Received: 23 August 2022 | Revised: 1 December 2022 | Accepted: 14 December 2022

DOI: 10.1002/ccr3.6810

Clinical Case Reports Open Access WILEY

CASE REPORT

A novel *RAD51* variant resulting in Fanconi anemia identified in an infant with multiple congenital anomalies

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Abstract

Fanconi anemia, FA, is a rare, multi-system disease caused by pathogenic variants in DNA repair genes. We report a novel *RAD51* variant in an infant with FA whose tracheobronchomalacia has not been described in FA. His severe presentation expands the phenotype of *RAD51*-associated FA, reported only in three patients previously.

KEYWORDS

Fanconi anemia, heterozygote, microcephaly, premature infant, RAD51 Recombinase, tracheobronchomalacia, whole genome sequencing

1 | INTRODUCTION

Fanconi anemia (FA) is a rare genetic condition associated with pathogenic variants of several genes involved in DNA repair. Clinically, FA can present at birth with multiple congenital anomalies and growth restriction, and progresses over time with bone marrow failure and increased risk of malignancy. The average age of onset of bone marrow failure is 7.6 years, with a cumulative probability of occurrence of 90% by age 40 years.[1] The risk of developing

cancers, including acute myelogenous leukemia and head and neck squamous cell carcinomas, is 500-fold higher compared to the general population.[1] Of the 23 recognized genes causing FA, 21 cause diseases with an autosomal recessive pattern of inheritance. The remaining two genes include *FANCB*, which causes X-linked recessive FA (2% of FA cases), and *RAD51*, which causes autosomal dominant FA.[1] Because only three patients with *RAD51*-related FA have been reported to date, delineation of the phenotype and natural history of this FA sub-type is still incomplete.[2–4] All known FA-associated genes play a crucial role in DNA repair, specifically in the regulation of homologous recombination to repair DNA interstrand cross-links. When this repair mechanism is impaired, individuals with FA become highly sensitive to DNA damage.[5] Such sensitivity to DNA damage correlates with the clinical phenotypes and increased cancer susceptibility and is the basis for laboratory testing (chromosomal breakages studies) measuring chromosomal sensitivity to DNA cross-linking agents.

We report an infant with multiple congenital anomalies caused by a novel de novo *RAD51* heterozygous pathogenic variant. The clinical presentation and DNA sensitivity to cross-linking agents in the patient's cells support the diagnosis of Fanconi anemia. In this rare subtype of FA, termed 'FA-R', the heterozygous *RAD51* variant is thought to act in a dominant negative manner to disrupt DNA repair.[2,3] The three individuals with variants in *RAD51* resulting in FA have all presented an atypical phenotype distinguished by the absence of bone marrow failure and cancer.[2–4]

2 | CASE REPORT

This study was approved by the Institutional Review Board of the University of Utah and the Privacy Board of Intermountain Healthcare. Informed consent for the testing was obtained from the patient's family.

The male infant was the product of a spontaneous pregnancy and the third-born child of nonconsanguineous parents. He was born via vaginal delivery at 32 weeks and 1 day of gestation following premature rupture of membranes 3 days prior. Birth parameters were as follows (z scores from Fenton growth chart): weight 940 g (z score −7.09); length 35 cm (z score −7.95); occipitofrontal circumference 23.5 cm (z score −8.75); APGAR scores 5 at 1 min and 8 at 5 min. Multiple fetal anomalies were noted on prenatal imaging, including polyhydramnios, fetal growth restriction, fetal ventriculomegaly, cerebellar hypoplasia, and duodenal atresia. Prenatal testing, including cell-free DNA and amniocentesis with SNP microarray, were normal.

At birth he required transient positive pressure ventilation for poor respiratory effort with heart rate <100 beats per minute. He was transitioned to CPAP (continuous positive airway pressure), and an Anderson tube was placed. On postnatal evaluation, the infant was found to also have microcephaly, posteriorly rotated ears, cryptorchidism, imperforate anus, right thumb hypoplasia with a normal left thumb, syndactyly of 4th and 5th digits of both feet, and multiple muscular ventricular septal defects. No café-au-lait macules or other skin findings were present.

An exploratory laparotomy with loop colostomy was performed on day of life 1. This procedure was complicated by a pulseless electrical activity code event following loss of the patient's airway during a difficult intubation. Pulses returned after approximately 90 s of compressions and successful intubation. He was successfully extubated to non-invasive positive pressure ventilation on postoperative day (POD) 3, then weaned to low-flow nasal cannula on POD 19. On POD 21 the patient developed respiratory distress with increased work of breathing and retractions which required escalation to high flow-nasal cannula. Bedside flexible nasolaryngoscopy was performed on POD 26 and demonstrated laryngomalacia and redundant arytenoid tissue with collapse on inspiration. On POD 42 he was escalated from high-flow nasal cannula to CPAP due to unexplained desaturation events. Chest radiographs showed diffuse hazy opacities bilaterally, but these findings were mild and stayed consistent throughout his hospitalization without showing evidence of severe parenchymal lung disease.

He returned to the operating room on day of life 46 for duodenal atresia repair and microlaryngoscopy and bronchoscopy. The otolaryngologist noted glossoptosis and large arytenoids but were not floppy or obstructive. At the glottic level, minimal vocal cord movement was noted with edema at level of the vocal cords. On day of life 51, the patient failed multiple extubation attempts because of sustained oxygen desaturations and hypoventilation. Chest radiographs at this time showed the same opacities that had been noted prior with no development of further lung disease. Ventriculomegaly and craniosynostosis were closely followed and an Ommaya reservoir was placed at 77 days of age. Microlaryngoscopy and bronchoscopy were performed during this procedure and demonstrated severe edema of the glottis, tracheal inflammation, and friability, and severe tracheobronchomalacia. Adequate gas exchange was easily maintained on stable, low ventilator settings: synchronized intermittent mandatory ventilation with peak inspiratory pressure of 15–30 cm H_2O, positive end-expiratory pressure of 5, rate of 20, and tidal volume between 4.2 and 5.5 ml/kg. The FiO2 requirement was mostly between 24% and 30%. The low ventilator settings, combined with chest radiographs and the evaluation by

otolaryngology, pointed to the likelihood of the patient's respiratory distress being an airway obstruction rather than central apnea or parenchymal lung disease.

After multiple discussions regarding quality of life and acuity of care needs throughout the patient's lifetime, the family opted for palliative care and the child died on day of life 101. An autopsy was not performed.

2.1 | Whole genome sequencing and chromosomal breakage analysis

Because of the clinical presentation with multiple major and minor congenital anomalies, a genetics consultation was obtained on day of life 1. Given the broad differential diagnosis, a Carbohydrate Deficient Transferrin and Chromosomal Breakage analysis for Fanconi Anemia was obtained in addition to rapid whole genome sequencing (WGS). Consent was obtained and peripheral blood samples were collected from the patient and both parents. Whole genome sequencing, performed at Rady Children's Institute for Genomic Medicine, San Diego, CA, reported a de novo heterozygous variant in the *RAD51* gene NM_002875.3 c.880G>A (p.Ala294Thr) on day of life 8. Chromosomal breakage analysis of the patient's white blood cells showed sensitivity to DNA cross-linking agents consistent with FA.

Based on the diagnosis, the team developed a care plan with the following recommendations: (a) brain imaging and early intervention monitoring because of previously reported developmental and brain anomalies; (b) monitoring for bone marrow dysfunction (although anemia and bone marrow dysfunction had not been reported in *RAD51*-related FA, they are common in the larger family of FAs); (c) caution in the use of radiography, because of the presumed impairment in DNA repair. Genetic counseling with family highlighted the fact that the variant appeared to be de novo, suggesting low recurrence risk in future children of this young couple.

3 | DISCUSSION

This is the first description of a novel *RAD51* variant in an infant with FA, associated with tracheobronchomalacia which has not been previously reported. His severe presentation further expands the phenotype of *RAD51*-associated FA.

RAD51-associated FA is rare and appears to have an atypical FA-like phenotype. The c.880G>A (p.Ala294Thr) variant described in our patient has not previously been reported in the ClinVar gene database.[6] Functional assays on the neighboring amino acid c.877G>A, p.Ala293Thr demonstrated an impaired ability to aid in homologous recombination, suggesting a dominant negative mechanism.[2] The reported variants in *RAD51*-associated FA are located in a highly conserved region, crucial to the production of functional RAD51 protein for DNA repair.

The variants in the three other patients with *RAD51*-associated FA reported to date (Table 1) were: c.877G>A, (p.Ala293Thr)[2]; c.391A>C, (p.Thr131Pro)[3]; and c.725A>G, (p.Gln242Arg).[4] Findings common to these three patients and our patient included chromosome instability, hypoplastic thumb, and microcephaly (Table 1). The other three patients had not yet developed cancer or bone marrow failure (cases reported at 13, 23, and 9 years of age).[2–4] Our patient had normal peripheral blood cell counts. His short survival (<4 months) did not allow for a meaningful evaluation of the risk for cancer or bone marrow failure, as these complications do not typically occur in infancy. Similarly, developmental and/or intellectual delay were observed in the other three patients but were not able to be assessed in our patient due to his short survival.

The more common autosomal recessive forms of Fanconi anemia have a broad range of phenotypic presentations. Some features present more frequently and include growth deficiency/short stature (43%), upper limb skeletal abnormalities (35%–40%), abnormal skin pigmentation (37%–40%), renal malformations (20%–27%), microcephaly (20%–27%), and male genitourinary tract abnormalities (15%–25%).[1,7] Including our patient, all four patients with *RAD51* variants have presented with growth deficiency, hypoplastic thumb, and microcephaly.[2–4] Our patient also had some less common FA features, including central nervous system defects (3%–11%), gastrointestinal tract defects (5%), congenital heart defects (6%–12%), and lower limb abnormalities (5%).[1,7] The other patients with *RAD51*-associated FA (Table 1) had central nervous system defects[2–4] and 1 had gastrointestinal tract defects.[2] None of the three other patients had congenital heart defects or lower-limb abnormalities. Genitourinary abnormalities are reported in our patient and one previously reported patient with *RAD51*-associated FA.[2] Although not seen in our patient, abnormal skin pigmentation[3,4] and renal malformations[3] have been reported in 2 and 1 of the previously reported patients, respectively. The severe tracheobronchomalacia that complicated intubation and extubation attempts was unusual and does not appear to have been reported previously in FA.[1,7] The inability to extubate was likely secondary to the severe tracheobronchomalacia and glottis edema and less likely to intrinsic lung disease given the stable chest radiographs, low ventilator settings, and minimal FiO_2. While prolonged intubation could contribute to the tracheobronchomalacia, its severity, disproportionate to the degree of prematurity, raises the possibility that this could be a novel finding in this rare form of FA.

TABLE 1 Clinical findings and gene variant information in the four described patients with *RAD51*-associated Fanconi anemia

	Patient 1 this report	Patient 2 Ameziane et al.[2]	Patient 3 Wang et al.[3]	Patient 4 Takenaka et al.[4]
RAD51 variant	c.880G>A (p.Ala294Thr)	c.877G>A, (p.Ala293Thr)	c.391A>C, (p.Thr131Pro)	c.725A>G, (p.Gln242Arg)
General	Growth deficiency	Growth deficiency, intellectual disability	Slight developmental delay that resolved in adolescence	Growth deficiency, intellectual disability, developmental delay
CNS	Microcephaly, cerebellar hypoplasia, ventriculomegaly	Microcephaly, hydrocephalus	Microcephaly, Type I Chiari malformation, tethered spinal cord	Microcephaly
Eyes/Ears	Posteriorly rotated ears		Microphthalmia, unilateral hearing loss	Myopia, strabismus, bilateral hearing impairment
Cardiac	3 muscular ventricular septal defects			
Pulmonary	Laryngomalacia, redundant arytenoid tissue, tracheo-bronchomalacia			Laryngomalacia
GI	Duodenal atresia, imperforate anus	Imperforate anus		Gastroesophageal reflux
GU	Cryptorchidism	Improperly formed left testicle	Pelvic left kidney	
Musculo-skeletal	Hypoplastic right thumb, bilateral syndactyly of the 4th and 5th digits of both feet	Thumb and radius abnormalities	Radial dysplasia, hypoplastic thumb, scoliosis, absence of L4 and L5 spinous processes	Hypoplastic thumb, scoliosis
Other			Café au lait macules	Café au lait macules

However, small size from prematurity cannot be excluded as contributing to the patient's respiratory complications. Additionally, one of the described patients with *RAD51*-associated FA had laryngomalacia for which she received supplemental oxygen for until the age of 6 years[4] (Table 1). This should be taken into consideration as another possible example of a structural respiratory abnormality linked to this form of FA, but her other phenotypic features (developmental delay, growth restriction, and microcephaly) cannot be ruled out as contributing factors.

The *RAD51* gene is located on chromosome 15 and encodes the DNA repair protein RAD51 Recombinase. RAD51 protects the replication fork of DNA from interstrand cross-links, which are produced in the presence of toxins, chemotherapeutic agents, and metabolic byproducts.[5] When interstrand cross-links are introduced into replicating DNA, RAD51 binds DNA and prevents its unwinding and continued processing so it can be repaired. RAD51 then acts during homologous recombination by mediating homologous strand exchange.[3]

Experiments on mice lacking FA genes have shown that bone marrow failure and skeletal abnormalities result, at least in part, from impaired differentiation of mesenchymal progenitor cells. Mesenchymal progenitor cells differentiate into osteoblasts, chondrocytes, and several other cell types. While the role of defective osteoblasts has been linked to bone anomalies in FA, chondrocyte function has yet to be explored and, if proven to be altered by abnormal RAD51, could provide an explanation for undescribed FA phenotypes like those observed in our patient. For example, chondrocyte dysfunction could conceivably be linked to the development of airway cartilage abnormalities, such as those observed in our patient but not described in typical FA cases. Experiments involving FA gene knockouts have only assessed the three most common genes in FA (*FANCA*, *FANCC*, and *FANCG*). Further research on the effect of defective *RAD51* on mesenchymal progenitor cell differentiation may reveal downstream effects not yet observed in other FA gene variants.[8]

Despite the inability to assess bone marrow failure and malignancy in our patient due to his short survival, the similarities of the other physical findings in all four patients suggests a relatively consistent though expanding phenotype for this rare subgroup of FA.[2–4] Since only three prior *RAD51*-associated cases have been reported to date, it is difficult to discern which characteristics in our patient, such as the respiratory tract anomalies, can be attributed to prematurity verses the underlying condition. Long-term follow up of the surviving patients with this form of FA is crucial before conclusions can be made on the risk of malignancy and bone marrow failure. For the time being, it is reasonable to follow the same recommendations of limiting radiation, monitoring for malignancy, and monitoring for bone marrow failure as outlined for all patients with FA.[1]

This report adds to the growing data on the significance of the *RAD51* gene in DNA repair and the pathogenesis of Fanconi anemia. This report describes a patient with tracheobronchomalacia disproportionate to the degree of his prematurity, which has not been described in the other patients with this condition and may add to the phenotype of *RAD51*-associated FA.

AUTHOR CONTRIBUTIONS

Shelby Geilmann: Conceptualization; data curation; visualization; writing – original draft; writing – review and editing. **Rachel Solstad:** Writing – original draft; writing – review and editing. **Rachel Palmquist:** Writing – original draft; writing – review and editing. **Josue Flores Daboub:** Writing – original draft; writing – review and editing. **Lorenzo D. Botto:** Writing – original draft; writing – review and editing. **Peter H. Grubb:** Writing – original draft; writing – review and editing. **Josh L. Bonkowsky:** Writing – original draft; writing – review and editing. **Nicola Longo:** Writing – original draft; writing – review and editing. **Sabrina Malone Jenkins:** Conceptualization; data curation; visualization; writing – original draft; writing – review and editing.

ACKNOWLEDGMENTS

Thanks to funding from the Center for Personalized Medicine, Primary Children's Hospital and Intermountain Precision Genomics, Intermountain Healthcare.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT

Written informed consent was obtained from the patient's parents to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Geilmann S, Solstad R, Palmquist R, et al. A novel *RAD51* variant resulting in Fanconi anemia identified in an infant with multiple congenital anomalies. *Clin Case Rep*. 2023;11:e06810. doi:10.1002/ccr3.6810