Case Report

Mid-trimester dilated fetal bowel leading to diagnosis of interstitial duplication 46,XX,dup(8)(q21.13q21.2) associated with extensive neonatal jejuno-ileal atresia

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Small bowel atresia constitutes congenital obstruction of the lumen of the duodenum, jejunum or ileum, and is one of the most common causes of neonatal bowel obstruction with a reported incidence of between 1.3 and 2.8 per 10,100 live births. Complete absence of the small bowel, or near total jejuno-ileal atresia (in the absence of malrotation or gastoschisis), are extremely rare. Mid-trimester prenatal sonographic finding of dilated fetal bowel led to the finding of interstitial 8q21.13q21.2 duplication. Following delivery at 32 weeks’ gestation, at laparotomy almost complete small bowel atresia was noted. Anastomosis between the existing small bowel and colon was performed. At 7 months of age, the infant continued to receive total parenteral nutrition supplemented by gastrosomy and oral-spoon formula feeding, and weighed 7 kg (50th centile). This is the first report of the association interstitial 8q21.13q21.2 duplication, which includes OMIM genes (RALYL, LRRCC1, and E2FS) and extensive small bowel atresia.

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Introduction

The most common etiology of neonatal intestinal obstruction is atresia [1]. Of 53 cases of neonatal intestinal obstruction reported by Singh and Pathak, more than half (27 cases) were intestinal atresia [1]. Of these, 9 cases (17%) were duodenal atresia, 7 cases (13%) jejunal atresia and 8 cases (13%) resulted from colonic atresia. Seven cases resulted from malrotation and 17 cases (32%) resulted from Hirshprung’s disease. Of the 27 cases of intestinal atresia, 8 (29.6%) manifested associated anomalies including 2 cases with anorectal malformation, 2 case with volvulus, one each with malrotation and meconium ileus, respectively [1]. Other rare etiologies of neonatal bowel (duodenal) obstruction include annular pancreas [2,3]. Small bowel atresia constitutes a congenital obstruction of the

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https://doi.org/10.1016/j.radcr.2022.08.021
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lumen of the duodenum, jejunum or ileum and is one of the most common causes of neonatal bowel obstruction occurring with an incidence of between 1.3 and 2.8 per 10,100 live births [4]. We report an unusual case in which mid-trimester sonographic diagnosis of dilated loops of fetal bowel led to diagnosis of interstitial 8q21.13q21.2 duplication and later confirmed extensive isolated neonatal small bowel atresia, consisting of almost complete absence of the jejunum and ileum.

Case report

A 22-year-old patient was followed during her first pregnancy. Her previous medical history was unremarkable. Genetic counseling at 22 weeks’ gestation following sonographic finding of dilated fetal bowel (Fig. 1), revealed a 3-generation family history unremarkable for birth defects, stillbirths, intellectual disabilities, recurrent pregnancy loss, early cancer diagnoses, and other known genetic conditions. Consanguinity was denied. She underwent amniocentesis with FISH, karyotype, microarray, AFAFP, and CFTR sequencing, in addition to pan-ethnic expanded carrier screening for autosomal recessive and x-linked disease risk. Both partner carrier-screening results were negative for all 274 conditions screened. FISH and karyotype identified 46,XX. Whole genome SNP-based microarray results reported a 2.6MB interstitial duplication 8q21.13q21.2(83,533,348-86,091,081)x3. This duplicated interval includes 3 OMIM genes, RALYL, LRRC1, and E2F5. No clinically established disorders have currently been reported with duplications of this region. No other DNA copy number changes or copy neutral ROH were detected within the present reporting criteria.

Since genetic duplication syndrome of this region has not been previously described, the copy number variant was reported as a variant of uncertain significance. The patient and her partner both elected to undergo parental qPCR studies to determine whether the duplicated region is inherited or de novo. Maternal follow-up variant-targeted qPCR analysis revealed direct inheritance of the duplication found in the prenatal analysis. Direct inheritance of a copy number variant from a phenotypically normal parent is generally considered not to be clinically significant. However, caution should be applied to this conclusion since incomplete penetrance or variable expressivity of symptoms can be associated with novel regions of imbalance for which the phenotypic spectrum has not been established. We also reviewed the 50% inherited risk for each of the patient’s offspring and subsequent pregnancies. If the patient inherited the duplication from a parent, 50% of her siblings would be expected to be obligate carriers. Family testing may be considered for family members of reproductive age, for genotype-phenotype correlation.
At 33 weeks' gestation, following premature rupture of the membranes and labor, Cesarean delivery was performed due to breech presentation. Birth weight was 1,950 grams and Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. Following birth, the infant underwent abdominal X-ray, which demonstrated a triple bubble sign with concern for proximal jejunal atresia. Thus neonatal imaging confirmed bowel obstruction. At laparotomy, almost complete small bowel atresia was noted. Only 7-8 cm of proximal jejunum and a small nubbin of terminal ileum were present. In essence, almost the entire small bowel was absent. The total length of the small bowel including the jejunum and ileum measured only about 10-11 cm in total. Anastomosis between the existing small bowel and colon was performed. At 7 months of age, the infant continues to receive total parenteral nutrition supplemented by gastrostomy and increasing oral-spoon formula feeding, and weighs 7 kg (50th centile).

**Discussion**

The duplicated interval in our case included 3 OMIM genes, RALYL, LRRCC1, and E2F5. As mentioned above, no clinically established disorders have hitherto been reported with duplications of this region.

RALYL is a protein-coding gene although its functionality is currently not well understood. It has been considered that it may be a member of hNRNPC (heterogeneous nuclear ribonucleoproteins) subfamily. Expression pattern was detected by multiple-tissue cDNA panel although the transcript was expressed highest in fetal brain tissue [5].

Leucine-Rich Repeat and Coiled-Coil Domain-Containing Centrosomal Protein 1 (LRRCC1) is a centrosome-associated protein required for maintenance of parent and progeny centriole contact and organization of mitotic spindles [6]. Overexpression causes chromatin condensation and nuclear fragmentation, characteristic of apoptosis [6]. It is found to be expressed in all adult and fetal tissues examined, with highest content in adult brain, followed by testis and ovary [6].

E2F Transcription Factor 5 (E2F5) encodes a predicted 345 amino acid protein that is 69% identical to E2F4 and is a transcription factor involved in TGF-beta superfamily of ligands [7]. Previously known as the ultimate recipients of CKD regulatory signals, E2F4/E2F5 and p107, act as transducers of TGF-beta receptor signals upstream of CDK. SMAD proteins therefore mediate transcriptional activation or repression depending on associated partners [8].

The accuracy of prenatal ultrasound in detecting non-duodenal jejunal and ileal atresia is extremely variable. Vrigone et al. in 2014, conducted a systematic review and meta-analysis and reported highly variable detection rates with values ranging between 10% and 100% with an overall prediction of 50.6% (95% confidence interval [CI], 38.0%-63.2%) [4]. When analyzed separately, detection rates of jejunal and ileal atresia were 66.3% (95% CI, 33.9%-91.8%) and 25.9% (95% CI, 4.0%-58.0%), respectively. Interestingly, in this report of 16 studies involving 649 fetuses, prenatal sonographic findings of fetuses with small bowel atresia, both dilated loops of bowel and polyhydramnios provided a low overall detection rate of non-duodenal small bowel atresia [4].

Total absence of the small bowel or near total jejuno-ileal atresia (in the absence of associated malrotation or gastroschisis), as in our above-described case are extremely rare [9,10]. Systematic English literature search (PubMed, MEDLINE) between 1966 and 2022 utilizing the search terms “prenatal ultrasound,” “small bowel atresia,” and “intestinal 8q21.13q21.2 duplication” confirm that morphologic findings associated with interstitial duplication 8q21.13q21.2 have not been reported previously. This rare case of extensive small bowel atresia emphasizes the inability of prenatal ultrasound to predict the degree of neonatal gastrointestinal atresia and the importance of obtaining microarray analysis following the prenatal sonographic depiction of structural fetal anomalies.

**Patient consent**

Please note that we have obtained the patient's informed consent for publishing our Case Report entitled: Small Bowel Atresia Associated with Intestinal Duplication 46,XX,dup(8)(q21.13q21.2).

**References**

[1] Singh V, Pathak M. Congenital neonatal intestinal obstruction: retrospective analysis at tertiary care hospital. J Neonatal Surg 2016;4(4):. doi:10.21699/ns.v5i14.393.

[2] Almoamin HAA, Kadem SH, Saleh AM. Annular pancreas in neonates; case series and review of literatures. Afr J Paediatr Surg 2022;19(2):97–101. doi:10.4103/ajps.180.20.

[3] Weiss H, Sherer DM, Manning FA. Ultrasonography of fetal annular pancreas. Obstet Gynecol 1999;94(5 Pt 2):852. doi:10.1016/s0029-8484(99)00498-6.

[4] Vrigone C, D’Antonio F, Khalil A, Jonh R, Manzoli L, Giuliani S. Accuracy of prenatal ultrasound in detecting jejunal and ileal atresia. Ultrasound Obstet Gynecol 2015;45(5):523–9. doi:10.1002/uog.14651.

[5] Ji CN, Chen JZ, Xie Y, Wang S, Qian J, Zhao E, et al. A novel cDNA encodes a putative hRALY-like protein, hRALYL. Mol Biol Rep 2008;35(1):61–7. doi:10.1007/s11033-007-9281-x.

[6] Muto Y, Yoshioka T, Kimura M, Matsunami M, Saya H, Okano Y. An evolutionarily conserved leucine-rich repeat protein CLERC is a centrosomal protein required for spindle pole integrity. Cell Cycle 2008;7(17):2738–48. doi:10.4161/cc.7.17.6591.

[7] Sardet C, Vidal M, Cobrinik D, Gong Y, Onufryk C, Chen A, et al. E2F-4 and E2F-5, two members of the E2F family, are expressed in the early phases of the cell cycle. Proc Natl Acad Sci 1995;92(6):2403–7. doi:10.1073/pnas.92.6.2403.

[8] Chen CR, Kang Y, Siegel PM, Massagué J. E2F4/5 and p107 as Smad cofactors linking the TGF-beta receptor to c-myc repression. Cell 2002;110(1):19–32. doi:10.1016/s0092-8674(02)00801-2.

[9] Besner GE, Bates GD, Boesel CP, Singh V, Welty SE, Corpron CA. Total absence of the small bowel in a premature neonate. Pediatr Surg 2005;40(5):396–9. doi:10.1017/s0038-0033-1358-9.

[10] Sham M, Singh D. Near total jeuno-ileal atresia: a management challenge. J Clin Neonatol 2013;2(2):103–5. doi:10.4103/2249-4837.16413.