Tribute to Fanconi- ‘Clinical acumen still counts’

by Austin G. Kulasekararaj and Shreyans Gandhi

Received: March 31, 2022.
Accepted: April 5, 2022.


Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval; the final version of the manuscript will then appear in a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.
**Tribute to Fanconi- ‘Clinical acumen still counts’**

Austin G Kulasekararaj¹,², Shreyans Gandhi¹

¹Department of Haematological Medicine, King’s College Hospital NHS Foundation Trust, London, UK. ²King’s College London, London, UK

“It is the doctor’s privilege to pursue an occupation which is also his favourite pastime” Guido Fanconi -‘a jack of all trades’¹

Fanconi anemia (FA), a predominantly autosomal recessive disease, most frequently presents with bone marrow failure (BMF). Hematological manifestations like BMF, clonal evolution to myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML),² predominate in FA and can be the presenting feature or the most significant cause for morbidity and mortality.³ However, other manifestations in FA such as solid tumours especially squamous cell carcinoma, as well as other organ/system affliction including renal, gastro-intestinal, cardiac, endocrine and musculo-skeletal systems need specialist input and coordinated management plans, as advances in treatments such as hematopoietic stem cell transplantation (HSCT) in FA,⁴ get more successful with improving overall survival.

As with many ‘multigenic’ diseases, phenotypic and genotypic correlation needs to be better understood that also predicts for the natural history and outcome of the disease. Chromosomal breakage analysis as a diagnostic tool for FA, is widely used but genotypic characterization is progressing rapidly and much needed.

In this issue,⁵ Altintas et al report on a large National Cancer Institute (NCI) retrospective cohort of 203 patients, with nearly 50% harbouring FANCA mutations.
Genetic characterization is based on an upstream (80%), ID complex (9-11%) or downstream (5-9%) defect and whether it results in a “null” or “hypomorphic” variant. Interestingly data collection divided them into, a field cohort (FC) (72%) (remote data collection through questionnaires) and a clinic cohort (CC) (28%) (review at the NIH clinical centre) to associate patterns with phenotypic correlation and presentation. This demarcation into two cohorts is arbitrary and introduces ‘ascertainment and assessment’ bias especially in FA patients with subtle physical features, but paradoxically underscores the importance and necessity for more systematic and detailed assessment and is able to correlate genotype to phenotypic abnormalities in the clinical cohort.

Although the findings are largely confirmatory, this report contains a lot of information from pioneers in the field of FA, which updates the current knowledge regarding how FA genotype affects the patient phenotypes including BMF, solid tumour development, pregnancy, and physical abnormalities.

A few significant observations in this large cohort study are practically relevant and underpins the value of tertiary/specialist centres with expertise in evaluation, screening, and future management strategies, including timing of hemopoietic stem cell transplant (HSCT) and exciting novel therapies.

All patients evaluated in the NIH clinical centre had physical abnormalities and interestingly only 5% (3/57) did not have pathogenic variants in the FA/BRCA DNA repair pathway, as compared to 22% in the field cohort. The counter argument to this is- patients with subtle features who remain undiagnosed into adulthood, are detected with additional anomalies and features of multi-system FA disease, when reviewed in specialist centres.
Although slightly less than a century has passed by since the first clinical description of FA by Dr Guido Fanconi, the genomic revolution has expanded the repertoire of pathogenic mutations from 15 FA genes in 2010 to at least 22 genes in the FA/BRCA DNA repair pathway in 2022. Although conventionally FA patients with mutations in upstream complex, have lesser physical abnormalities and ‘milder’ phenotype in contrast to the ID complex, but upon assessment at a tertiary centre subtle non-VACTERL-H/PHENOS abnormalities were evident on physical assessment, especially in FANCA/FANCC patients. This clearly signifies the ‘added value’ of comprehensive evaluation in a specialist centre with multidisciplinary clinical, genetic and biological expertise, as at least a ‘one-stop’ clinic and subsequent remote monitoring in the era of telemedicine, the latter only strengthened by the COVID-19 pandemic.

Bone marrow failure (BMF) was present in 86% of the cohort, with increased risk of MDS/AML in FANCC cases. Clinical features and other tools to predict development of BMF and clonal evolution, is extremely helpful and aids in planning for pre-emptive HSCT. Ability to predict early BMF in FA patients with PHENOS features which interestingly overlaps with the previously reported congenital abnormality score (CABS) and well described association with absent radii is valuable. Chromosomal abnormalities and also markers of clonal haemopoiesis, and their role in prediction models for BMF and development of MDS/AML in FA will become refined and redefined in the near future.

The risk of development of solid cancer and metabolic/endocrine (mainly hypothyroidism) abnormalities are well described in FA due to disease and/or therapy, especially after HSCT and gain even more value in a systematic algorithm of monitoring.
Increased risk of solid tumours in patients with FANCA variants involving exon17-20, which is essential for nuclear localisation; fertility preservation and ability to conceive for female patients with c.3624C>T synonymous variant in FANCA gene; clinical heterogeneity between FA siblings with identical variants, and lack of ‘hotspot’ mutations in FANCA compared to FANCD2 are some of the novel findings, are some interesting observations which would need further validation and biological explanation.

Age of onset and registration of FA patients in this study is 5.4 and 11.2 years respectively, with upper limit close to 60 years. No additional correlation between age of presentation and physical features is presented. This is critically important to evaluate in future studies and useful for adult haematologists who usually deal with ‘non-syndromic’ diseases, as most of the inherited BMF syndromes including FA presenting in adulthood manifest with subtle physical features, less cytopenia and more solid cancers or lung/liver fibrosis, the latter in the context of telomeropathies. It is possible, and slightly speculative, if some of the adult-onset FA could belong to upstream complex in view of the milder phenotype reported for FANCA genotype in paediatric and adolescents. Phenotype-Genotype analysis without question, will still develop and can help in predicting the natural history and multi-system manifestations of FA, including prognosis for counselling, and risk-stratified management strategies. It still has to achieve it’s ‘max’ out potential, and hence will find utility. The FC and CC modelling that authors have developed in this study, as well as the description of the PHENOS phenotype is also a step in that direction. Mutational diversity as well as inconsistent phenotype, however limit their utility beyond a certain point.
These large phenotype-genotype correlations in FA will help understand the natural history and biology of the disease and thereby advance the field of therapeutics which is progressing to correct bone marrow failure (gene therapy and gene editing)\(^{10,11}\), halt the progression of BMF (modulate endogenous aldehyde metabolites or microbiome)\(^{12}\) and restore stem cells (Eltrombopag) whilst simultaneously using novel strategies to prevent/treat solid cancers in FA.