Necrotizing Enterocolitis in Two Siblings and an Unrelated Infant with Overlapping Chromosome 6q25 Deletions

Hannah C.D. Esdal^a Muhammad B. Ghbeis^j Daniel A. Saltzman^c
Donavon Hess^c Janet R. Hume^d Robyn C. Reed^g Susan A. Berry^e
Eric Hoggard^f Betsy Hirsch^b Linda B. Baughn^h Lisa A. Schimmentiⁱ

^aDepartment of Pediatrics, and ^bDivision of Molecular Pathology and Genomics, Department of Laboratory Medicine and Pathology, University of Minnesota, ^cDepartment of Pediatric Surgery, Divisions of ^dCritical Care and ^eGenetics and Metabolism, Department of Pediatrics, and ^fDivision of Pediatric Radiology, Department of Radiology, University of Minnesota Masonic Children's Hospital, and ^gDepartment of Pathology, Children's Hospitals and Clinics of Minnesota, Minneapolis, MN, ^hDivision of Laboratory Genetics and Genomics, Department of Laboratory Medicine and Pathology, and ⁱDepartment of Otorhinolaryngology and Clinical Genomics, Mayo Clinic, Rochester, MN, and ^jDivision of Cardiovascular Critical Care, Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

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Abstract

The pathogenesis of necrotizing enterocolitis (NEC) remains poorly understood but is thought to be multifactorial. There are no specific recurring chromosomal abnormalities previously associated with NEC. We report 3 cases of intestinal necrosis associated with large chromosome 6 deletions. The first patient was found to have a 7.9-Mb deletion of chromosome 6 encompassing over 40 genes, arr[GRCh37] 6q25.3q26(155699183_163554531)×1. The second patient had a 19.5-Mb deletion of chromosome 6 generated by an unbalanced translocation with chromosome 18, 46,XY,der(6)t(6;18)(q25.1;p11.23), arr[GRCh37] 6q25.1q27(151639526_171115067)×1, 18p11.32p11.23(131700_7694199)×3, which included the whole 7.9-Mb region deleted in the first patient.

The third patient was the younger sibling of the second patient with an identical derivative chromosome 6. The shared abnormal chromosome 6 region includes multiple genes of interest, particularly *EZR*. Mouse models have demonstrated that *Ezr* is expressed in microvillar epithelium and helps regulate cell-cell adhesion in the gut. We hypothesize that deletion of this shared region of 6q leads to gastrointestinal vulnerability which may predispose patients to intestinal necrosis.

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Necrotizing enterocolitis (NEC) is characterized by intestinal ischemic necrosis and is among the most common surgical emergencies associated with high morbidity and mortality in neonates [Gephart et al., 2012]. NEC occurs in approximately 0.1% of all live births and 3–12% of very low-birth-weight infants (<1,500 g), with a risk

inversely related to gestational age [Dominguez and Moss, 2012]. NEC may also rarely occur in term and late-preterm infants with underlying conditions [Dominguez and Moss, 2012; Gephart et al., 2012; Christensen et al., 2013]. The exact pathogenesis of NEC is poorly understood. Multiple risk factors have been implicated including prematurity, sepsis, and congenital heart disease [Dominguez and Moss, 2012; Gephart et al., 2012; Christensen et al., 2013]. A genetic basis for NEC has also been considered, but only a few studies have suggested specific polymorphisms that may be associated with an increased risk of the disease [Treszl et al., 2003; Szebeni et al., 2006; Moonen et al., 2007; Sampath et al., 2011]. Additionally, some individual infants have been reported who developed NEC and had known microdeletions [Cichocki et al., 2008; Burjonrappa and Schwartzberg, 2016]. Current literature does not describe any specific recurrent chromosomal abnormalities associated with NEC.

We report 3 cases of intestinal necrosis associated with deletions of the long arm of chromosome 6. Both interstitial and terminal deletions of 6q are rare [McLeod et al., 1990; Hopkin et al., 1997]. Terminal deletions of 6q were first reported in 1973 and have since been characterized by a common phenotype of developmental delay, facial dysmorphisms, seizures, and brain abnormalities [Mikkelsen and Dyggve, 1973; Hopkin et al., 1997; Eash et al., 2005; Elia et al., 2006; Striano et al., 2006]. Critical regions within the terminal portion of 6q have previously been described to include 6q27. For example, the *C6orf70* gene maps to 6q27 and is thought to have a role in periventricular heterotopia [Conti et al., 2013]. Interstitial deletions of 6q were first reported in 1975 and are more commonly characterized by developmental delay, ear anomalies, hypotonia, and postnatal growth retardation [Milosević and Kalicanin, 1975; Nagamani et al., 2009]. Critical regions for interstitial 6q deletions have also been proposed, specifically the 6q25.3 region which contains the *ARID1B* gene [Ronconi et al., 2016]. The 3 cases we report include 1 patient with an interstitial deletion of 6q and 2 siblings with an unbalanced translocation resulting in a terminal deletion of 6q. All 3 patients share an overlapping region of chromosome 6 copy number loss that spans 7.9 Mb from 6q25.3 to 6q26.

Clinical Reports and Results

Patient 1

The patient was a 16-month-old female born at 36 weeks and 3 days gestational age with acyanotic tetralogy of Fallot characterized by a large ventricular septal defect, overriding aorta, mildly

Fig. 1. Abdominal radiographs. Patient 1: **A** Anteroposterior view showing diffusely dilated bowel with circumferential pneumatosis of the colon (red arrow) and branching portal venous gas in the liver (yellow arrow). **B** Left lateral decubitus view showing diffusely dilated bowel with air fluid levels, no free air, but linear pneumatosis (arrow) and portal venous gas. Patient 2: **C** Anteroposterior view showing extensive linear and circumferential pneumatosis (arrow) in the right lower quadrant. **D** Cross-table lateral view showing extensive linear and circumferential pneumatosis (arrow), but no free air. Patient 3: **E** Supine abdomen X-ray showing diffuse dilated small bowel and linear pneumatosis of the ascending colon (arrow) extending into cystic pneumatosis in the transverse colon.

dysplastic pulmonary valves, and small branch pulmonary arteries. Her appearance was remarkable for microcephaly, large simplified helices of the ears which were posteriorly rotated and low set, broad nasal tip, high-arched palate, hypoplastic fingernails, fifth digit clinodactyly, and generalized hypotonia. Medical history was also notable for global developmental delay and failure to thrive for which she received a gastrostomy tube. Ophthalmologic exam demonstrated nystagmus with alternating esotropia and de-

Fig. 2. Intestinal pathology. Gut ischemic necrosis in 2 patients with chromosome 6q25 deletions. All samples show loss of villous and surface epithelium (red arrows). Pneumatosis is present in patient 1 (green arrows). Patient 1: stomach (A) and jejunum (B). Patient 2: small intestine (C, D). HE. $\times 40$ –100.

layed pupillary response with potentially abnormal optic nerves; an electroretinogram was not performed. Distortion product otoacoustic emissions were absent in her left ear and present in the right. Skeletal survey revealed mild osteopenia with unremarkable endocrine studies including normal vitamin D, phosphorus, and magnesium levels. Brain MRI was within normal limits, and no seizure activity was noted.

At 4 months of age, she was hospitalized with RSV bronchiolitis and possible pneumonia and required mechanical ventilation. At 6 months of age, after clinical recovery from this infection, a pulmonary artery band was placed; her ventricular septal defect was not repaired due to a diminutive superior vena cava and inferior vena cava preventing required intraoperative cardiac bypass cannulation. At 14 months of age, the patient underwent pulmonary artery band removal and ventricular septal defect patch closure; her postoperative course was complicated by a complete heart block requiring permanent pacemaker implantation. On postoperative day 5, she developed fever, bloody stools, and abdominal compartment syndrome (Fig. 1). She underwent emergent decompressive laparotomy which showed signs of small bowel necrosis, managed initially with a silo, but upon re-exploration subtotal ischemia was discovered prompting extensive resection. Histopathological examination revealed widespread transmural isch-

emic necrosis with focal acute serositis (Fig. 2), consistent with NEC. After a protracted hospital course, she developed multisystem organ failure and died. The exact etiology for disturbed gut perfusion and resultant intestinal necrosis was not clearly identified. Her parents declined an autopsy.

Cytogenetic analysis by G-banding revealed a deletion of 6q that initially appeared to be terminal with a karyotype of 46,XX,del(6)(q25.3). However, using a custom oligonucleotide microarray (Agilent 180,000 platform), this deletion was more definitively characterized as interstitial, with refined breakpoints arr[GRCh37] 6q25.3q26(155699183_163554531) $\times 1$ (Fig. 3). This finding represents a 7.9-Mb deletion that includes over 40 genes (Table 1). The North Dakota newborn blood spot screening was initially abnormal for amino acids and acylcarnitines and was not repeated.

Patient 2

The second patient was a 6-month-old male born at 39 weeks and 2 days gestational age. His appearance was notable for a triangular-shaped head, hypertelorism, ankylosis of the left eyelid, small ocular apertures, incomplete cleft of the soft palate, hypoplastic fingernails, finger contractures, sternal skin tag, and hypertonica. Fetal imaging had demonstrated hydrocephalus and a

Fig. 3. A Chromosome 6 with arrows indicating the deleted region in patient 1. Chromosome images for patient 2 and 3 are unavailable. **B** Aligent array for chromosome 6 in patient 1 with deleted region highlighted and hg19 coordinates listed beneath. **C** View of UCSC genome browser for deleted area with candidate genes highlighted.

horseshoe kidney without renal artery stenosis, confirmed on postnatal imaging. MRI of the brain and spine were remarkable for dilated lateral and third ventricles consistent with aqueductal stenosis, abnormal corpus callosum, and a small cerebellum. The patient underwent an endoscopic third ventriculostomy and external ventricular drain placement within the first month of life. Distortion product otoacoustic emissions were absent in both ears. The echocardiogram showed a small atrial septal defect. The patient was noted to have hypertension at baseline of unclear etiology managed with amlodipine. He also had intestinal malrotation and underwent a Ladd's procedure with appendectomy and gastrostomy tube placement within the first month of life prior to discharge home.

The patient subsequently presented at 2 months of age with vomiting and irritability. He underwent emergent exploratory laparotomy and was found to have gastric fundus necrosis with small bowel perforation resulting in an *Escherichia coli* septic shock. Total gastrectomy, proximal jejunum resection, duodenostomy, and jejunostomy were performed. Histopathological examination revealed extensive transmural ischemic necrosis of the stomach and jejunum (Fig. 2). Following the gastrectomy, his hospital course was complicated by duodenal perforation one week later which was repaired. He developed a distal esophageal leak leading to emergent placement of an orogastric tube to occlude the esophageal opening. The patient was also noted to have abnormal mouth movements and bilateral rhythmic movements of his arms during the first month of this admission. His EEG was inconclusive; however, BRAINZ monitor (real time, amplitude-integrated EEG) suggested subclinical seizures leading to initiation of treatment with Keppra. A repeat brain MRI at this time showed worsening

hydrocephalus with new intraparenchymal and scattered sub-arachnoid hemorrhage. A prolonged hospital course included recurrent episodes of intestinal pneumatosis with features suggestive of NEC (Fig. 1) and multi-organ failure. The patient developed fever, abdominal distention, bloody stools, and died. Abdominal X-rays from this time demonstrated widespread pneumatosis and free air, suggestive of bowel perforation. CSF cultures were obtained and positive for coagulase-negative *Staphylococcus aureus*. Autopsy identified dense intra-abdominal adhesions; the remaining bowel was largely viable with focal areas of mucosal necrosis. There was no gross or microscopic evidence of ischemic necrosis suggestive of NEC of the remaining bowel. Acute bronchopneumonia involving both lower lobes and the left upper lobe was the likely proximate cause of death. The exact etiology for disturbed gut perfusion and resultant gastric and initial intestinal necrosis was not identified.

Cytogenetic analysis by G-banding revealed a derivative chromosome 6 with its distal long arm replaced by an extra copy of the short arm of chromosome 18, resulting from an unbalanced translocation. The karyotype was designated as 46,XY,der(6)t(6;18)(q25.1;p11.23). These regions of 6q loss and 18p gain were further characterized by microarray (Agilent custom 180,000 probe platform) as arr[GRCh37] 6q25.1q27(151639526_171115067)×1,18p11.32p11.23(131700_7694199)×3 (Fig. 3). The copy number loss on chromosome 6 spans approximately 19.5 Mb and encompasses more than 90 genes. The region of copy number gain on chromosome 18 spans approximately 7.6 Mb. The patient's father was subsequently found to carry the balanced form of this translocation 46,XY,t(6;18)(q25.1;p11.23). A review of the family history also revealed that a paternal great aunt carried the

Table 1. Genes within the shared deleted region arr[GRCh37] 6q25.3q26(155699183_163554531)×1

Gene symbol
<i>NOX3, tRNA-Pseudo, LOC105378068, MIR1202, SNORD28B, ARID1B, MIR4466, TMEM242, ZDHHC14, MIR3692, AK092386, SNX9, SYNJ2, AK026758, SYNJ2-IT1, SERAC1, GTF2H5, TULP4, SNORA116, MIR7161, TMEM181, DQ586009, DYNLT1, SNORA116, SYTL3, MIR3918, EZR, AX747826, EZR-AS1, OSTCP1, C6orf99, RSPH3, TAGAP, LOC101929122, FNDC1, AK130765, MIR_633, LINC02529, BC016015, SOD2, WTAP, LOC100129519, SOC2OT1, ACAT2, TCP1, SNORA20, SNORA29, MRPL18, PNLDC1, MAS1, IGF2R, AIRN, LOC729603, SLC22A1, SLC22A2, SLC22A3, LPAL2, LPA, PLG, MAP3K4, AGPAT4, AGPAT4-IT1, PRKN (PARK2), LOC105378098, PACRG, PACRG-AS2, AK058177</i>
Sources: RefSeq and UCSC Genome Browser (ucsc.genome browser; hg19), order approximate.

same balanced translocation and experienced multiple pregnancy losses. The patient's Minnesota newborn blood spot screen was normal.

Patient 3

The third patient is a male sibling of the second patient born 4 years later. He was born at 38 weeks and 2 days of gestational age and the presence of the unbalanced chromosome translocation had been demonstrated on prenatal cytogenetic testing. Additional prenatal workup included fetal ultrasounds which showed normal growth, agenesis of the corpus callosum, ventriculomegaly, hypoplasia of the cerebellum, enlarged cisterna magna, resolved cystic hygroma, tricuspid valve thickening, horseshoe kidney, and a 2-vessel cord. At the time of birth, his appearance was notable for a flat nasal bridge, mild micrognathia, cleft of the soft palate, low-set ears, broad and slightly webbed neck, curvature of the lower spine, sacral dimple, and diffuse hypotonia. Postnatal spinal ultrasound demonstrated a tethered cord with a conus level at L4–5 and a sacral meningocele. Subsequent brain MRI confirmed agenesis of the corpus callosum and additionally demonstrated pontocerebellar hypoplasia, global cystic enlargement of the posterior fossa and associated torcular elevation as well as cerebral white matter injury. Spine MRI confirmed a deficiency of the posterior elements of S1–2 with a small dorsal meningocele. Ophthalmologic exam revealed optic atrophy and mottling of the retina. Abdominal ultrasound confirmed the horseshoe kidney suspected prenatally as well as a duplicated versus left-sided inferior vena cava. An upper gastrointestinal study did not show bowel malrotation. An echocardiogram revealed a bicuspid aortic valve, mild mitral valve insufficiency, and hypoplasia of the transverse aortic arch. Intervention for the aortic coarctation was not pursued given palliative care preferences of parents.

At 4 days of life, the patient developed bloody stools, and abdominal films obtained demonstrated pneumatosis (Fig. 1). The patient was placed on 2 weeks of bowel rest without procedural intervention. A sepsis workup was also initiated at that time, and the first blood culture returned positive for *Bacillus* species. The patient was placed on a 2-week course of antibiotics for bacteremia and subsequent blood cultures were negative. Enteral feedings were slowly initiated via nasogastric tube at the end of the period of bowel rest. Concern for possible seizure-like activity with lip smacking also developed; however, this was not further investigated per palliative care preferences of parents. At one and a half

months of age, the patient was stable enough to discharge home, and the parents opted to continue feedings via a nasogastric tube at home rather than pursue surgical gastrostomy tube placement. The patient was discharged home on hospice care and is currently alive at 2 months of age.

Genetic analysis revealed an unbalanced translocation identical to his brother's with microarray (Agilent custom 180,000 probe platform) showing arr[GRCh37] 6q25.1q27(151639526_171115067)×1,18p11.32p11.23(131700_7694199)×3 (Fig. 3). The patient's Minnesota newborn blood spot screen was normal.

Discussion

The first 2 patients reported here both died of complications from intestinal necrosis beyond the neonatal period and shared an overlapping region of chromosome 6q25.3q26 copy number loss. The third patient reported with the shared chromosome 6q25.3q26 copy number loss similarly developed intestinal necrosis and is currently in hospice care at 2 months of age. Although specific, recurring chromosomal abnormalities have not previously been reported to be associated with NEC, these 3 cases raise the question of whether certain chromosome 6 deletions predispose individuals to intestinal necrosis.

The shared region of deletion spans from 6q25.3 to q26 (155699183_163554531; hg19) and includes multiple genes and transcripts (Table 1). Included in this region is the *EZR* gene, Ezrin, which is important for microvillar development and intestinal homeostasis in mouse models [Saotome et al., 2004; Casaletto et al., 2011]. This gene, also known as villin-2 (*VIL2*) or cytovillin (*CVIL*), encodes a cytoplasmic peripheral membrane protein which functions as a protein-tyrosine kinase substrate in microvilli. As a member of the Ezrin, Radixin, and Moesin (ERM) protein family, this protein serves as an intermediate between the plasma membrane and the actin cyto-

Table 2. Clinical features observed in patients previously reported with similar chromosome 6 deletions

	Our patients			Nagamani et al., 2009			
	P 1	P 2	P 3	P 1	P 2	P 3	P 4
Sex	F	M	M	M	F	F	M
Cytogenetic band deleted	6q25.3q26	6q25.1qter	6q25.1qter	6q25.2q25.3	6q25.2q26	6q24.3q25.3	6q25.2q27
Deletion coordinates (hg19)	155699183– 163554531	151639526– 171115067	151639526 –171115067	155336861– 169178124	154841486– 161623426	149951406– 160276072	155336861– 169178124
Age at report	16 m	6 m	2 m	4 ys	18 m	11 m	15 m
Growth restriction	+	+	–	–	–	+	+
Developmental delay	+	+	NR	+	+	+	+
Structural brain abnormalities	–	+	+	NR	–	+	+
Seizures	–	+	+	–	+	–	–
Hypotonia	+	–	+	–	+	+	–
Hypertonia	–	+	–	–	–	–	+
Retinal or eye abnormalities	+	+	+	–	+	–	+
Ear abnormalities	+	+	+	+	+	+	+
Hearing loss	+	+	NR	+	+	+	+
Congenital heart disease	+	+	+	–	–	–	+
Intestinal necrosis	+	+	+	–	–	–	–
<i>DYNLT1</i> , <i>EZR</i> , <i>TAGAP</i> , and <i>SLC22A1</i> included in deletion	+	+	+	<i>DYNLT1</i> and <i>EZR</i> included	+	+	+

Included patients are those who had microarrays demonstrating a deletion overlapping the *EZR* gene within the shared deleted region from 6q25.3 to q26 (155699183_163554531; hg19). A literature review was conducted to ensure list completeness. Specifically, all results that returned in searching PubMed for *DYNLT1*, *EZR*, *TAGAP*, *SLC22A1*, 6q25 deletion, and 6q26 deletion were reviewed. m, months; NR, not reported; ys, years; +, present; –, absent.

skeleton [Sato et al., 1992; Berryman et al., 1993]. Ezrin localizes to the apical surface of epithelial cells and is a key component in villus morphogenesis and epithelial cell polarity [Takeuchi et al., 1994; Berryman et al., 1995; Crepaldi et al., 1997; Bonhila et al., 1999; Speck et al., 2003]. Mouse studies indicate that Ezrin plays a central role in organizing the terminal web region of intestinal epithelial cells and is essential for formation of discrete villi from stratified epithelium. Homozygous null *Ezr*^{−/−} mice have a grossly normal appearance at birth; however, they do not survive past the neonatal period and have abnormally formed intestinal villi as the only identified malformation [Saotome et al., 2004].

A human phenotype associated with the *EZR* mutation was recently suggested by Riecken et al. [2015] who reported 2 siblings with profound intellectual disability and homozygous mutations in *EZR*, p.Ala129Thr. In vitro functional studies of this missense allele demonstrated normal cell membrane localization compared to the wildtype protein when expressed in fibroblasts, but failure to bind RAS and thus activate the RAS pathway [Riecken et al., 2015]. NEC was not reported in these patients with *EZR* point mutations; however, it may be that amino acid substitutions are phenotypically different

than whole gene deletions. The heterozygous variant, p.Ala129Thr, was reported in the ExAc database (exac.boardinstitute.org, accessed 1/12/16) 25 times in 121,410 alleles, giving a calculated allele frequency of approximately 0.0002. No homozygous cases were reported in ExAc.

It is intriguing to consider whether there may be an association between disruption in *EZR* protein expression and development of repeated and lethal intestinal necrosis. For example, it is possible that disruption of *EZR* protein expression may compromise gut barrier function, resulting in bacterial translocation and subsequent release of inflammatory mediators or local bacterial invasion leading to pneumatosis and local necrosis. Further studies would be required to test this hypothesis in tissue or animal models. However, patients with single copy chromosome 6 deletions encompassing the *EZR* gene who have not been affected by intestinal necrosis have been reported (Table 2). It is possible that the stress of cardiac surgery or other interventions in our patients predisposed them to gut necrosis, which was not observed in other patients. Alternatively, a mutation in the homologous allele could also be considered. Ezrin knockout mouse models could potentially help illuminate

whether intestinal necrosis can result from the absence or deficiency of the Ezrin protein.

Other candidate genes within the shared deleted region should also be considered. Genes potentially related to gut integrity within this region include *TAGAP*, *SLC22A1*, and *DYNLT1*. Variation within the *TAGAP* gene has been associated with a risk of celiac and Crohn's disease [Eyre et al., 2010; Parmar et al., 2012; Connelly et al., 2014]. *SLC22A1* is a polyspecific cation transporter in the intestine, among other organs, which is critical for the elimination of various amines, drugs, and environmental toxins; however, knockout mice displayed no obvious phenotypic abnormalities [Jonker et al., 2001]. *DYNLT1* polymorphisms have been suggested to play a role in microtubule and mitochondrial regulation and may contribute to cellular hypoxic tolerance [Xu et al., 2013]. Overall, more studies are needed to clarify which genes, if any, within this region predispose individuals to NEC.

Of note, the siblings described in this report also had a partial duplication of chromosome 18p resulting from their unbalanced translocations. Review of the literature suggests that duplication of 18p is rare and most reported cases have had mild or no phenotypic effect [Marical et al., 2007; Rodriguez et al., 2007]. Thus, the siblings' ter-

minal chromosome 6 deletion was likely more clinically significant than their partial trisomy of chromosome 18.

In conclusion, we report 3 patients with intestinal necrosis with large overlapping chromosome 6 deletions. The genes of interest within this region include *EZR* among others. More studies are needed to elucidate whether loss or absence of genes within this region predispose individuals to intestinal vulnerability.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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