
MDS	0·03	−0·34, 0·41	None	18·87
AML	−0·05	−0·12, 0·02	None	5·66

MDS, myelodysplastic syndromes; AML, acute myeloid leukaemia.

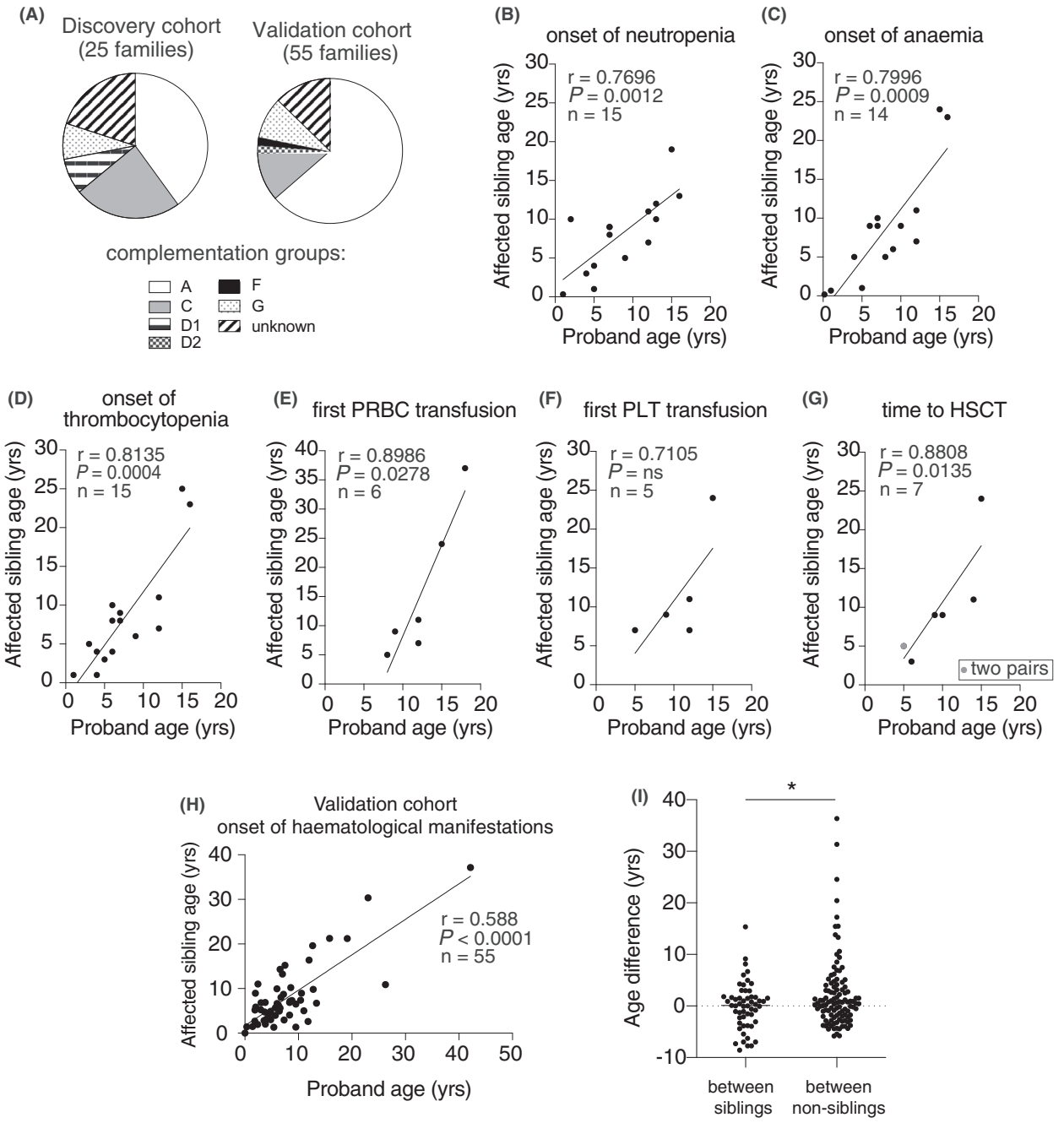

Fig 1. The haematological course was similar between probands and affected siblings with Fanconi anaemia (FA). (A) The FA complementation group of the discovery cohort and the validation cohort. (B) The onset of neutropenia (ANC < 1 000/μl) among the discovery cohort was significantly correlated between sibling pairs. (C) The onset of anaemia (Hb < 100 g/l) among the discovery cohort was significantly correlated between sibling pairs. (D) The onset of thrombocytopenia (platelets < 100 000/μl) among the discovery cohort was significantly correlated between sibling pairs. (E) The time to first packed red blood cell (PRBC) transfusion among the discovery cohort was significantly correlated between sibling pairs. (F) The time to first platelet (PLT) transfusion among the discovery cohort did not reach a statistically significant level of correlation between sibling pairs. (G) The time to haematopoietic stem cell transplantation (HSCT) among the discovery cohort was significantly correlated between sibling pairs. (H) The onset of haematological manifestations (defined by the presence of any of the following: bone marrow failure, myelodysplastic syndromes or acute myeloid leukaemia) in the validation cohort showed significant correlation between them. (I) The age differences at the onset of haematological manifestations were smaller between siblings than between non-siblings ($P = 0{\cdot}0328$ by unpaired t test). [Colour figure can be viewed at wileyonlinelibrary.com]

Cohen's kappa coefficient (Table I). We found moderate agreement in kidney abnormalities and microcephaly, weak agreement in other skeletal abnormalities, low birth weight, tracheo-oesophageal fistula, growth retardation and learning disability. Development of MDS or AML was not likely to occur in the same sibling pair.

A median age of onset of haematological manifestations were 5·69 [95% confidence interval (CI) : 4·42–8] in the discovery cohort. The most frequent FA complementation group was FA-A, observed in 10 families (40%), followed by FA-C in six families (24%) (Fig 1A). The validation cohort had a median age of onset of 6·48 (95% CI: 5·67–7·16). The most frequent complementation group was FA-A (63·6%), followed by FA-C (10·9%) and FA-G (9·1%).

The Spearman rank correlation coefficient calculated from the discovery cohort showed that the onset of neutropenia, anaemia and thrombocytopenia was significantly correlated between siblings among evaluable pairs (Fig 1B–D). The ages at the first transfusion of packed red blood cells (PRBC) and of platelets were available for six and five sibling pairs respectively. The age of first transfusion was highly correlated between siblings for PRBC (Fig 1E), but not statistically significant for platelets (Fig 1F). Time to HSCT information was available in seven sibling pairs, which showed a significant correlation between siblings (Fig 1G).

To assess whether the onset of haematological manifestations of a proband is significantly correlated with that of affected siblings in a larger validation sibling cohort, we computed the Spearman rank correlation coefficient on all evaluable sibling pairs in the IFAR. This analysis confirms a significant correlation in the onset of haematological manifestations (see *Patients and methods* for definition) between siblings ($r = 0{\cdot}588$, $P < 0{\cdot}0001$, $n = 55$ pairs) (Fig 1H). We also examined whether similar haematological course observed in our sibling study is just due to the nature of the underlying disease, FA. To address that, we tested whether the age differences at the onset of haematological manifestation were smaller between sibling pairs than between non-sibling pairs. We used a median age from 604 subjects from the non-sibling cohort for calculation of age differences with that of 110 subjects in the validation sibling cohort. This analysis showed that there was a median of 0·12-year (95% CI: −1·07 to 1·27) age difference at the onset of haematological manifestation between siblings, while a median of 0·58-year (95% CI: −0·18 to 1·2) age difference was observed between non-siblings (Fig 1I).

Discussion

Siblings with FA share multiple factors that may influence disease course, such as epigenetic factors, causative genetic variants, diet and social environment. Siblings also share not only the *FANC* genotype, but also may share other genotypes that may influence the FA disease phenotype. For example, FA patients with an *ALDH2*2* variant allele have earlier presentation of BMF or MDS/AML,[12] presumably due to increased DNA damage produced by un-metabolized aldehydes. It is possible that siblings also share such adverse or protective variants outside of the FA pathway, which subsequently either accelerate or delay the onset of haematological manifestations. Therefore, we hypothesized that siblings have similar clinical course because they share the same causative variants and/or environmental factors. Indeed, our analyses showed significant correlation in the onset of various haematological manifestations in the discovery cohort. This similarity is confirmed by assessment of the validation cohort. We note that the age at onset of haematological manifestations was slightly younger in the discovery cohort, which may be due to the fact that these subjects were referred to a specialized FA centre due to more severe disease and/or more frequent monitoring at these centres.

This is the largest report showing that patients with FA and their affected siblings are likely to have a similar haematological course. This is important in the counselling of parents with multiple affected children. Additionally, it can help in anticipatory guidance and planning of clinical care including timing of transplant for the affected sibling. Being prepared helps parents and patients deal with their clinical course better and also may improve their compliance with the treatment. Congenital anomalies did not occur in the same pattern in siblings except for kidney abnormalities and microcephaly to a moderate degree. The lack of strong correlation in most developmental abnormalities between sibling pairs is consistent with stochastic events leading to specific stem cell death during development. These findings now formally support the clinical observations that a significant difference in size/growth retardation and number of congenital anomalies is observed between affected siblings from the same family. The presence of a proband with MDS or AML was not predictive of development of MDS/AML in affected siblings; however, this analysis is limited by small sample sizes, rare events especially for AML as well as age differences between siblings. Interestingly, common clonal acquisitions (abnormalities of chromosome 1, 3 and 7)[13,14] observed in most patients with FA point to the possibility of stochastic events leading to clonal evolution, which could be confirmed in future studies in larger number of sibling pairs. Limitations of our study include its retrospective nature resulting in a possible loss of data and limited sample sizes, and descriptive analyses. However, it provides the contextual basis for the future studies addressing underlying mechanisms of clinical similarities for hematological manifestations and dissimilarities for congenital anomalies and clonal evolution between siblings.

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Author contribution

MJ, ROR, GU and EG collected data. MJ, CSJ and JMC analyzed results. MJ and AS made the figures. ROR, FPL and AS managed the IFAR. ADA established the IFAR and obtained follow-up clinical information. PAM, SMD and FB established and maintained patient cohorts. MJ, PAM, AS and FB designed the research. MJ, PAM, ADA, SMD, AS and FB wrote the paper.

Conflicts of interest

The authors declare no competing financial interests.

Supporting Information

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

Table SI. Demographics of the discovery cohort.

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