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BRIEF COMMUNICATION

Prenatal Diagnosis of Radial Ray Defect Associated with Fanconi Anemia: a Case Report

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Abstract Fanconi anemia (FA) is a rare genetic disorder with multisystem involvement. Confirmatory genetic testing is possible by diagnostic clues on examination of the proband within the differential diagnosis. We describe a fetus with radial ray defect in a primigravida. Cytogenetic testing for breakages confirmed Fanconi anemia as the etiology. Molecular testing by next generation sequencing did not reveal a point change in any of the twenty-one genes known to be associated with FA. A confirmed fetal autopsy phenotype and the cytogenetic report allowed for the identification of a homozygous deletion of exon 4–6 in the FANCC gene on re-analysis of the molecular dataset. This case exemplifies the utility of a step wise approach to the diagnosis of prenatally diagnosed radial ray defects and the importance of genetic counseling and prenatal testing.

Keywords Fanconi anemia · FANCC gene · Chromosome breakage · Next generation sequencing · Prenatal diagnosis · Radial ray defect

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Introduction

Radial ray defects (RRDs) are a large heterogeneous group of disorders that include partial or complete absence of the radius and/or radial ray structures. Some of the disorders associated with radial ray defect include Holt Oram syndrome, thrombocytopenia-absent radius (TAR) syndrome, VACTERL association, diabetic embryopathy, teratogens like valproate, Cornelia de Lange, SALL4 related disorders, chromosomal aneuploidies and Fanconi anaemia [1, 2]. It has a heterogeneous phenotype, characterised by physical abnormalities, bone marrow failure, and increased risk for malignancy. Fanconi anemia (FA) can be inherited in an autosomal recessive/dominant or X-linked manner. Chromosomal instability, especially on exposure to alkylating agents, may be shown in affected subjects and is the basis for the diagnostic test. Mutations in at least 21 genes are known to cause FA [3–5]. Of the skeletal abnormalities, radial ray defects such as hypoplasia of the thumbs and radial hypoplasia are the most common [6]. We describe an antenatally detected radial ray deficiency confirmed to have FA. We also discuss the importance of phenotyping, relevant investigations and molecular confirmation for appropriate genetic counseling of the family.

Case Report

A third gravida with a history of two previous abortions, nonconsanguineous marriage and normal chromosomes of the couple on karyotyping, presented at 19 weeks for her first antenatal visit. The anomaly scan revealed a nuchal fold of 2.4 mm, echogenic bowel(Fig. 1a), atrioventricular septal defect (Fig. 1d), bilateral absent radii (Fig. 1c) and absent thumb (Fig. 1b). There was no history of diabetes,

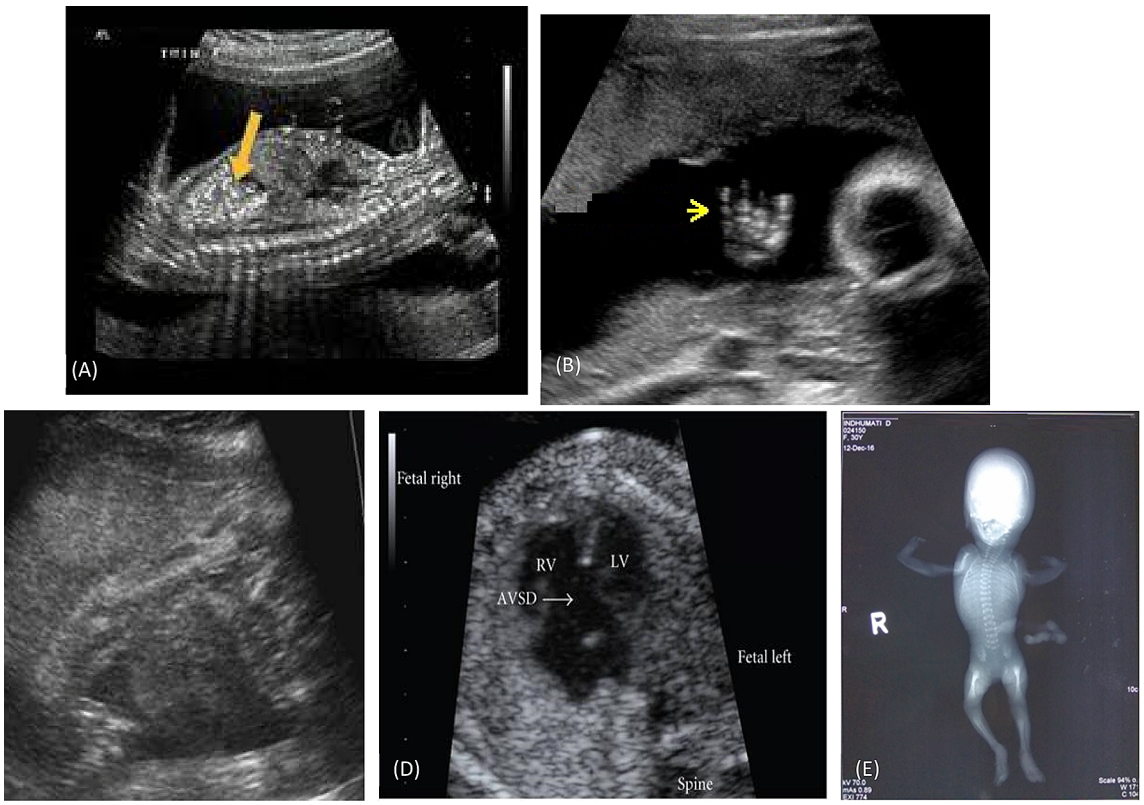


Fig. 1 The ultrasound images (**a**); (**b**); (**c**); (**d**); Infantogram (**e**)

hypertension or teratogenic exposure in the form of drug intake/infection/radiation. There was no family history of recurrent abortions or intrauterine deaths. After adequate counseling, the couple opted not to continue the pregnancy. However, to investigate the etiology of the malformation, they consented for prenatal amniocentesis along with cordocentesis. Chromosomal breakage analysis using mitomycin C showed increased chromosome breakage and rearrangements favoring the diagnosis of chromosome breakage syndrome (Fanconi anemia in this fetus). The karyotype showed a normal female chromosome complement.

Fetal autopsy was performed for detailed phenotyping for dysmorphism and fetal malformations. There was hypotelorism, flat nasal bridge, short neck, short middle segment with radial ray defect with three fingers each in both upper limbs and an absent thumb in the left upper limb. There was a large ventricular septal defect and atrial septal defect. The diaphragm was continuous with no breach. In the abdominal cavity, the appendix was seen in left superior quadrant with evidence of intestinal malrotation. Liver, spleen, both kidneys, ureters and bladder were grossly normal with female internal genitalia. Infantogram showed normal mineralization with normal vertebral bodies and pedicles. Bilateral absent radius was seen [Fig. 1e].

Based on the fetal phenotype and stress cytogenetic analysis with mitomycin C, a diagnosis of Fanconi anaemia was made. Clinical exome sequencing was performed to identify a mutation in one of the 19 FA associated genes. No mutations were identified. However, as the fetal phenotype and mitomycin breakage analysis strongly suggested Fanconi anemia, the data was re-analysed to look for deletions/duplications that can be present in patients with FA. Homozygous deletion of exon 4–6 in the FANCC(+) gene was identified (Fig. 2), which is a pathogenic mutation for Fanconi anemia [7, 8].

Discussion

Fanconi anemia is an inherited disorder of DNA repair with an increased predisposition to malignancies. It is an important differential of radial ray defects. These defects can be detected by ultrasonography, but establishing a definite diagnosis requires further testing.

In the present case, a possibility of Fanconi anaemia among other differentials was entertained based on ultrasonographic findings of radial ray defects. These findings were confirmed on fetal autopsy. Radial ray defect with a congenital heart disease was strongly suggestive of Holt Oram syndrome [9] and this was excluded only after the

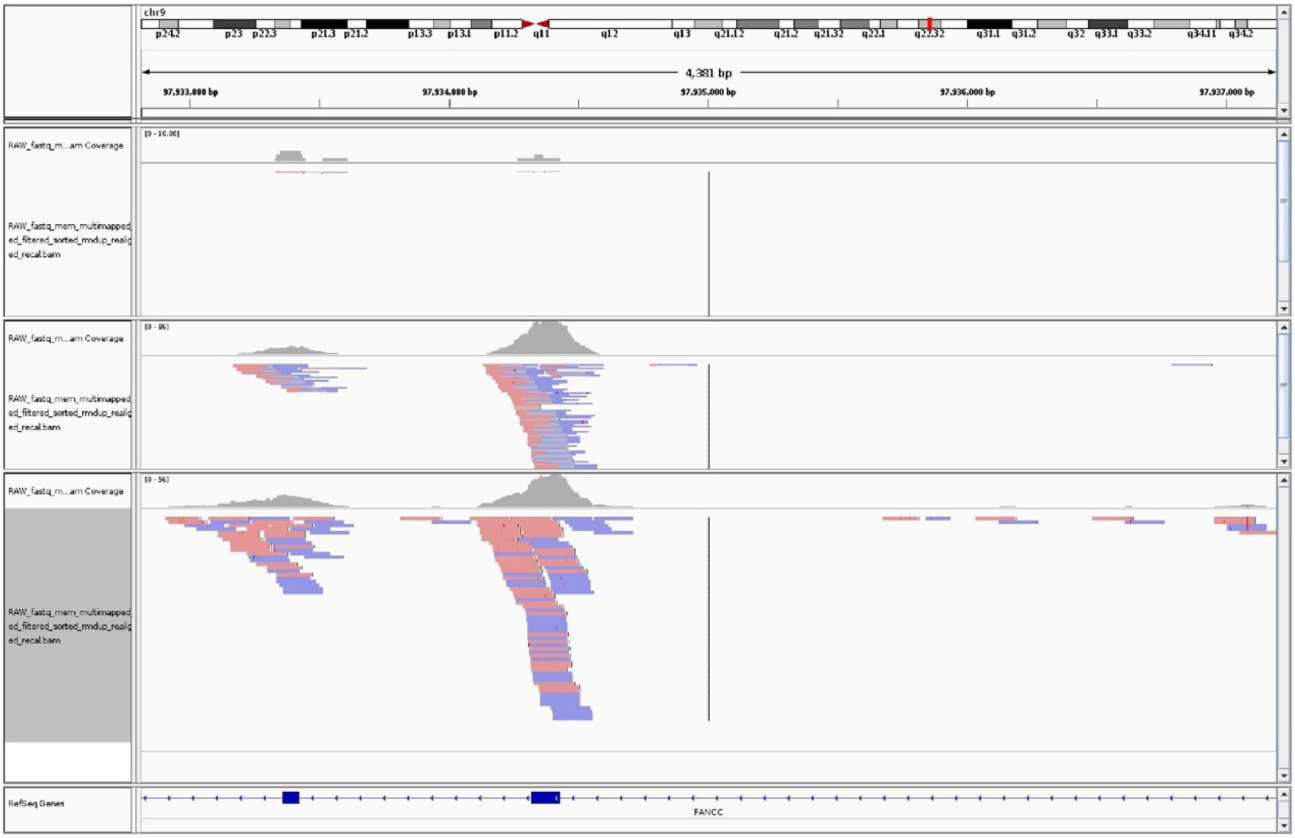
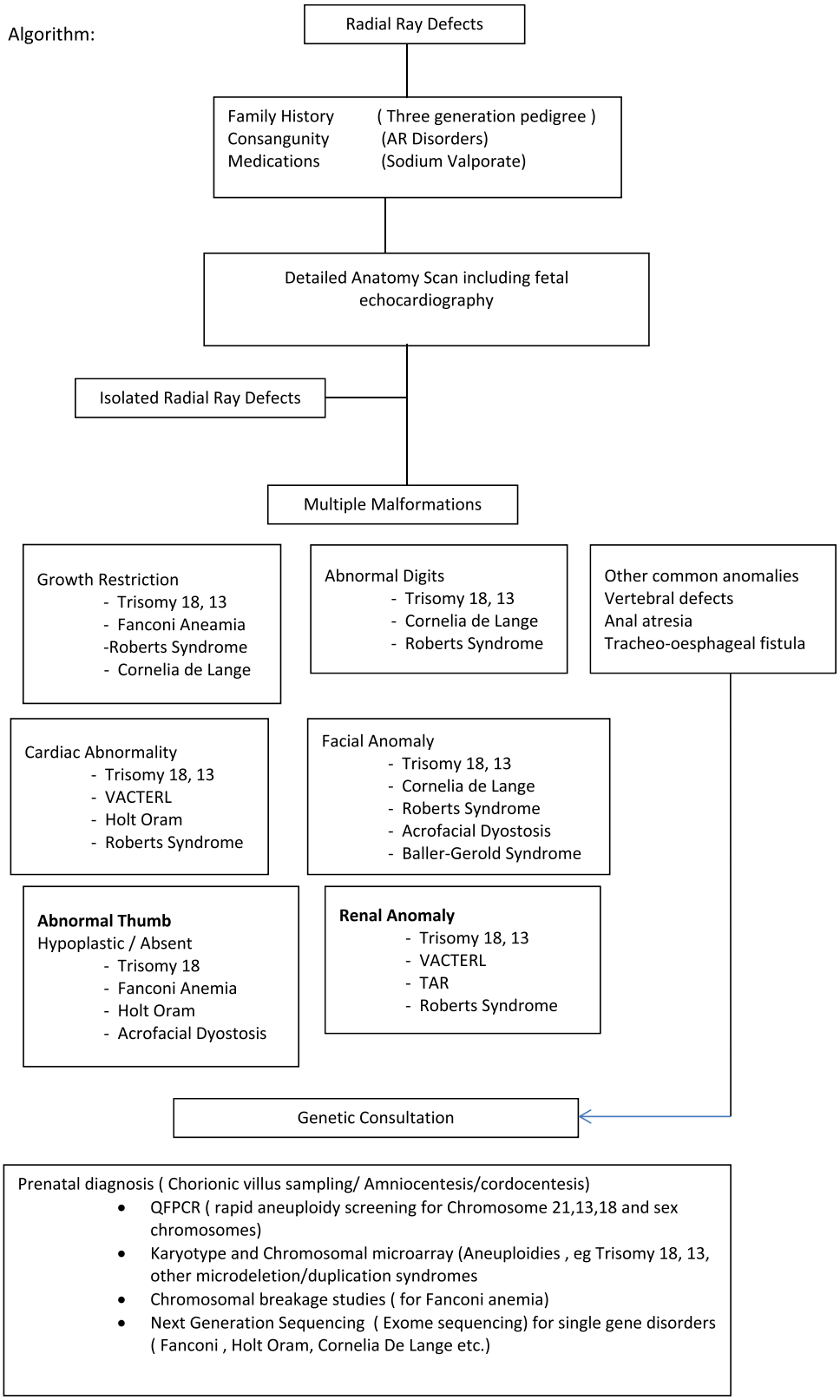


Fig. 2 IGV visualization of Exon 5-6 of FANCC gene in Clinical Exome of fetus Top window indicates no reads in Exon 5 and Exon 6 region when compared with other randomly selected control samples (Control1, Control2). This suggests a possibility of homozygous deletion. Coloured bar (Blue,Pink) represents mapped reads to the exonic region

chromosomal breakages were identified. The other common syndromes associated with radial ray defects like Thrombocytopenia absent radius, trisomy 18 and VACTERL association were excluded. SALL-4 related disorders are difficult to exclude on fetal autopsy and requires molecular testing. In a prenatal series of 66 cases with forearm anomalies, chromosomal anomalies and genetic syndromes accounted for 29.7% each and 23% had isolated forearm defects. In 70% of cases a correct prenatal diagnosis was made. Bilateral lesions or unilateral defects with additional malformations had a higher genetic basis compared to unilateral, isolated lesions [10].

Though exome sequencing is the first tier test for genetically heterogeneous monogenic disorders, it is not currently the standard practice for identification of germline copy number variations [11]. The comprehensive molecular testing for Fanconi anemia includes an NGS panels to examine all the genes associated with FA. However deletions–duplications associated with the phenotype require specific analysis, either of the NGS dataset or other molecular methods [12]. A defined clinical diagnosis allows for deeper interrogation to confirm the molecular diagnosis as in this case where the initial analysis of NGS data did not reveal any point mutation. However, reanalysis of data identified homozygous deletion of exon 4–6 in FANCC gene, highlighting the importance of a defined phenotype for molecular testing.

Accurate prenatal diagnosis is required for prognosis, management, genetic counseling including the risk of recurrence. In this case, timely detection helped the parents in making informed decisions. The risk of recurrence is 25% in each pregnancy as it is autosomal recessive (FANCC gene). The couple has been counseled about the option of prenatal diagnosis by CVS/amniocentesis for subsequent pregnancy. The first line of evaluation in the next pregnancy will be to offer prenatal diagnosis by CVS irrespective of the ultrasound findings. Management protocol is mentioned in the algorithm.



Genetic Counselling: It is imperative to mention that Fanconi anemia is a genetically heterogeneous condition. It can be inherited in an autosomal recessive manner, an autosomal dominant manner or an X-linked manner. The most common mode of inheritance is autosomal recessive with a risk of recurrence of 25% in each

pregnancy. Fanconi's can have physical, hematological or mixed presentation. Therefore even in the absence of radiological features prenatal diagnosis has to be offered in the form of CVS or Amniocentesis in the background of family history of an affected sibling.

Conclusion: Radial ray defects when diagnosed on ultrasound should raise a suspicion of associated syndromes. This case highlights the importance of detailed evaluation including fetal autopsy along with prenatal genetic testing to confirm the molecular etiology.

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