

Case Report

Genetically proven fanconi anemia: a case report

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ABSTRACT

Fanconi anemia (FA) is a rare autosomal recessive disorder characterized by congenital malformations, haematological problems and predisposition to malignancies. It was first described by Guido Fanconi, a Swiss Paediatrician in 1927. The prevalence of FA is 1 to 5 cases per million. The genes that have been found to be mutated in FA patients are called FANC. 16 different FANC genes have been reported, among which 60-65% account for the mutations seen in FANCA genes which is the most frequently seen in FA patients. The disease is most commonly seen in children between 5-15 years. Diagnosis is based on the congenital physical abnormalities and confirmed by genetic testing. Here we report a rare case of Fanconi Anemia in a 4 year old female child with the characteristic clinical findings and the diagnosis was confirmed by genetic studies.

Keywords: Fanconi anemia, genetic mutations, molecular testing, FANCL gene

INTRODUCTION

Fanconi anemia (FA) is a genetically rare autosomal recessive disorder characterized by congenital malformations, haematological problems and predisposition to malignancies.¹ In 1927, a Swiss paediatrician Guido Fanconi first described it as a familial form of aplastic anaemia in three brothers with short stature, hypogonadism and skin pigmentation.²

The genes that have been found to be mutated in FA patients are called FANC. Sixteen distinct FANC genes have been reported, among which mutations in FANCA are the most frequent among FA patients.³ The FANCA gene is a hyper-mutable gene as several mutations and polymorphisms have been identified.^{3,4} The prevalence of FA is approximately 1 to 5 cases per million.⁵

FA is seen in children between 5-15 years, in both sexes equally, and is characterized by progressive bone marrow failure and increased predisposition for acute myeloid leukaemia and other solid tumors. Diagnosis is by various congenital physical features, hematologic abnormalities

(pancytopenia, macrocytic anaemia and progressive bone marrow failure) and genetic testing. Bone marrow transplantation is the definitive treatment that restores the hematopoiesis.

CASE REPORT

A 4 year old female child born out of a consanguineously married parents presented with history of acute onset of fever and cough. Her birth history revealed that she was a preterm baby of weight 1.4 kgs delivered by cesarean section. General examination revealed pallor, short stature, triangular facies with microcephaly, small eyes, low set ears, multiple café-au-lait spots, hyperpigmentation of the intertriginous areas, and proximally placed thumb.

Except for the PDA which was ligated at the age of 1 year nothing else was relevant on systemic examination. Ophthalmic, hearing assessments were normal. Ultrasound of the abdomen was done to rule out renal anomalies which was normal study.



Figure 1: Short stature.

Laboratory investigations showed anaemia (Hb-9gm%) with persistent thrombocytopenia (platelet count- 70,000) suggestive of ongoing marrow failure. Peripheral smear with moderate anisocytosis and the presence of few macrocytes.

Genetic mutation tests were done after obtaining consent from the parents. DNA extracted from blood was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to mean >80-100X coverage on Illumina sequencing platform. The sequences obtained are aligned to human reference genome (GRCh37/hg19) using BWA program and analyzed using Picard and GATK-Lite toolkit to identify variants relevant to the clinical indication.



Figure 2: Café-au-lait spots.



Figure 3: Thumb abnormality.

Gene annotation of the variants is performed using VEP program against the Ensembl release 84 human gene model. Clinically relevant mutations were annotated using published variants in literature and a set of diseases databases - ClinVar, OMIM, GWAS, HGMD and SwissVar. Common variants are filtered based on allele frequency in 1000Genome Phase 3, ExAC, EVS, dbSNP141, 1000 Japanese Genome and internal Indian population database. Non synonymous variants effect is calculated using multiple algorithms such as polyphen-2, SIFT, mutation taster2, mutation assessor and LRT. Only non-synonymous and splice site variants found in the fanconi anemia panel genes were used for clinical interpretation.



Figure 4: Low set ears.

A homozygous silent variation in exon 13 of the FANCL gene (chr2:58387243; C>T; Depth: 100x) that results in the synonymous amino acid change of Lysine at codon 364 proximal to donor splice site (p.Lys364(=);

ENST00000233741) was detected (Table). This FANCL variation is classified as a likely pathogenic variant. Hence the diagnosis of fanconi anemia was made on the basis of various congenital physical features, abnormal

haematological findings and genetic mutation tests. The treatment option of bone marrow transplantation has been discussed.

Table 1: Likely pathogenic variant causative of the reported phenotype was identified.

Gene (Transcript)	Location	Variant	Zygoty	Disease (OMIM)	Inheritance	Classification
FANCL(-) (ENST00000233741)	Exon 13	c.1092G>A (p.Lys364(=))	Homozygous	Fanconi anemia of complementation group L	Autosomal recessive	Likely pathogenic

DISCUSSION

Fanconi anemia (FA) is characterized by physical abnormalities, progressive pancytopenia, cellular hypersensitivity to DNA-cross-linking agents, bone marrow failure, chromosomal breakage and increased risk for malignancy. Physical abnormalities, seen in approximately 75% of affected individuals, include short

stature, hyperpigmentation of the skin and intertriginous areas, skeletal malformations of the upper and lower limbs, microcephaly, renal problems, hearing defects, cardiac disease, gastrointestinal problems, ophthalmic and genitourinary tract anomalies like hypogonadism. Progressive bone marrow failure with pancytopenia typically presents in the first decade, often initially with thrombocytopenia or leukopenia.⁶

Table 2: Various abnormalities present in FA.¹⁰

Body	Abnormalities
Skeletal	Radial ray defects, hypoplasia of the thumbs and radial hypoplasia, congenital hip dislocation, scoliosis, and vertebral anomalies, microcephaly
Skin	Generalised skin hyperpigmentation, cafe au lait spots, and areas of hypopigmentation
Endocrinological	Growth hormone deficiency (with altered growth both in utero and postnatally) or hypothyroidism, or abnormalities of glucose/insulin levels
Eyes and ears	Microphthalmia, conductive deafness
Renal tract	Unilateral renal aplasia, renal hypoplasia, or double ureters
Genital tract	Hypogonadism, hypospadias, and infertility (males), Underdeveloped genitalia and uterine anomalies (females)
Gastrointestinal tract	Atresia (oesophageal, duodenal, jejunal), imperforate anus, tracheo-oesophageal fistulae
Cardiac	Patent ductus arteriosus, ventricular septal defect, pulmonary stenosis, aortic stenosis and coarctation
Nervous system	Hydrocephalus, absent septum pellucidum, and neural tube defects

The genetic studies help to identify the gene mutations. The mutated genes in FA patients are called FANCA. 16 distinct FANCA gene have been identified. All the FANCA genes are autosomal recessive except FANCB, as this gene is located on the X chromosome.⁷ Among these FANCA gene abnormalities account for approximately 60–65% of FA patients and more than 100 types of mutations have been found throughout the FANCA gene.⁸ These include microdeletions, large deletions, microinsertions and point mutations.⁹ The hyper-

mutability of FANCA is due to the dispersion of large number of repetitive elements throughout the gene.

In our case, the characteristic clinical findings arouse the suspicion of FA. The homozygous silent variation in the exon 13 of FANCL gene. Fanconi anemia of complementation group L (OMIM#614083) is caused by homozygous or compound heterozygous mutations in the FANCL gene (OMIM#608111). The observed variation has previously been reported in a patient affected with Fanconi anemia. RNA analysis of this variant revealed

skipping of exon 13 in the messenger RNA, resulting in deletion of 72 nucleotides encoding 24 amino acids from a RING finger domain.¹⁰ The p.Lys364 (=) variant is not present in the 1000 genomes database and has a minor allele frequency of 0.002% in the ExAC database. The in silico prediction² of the variant is damaging by mutation taster.² The reference codon is conserved across species. Based on the above evidence, this FANCL variation is classified as a likely pathogenic variant and has to be carefully correlated with the clinical symptoms.

20% of patients with Fanconi anemia can develop cancers (acute myeloid leukemia, myelodysplastic syndrome, squamous cell carcinomas of the head and neck, esophageal and tongue carcinoma, tumors of the liver, brain, skin, kidney, stomach and large bowel.¹¹ The only proven long-term cure of the bone marrow manifestations is successful allogeneic hematopoietic stem cell transplantation (HSCT).¹²

Other haematological supportive measures include blood transfusions, androgens, and cytokines. Androgens, usually oral oxymethalone, are often therapeutically used because they enhance production and urinary excretion of erythropoietin and increase bone marrow cellularity. FA can be considered for gene therapy in view of the serious haematological complications.¹³

CONCLUSION

Fanconi anaemia is a genetic condition that can present with various congenital defects and can predispose to malignancy later which is the main cause for morbidity and mortality.

Diagnosis is confirmed by genetic studies and should also be done if possible in all the cases of suspected FA, siblings, parents and close blood relatives. The screening of the FANCL gene for mutations supports the clinical diagnosis of FA. The only proven long-term cure is allogeneic hematopoietic stem cell transplantation. Gene therapy is an emerging treatment modality.

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REFERENCES

1. Andrea AD, Grompe M. The Fanconi anaemia/BRCA pathway. *Nat Rev Cancer*. 2003;3:23-34.
2. Fanconi G. Familiaere infantile perniziosaartige Anaemie (pernizioeses Blutbild und Konstitution). *Jahrbuch Kinderheild*. 1927;117:257-80.
3. Winter JP, Joenje H. The genetic and molecular basis of Fanconi anemia. *Mutat Res*. 2009;668:11-9.
4. Ten I, Foe JR, Rooimans MA, Collins BL, Alon N, Wijker M, et al. Expression cloning of a cDNA for the major Fanconi anaemia gene, FAA. *Nat Genet*. 1996;14:320-3.
5. Kutler DI, Singh B, Satagopan J. A 20-year perspective on the International Fanconi Anemia Registry (IFAR). *Blood*. 2003;101:1249-56.
6. Kerviler E, Guermazi A, Zagdanski AM, Gluckman E, Frija J. The clinical and radiological features of Fanconi's anaemia. *Clin Radiol*. 2000;55:340-5.
7. Meetei AR, Levitus M, Xue Y, Medhurst AL, Zwaan M, Ling C. X-linked inheritance of Fanconi anemia complementation group B. *Nat Genet*. 2004;36:1219-24.
8. Wijker M, Morgan NV, Herterich S, Berkel CG, Tipping AJ, Gross HJ, et al. Heterogeneous spectrum of mutations in the Fanconi anemia group a gene. *Eur J Hum Genet*. 1999;7:52-9.
9. Morgan NV, Tipping AJ, Joenje H, Mathew CG. High frequency of large intragenic deletions in the Fanconi anemia group a gene. *Am J Hum Genet*. 1999;65:1330-41.
10. Chandrasekharappa SC, Lach FP, Kimble DC, Kamat A, Teer JK, Donovan FX, et al. NISC comparative sequencing program. massively parallel sequencing, acgh, and rna-seq technologies provide a comprehensive molecular diagnosis of fanconi anemia. *Blood*. 2013;121(22):138-48.
11. Alina D. *Acta Medica Marisiensis*. 2014;60(3):125-8.
12. Andrea A. Susceptibility pathways in Fanconi anemia and breast cancer. *N Engl J Med*. 2010;362:1909-19.
13. Tischkowitz MD, Hodgson JSV. Fanconi anemia. *J Med Genet*. 2003;40:1-10.

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