

# Postnatal diagnosis of de novo complex der(8) in a boy with prenatal diagnosis of recombinant chromosome 8 syndrome

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## Key Clinical Message

Recombinant chromosome 8 syndrome is caused by duplication of 8q and deletion of 8p. A fetus with anomalies was misdiagnosed with this syndrome based on an amniocyte karyotype. Postnatal chromosomal microarray and other studies identified a de novo derivative chromosome 8. For fetal anomalies, detailed genetic studies may be required.

## KEYWORDS

congenital heart disease, double outlet right ventricle, myelomeningocele, neural tube defect, recombinant chromosome 8

## 1 | INTRODUCTION

The recombinant chromosome 8 syndrome (Rec8 syndrome) is caused by duplication of 8q22.1-qter and deletion of 8pter-p23.1 and is derived from meiotic recombination of a parental pericentric inversion 8 chromosome. Here, we report a newborn male who was prenatally diagnosed with Rec8 syndrome based on a 450 G banding karyotype of amniotic cells undertaken because of fetal anomalies. After birth, findings inconsistent with Rec8 syndrome including neural tube defect and atypical facial features prompted chromosomal microarray analysis which revealed a heretofore unreported complex rearrangement of chromosome 8 including 8q and 8p duplications. Parental karyotypes were normal, and thus, the rearrangement is de novo. The purpose of this report was to alert providers to the possibility of in utero misdiagnosis of Rec8 syndrome as well as present phenotypic details of this unique patient. Our findings support the hypotheses of others that 8q and 8p duplications are associated with cardiac defects. Prenatal chromosomal microarray analysis in addition to cytogenetic studies would have yielded the correct diagnosis and should be considered for evaluation of fetal anomalies.

The recombinant chromosome 8 syndrome (Rec8 syndrome) is a recognizable pattern of malformation caused by duplication of 8q22.1-qter and deletion of 8pter-p23.1. In all cases, the Rec8 chromosome is derived from meiotic recombination of a parental pericentric inversion 8 chromosome.<sup>1</sup> The Rec8 syndrome (OMIM 179613) was first described by Fujimoto et al,<sup>2</sup> and a detailed natural history of 42 affected individuals was reported by Sujansky et al<sup>3</sup> in 1993. The molecular breakpoints of the inversion 8 chromosome (inv8) were defined by Graw et al<sup>4</sup> and allow the disorder to be distinguished from other recombinant 8 disorders.<sup>5</sup> The Rec8 phenotype includes characteristic facial features (wide face, hypertelorism and/or telecanthus, thin upper lip, infraorbital creases, thick upper gingival frenulum), cleft lip and/or palate, complex congenital heart disease (particularly conotruncal defects), urogenital anomalies (cryptorchidism, urinary tract anomalies), and universal severe psychomotor delay.<sup>6-8</sup>

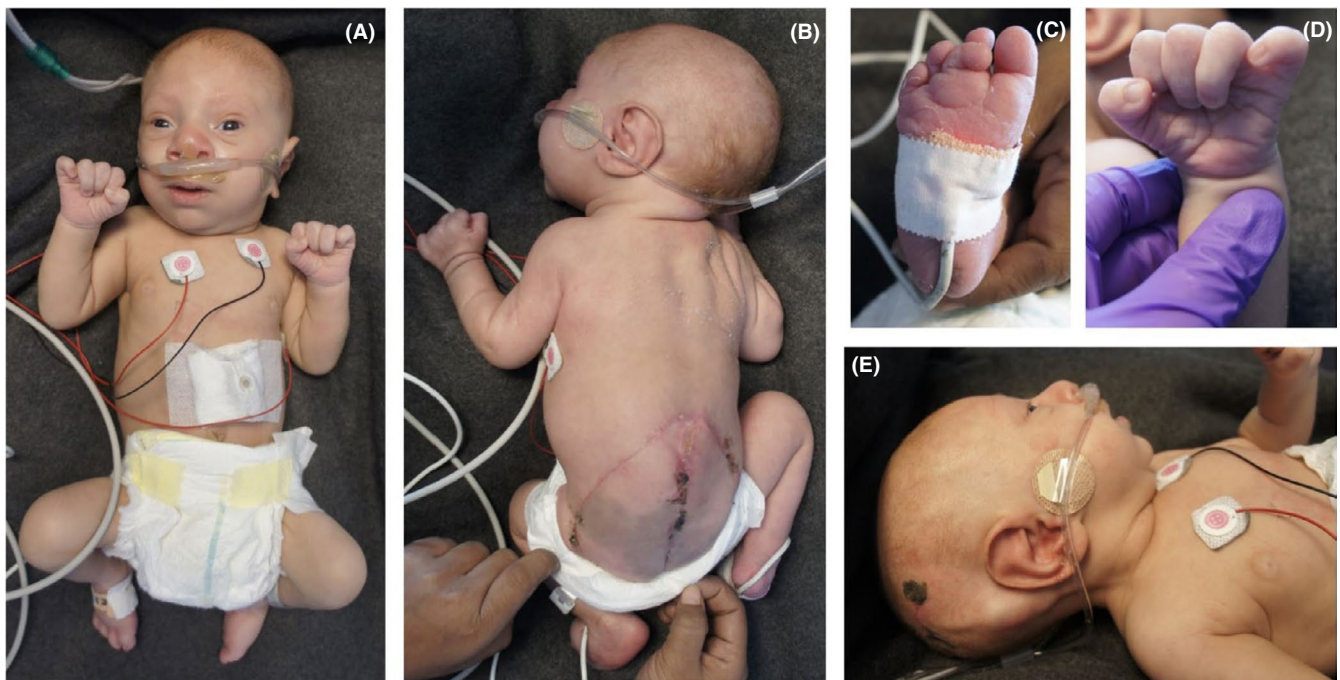
We are reporting on a newborn male who was prenatally diagnosed with Rec8 syndrome based on a 450-band karyotype of amniotic cells undertaken due to recognition of fetal anomalies. After birth, multiple findings were inconsistent with Rec8 syndrome, including a neural tube defect

and atypical facial features. This prompted a chromosomal microarray analysis, which revealed an unreported complex rearrangement of chromosome 8. Parental karyotypes were normal, signifying this rearrangement to be *de novo*. The goal of this patient report is to alert providers to the possibility of misdiagnosing Rec8 syndrome as well as present the phenotypic details of this unique patient.

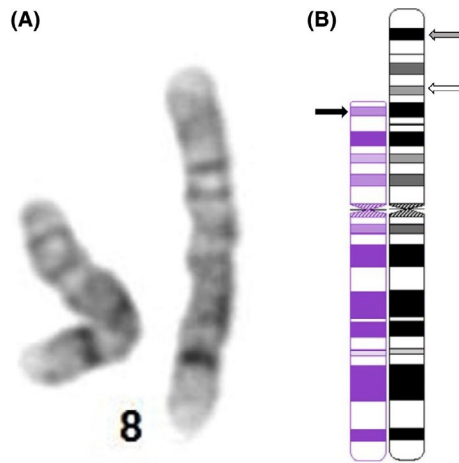
## 2 | CLINICAL REPORT

The male patient was a 2.65 kg, borderline small for gestational age infant born to a 27-year-old G2P0010 Mexican mother and nonconsanguineous 50-year-old Mexican father via vertex vaginal delivery at 39-week gestation. The pregnancy was complicated by multiple fetal anomalies including myelomeningocele, hydrocephalus, and cardiac defects, as noted during prenatal care in Mexico. There were no known teratogenic exposures, and family history was negative for congenital anomalies. Other than frequent fetal ultrasounds, no other fetal imaging studies, such as fetal MRI, were obtained. Decreased fetal movement at 37-week gestation prompted evaluation at our center, and subsequent amniocentesis revealed an abnormal male karyotype interpreted as Rec8 at 450-band resolution. After delivery, Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Birth growth parameters were 5th centile for weight, 3rd centile for length, and 24th centile for head circumference. Initial physical examination revealed

a large anterior fontanel measuring  $12 \times 7.5$  cm, a prominent occiput, upsloping and shallow orbits, bilaterally broad pinnae, small fingernails and toenails, abnormal toes with the third toe crossing under other toes bilaterally, and a flat open lower thoracolumbar defect of the spine measuring  $8.5 \times 5.5$  cm. (Figure 1 for clinical photographs taken at 34 days of age). He had no movements of the lower extremities but had appropriate movement of the upper extremities. Radiological studies revealed myelodysplasia with associated vertebral body segmentation of the lumbar spine, multiple bilateral dysplastic ribs, and double manubrial ossification center. An echocardiogram showed a double outlet right ventricle, large paramembranous ventricular septal defect, mildly hypoplastic left ventricle, and moderate mitral stenosis. Ultrasound study of the head revealed hydrocephalus of the lateral and third ventricles with decompressed fourth ventricle and findings consistent with Chiari 2 malformation including interdigitation of the falx, Luckenschadel skull, and enlarged massa intermedia. Renal ultrasound showed mild left pelviectasis, and voiding urethrocytography showed atonic neurogenic bladder. He was able to urinate spontaneously. On day of life 1, a ventriculoperitoneal shunt was placed and the neural tube defect debrided and closed. He developed pulmonary hypertension and required high flow nasal cannula respiratory support for the first two weeks of life. Additionally, he required g-tube placement at 3 weeks of life. The infant showed significant global developmental delay and was discharged home at 34 days of life on hospice care in view of the poor cardiac prognosis.



**FIGURE 1** A and E, Frontal and profile view of the patient showing upslanting shallow orbits, broad pinnae, and VP shunt. B, Dorsal view of the surgical wound from the correction of large myelomeningocele. C and D, The infant has abnormal toes with the third toe crossing under the others and small fingernails



**FIGURE 2** A, The patient's chromosome 8 with GTW bands. B, Patient's chromosome 8 ideogram illustrating 8qter to 8q24.1 duplication (gray arrow), 8p11.2 to 8p23.1 duplication (white arrow), and 8pter to 8p23.1 deletion (black arrow)

A developmental evaluation at 15 months showed his growth parameters were weight 7.25 kg ( $-4$  SD), length 75 cm (10th centile), and head circumference 49.5 cm (90th centile). He was bottle fed and taking pureed foods. Developmental skills were at the 6- to 7-month level for cognition, speech, and fine motor skills. Gross motor skills remained at the 1- to 2-month level with minimal head control secondary to his enlarged head.

### 3 | MATERIALS AND METHODS

#### 3.1 | Prenatal chromosome study

Metaphase spreads were obtained from amniotic cells using standard procedures. GTW banding with resolution of 450 bands was obtained. No other types of banding studies were performed prenatally.

#### 3.2 | Postnatal genetic studies

Chromosome microarray analysis was performed on peripheral blood DNA isolated according to established protocols, using FDA-cleared Affymetrix Cytoscan Dx microarray (ThermoFisher Scientific, USA). This microarray contains over 2.69 million probes with an interprobe distance of 1148 base pairs. Single long continuous absence of homozygosity (AOH) larger than 10 Mb or total autosome AOH proportion larger than 3% was reported. High-resolution chromosome analysis of the patient's peripheral blood lymphocytes at 550 bands was performed as well as parental chromosome studies.

Karyotype reporting was expressed in accordance with the 2016 International System for Human Cytogenetic Nomenclature (ISCN) and the hg19 build of the human genome.

## 4 | RESULTS

Prenatal GTW-banding analysis from the amniotic fluid cells at 450-band resolution revealed an abnormal chromosome 8 erroneously interpreted as Rec8: 46,XY,rec(8)dup(8q)inv(8)(p23.1q22.1).

Postnatal chromosome microarray analysis of peripheral blood showed partial 8p monosomy/partial 8p trisomy/partial 8q trisomy. Specifically, there was a 6.8 Mb deletion of 8pter-p23.1 (loss of 15 OMIM genes), a 28.5 Mb duplication of 8p23.1-p11.2 (129 OMIM genes), and a 26.0 Mb duplication of the 8q24.12-8qter segment that houses 111 OMIM genes. The 8pter-p23.1 deletion observed in this patient is identical to the 8p deletion observed in Rec8 patients; however, the 8q duplicated segment starts at band 8q24.1 instead of 8q22 and the 8p duplication segment is typically not observed in Rec8 patients.

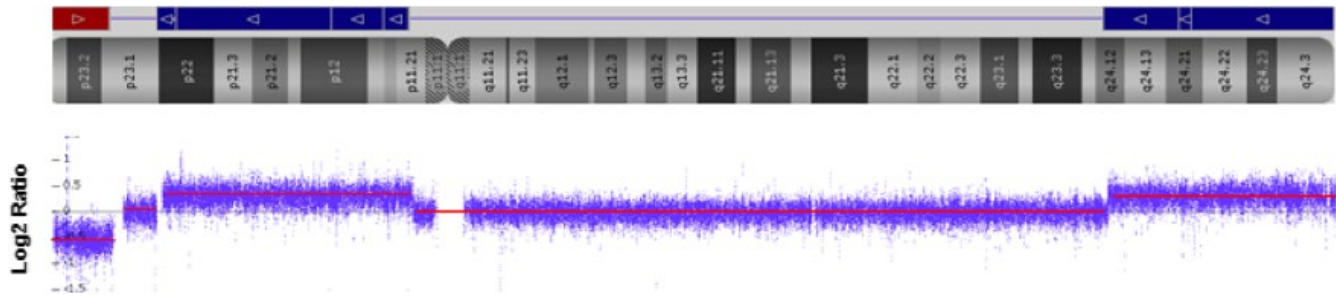
A high-resolution chromosome study at 550-band resolution from the infant's peripheral blood was performed at 8 months of age and showed results consistent with the microarray analysis: that is, a complex unbalanced chromosome arrangement with a derivative chromosome 8 in all cells examined. The unbalanced chromosome complement had a loss of the segment from the 8pter to 8p23.1 and a duplication of the segment from 8qter to 8q24.1 and an inverted duplication of 8p11.2 to 8p23.1. The extra copy of the 8qter to 8q24.1 is attached to the inverted segment of 8p11.2 to 8p23.1. Therefore, the patient's correct karyotype is 46,XY,der(8)(8qter->8q24.1::8p11.2->8p23.1::8p23.1->8qter)dn (Figure 2).

Chromosomal analyses of parents were normal 46,XX and 46,XY, and hence, the der(8) chromosome in the child is de novo and is not derived from a parental inv(8).

## 5 | DISCUSSION

This patient has a novel complex der(8) chromosome which is de novo. He was prenatally misdiagnosed as having Rec8 syndrome based on a low-resolution amniocyte karyotype obtained because of the multiple fetal anomalies including a myelomeningocele, hydrocephalus, and cardiac defects. Postnatal dysmorphism evaluation identified nontypical facial features for Rec8, including upsloping orbits, broad pinnae, and absence of prominent lateral nasal folds. Other nontypical features included a lumbar myelomeningocele and associated hydrocephalus/Chiari 2 malformation, dysplastic ribs, and overfolded toes. Subsequent chromosomal microarray analysis and high-resolution karyotype correctly identified a unique der(8) chromosome that resembles the Rec8 chromosome but differs by having inverted dup(8p) in addition to the dup(8q) and del(8p) (Figure 3). The 8q breakpoints in this patient also differ from typical Rec8: 8q24.1 and 8q22.1, respectively.





**FIGURE 3** Microarray showing three genomic abnormalities: 6.8 Mb terminal deletion of chromosome 8p (8pter-p23.1), a 28.5 Mb interstitial duplication of 8p23.1-p11.2, and a 26.0 Mb terminal duplication of chromosome 8q (8q24.12-8qter)

Regarding genotype-phenotype correlation, the presence of the inverted duplication/deletion 8p has perhaps increased risk of cardiac defects, as the *GATA4* gene (OMIM 600576), located in 8p23.1, is involved with congenital heart defects including double outlet right ventricle and ventricular septal defects.<sup>9</sup> In addition, some genes in the deleted 8p23.2-pter region, such as *ARHGEF10* (OMIM 608136), *CSMD1* (OMIM 608397), and *DLGAP2* (OMIM 605438), are directly related to neurological conditions such as developmental delay, language abnormalities, autism, and epilepsy. The gene *CLN8* (OMIM 607837) has been associated with central nervous system development, which may play a role in the severe neural tube defect in our patient. Concurrently, large interstitial duplications of 8p >20 Mb have been linked to severe brain anomalies and intellectual disabilities, as genes responsible for brain development such as *FGFR1* (OMIM 136350) are present in this region and participate in the neural crest cell migration.<sup>10</sup>

Currently, there is too little information to speculate on the origin of the *de novo* der(8) chromosome in this patient. As the karyotypes of both parents were normal, the child's chromosome abnormality is not the result of meiotic recombination of a parental inversion chromosome (as is the case with Rec8 syndrome) and the mechanism leading to it is unknown. There are very few reported individuals with invdup8p in addition to dup8q and del8p. The most similar patient was reported by Sánchez-Casillas et al<sup>11</sup> and had the same 8p deletion, a larger 8q duplication, and a much smaller 8p duplication. Her phenotype was significantly milder in growth and developmental delays, and she had no congenital heart disease. The phenotypes of individuals with invdup-del8p only (ie, absence of 8q dup) do share features with both Rec8 and our patient, specifically widely spaced eyes, broad nose, intellectual disability, and congenital heart defects.<sup>12</sup>

In summary, we present a patient with a novel der(8) chromosome including invdupdel8p and dup8q whose phenotype has some overlap with Rec8 and other patients with similar cytogenetic findings, but who has a neural tube defect previously unreported in der(8) patients. He was misdiagnosed prenatally as having Rec8 syndrome based on a low-resolution

amniocyte karyotype, with failure to recognize that the presence of a neural tube defect made Rec8 unlikely. Prenatal chromosomal microarray analysis in addition to cytogenetic studies would have yielded the correct diagnosis and should be considered for evaluation of fetal anomalies.<sup>13</sup>

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## CONFLICT OF INTEREST

None declared.

## AUTHOR CONTRIBUTION

MSO was involved in the care of the patient, as well as drafting and revising the manuscript. JEC was involved in the care of the patient, as well as drafting and revising the manuscript. HX was involved in drafting the sections specific to the genetic testing, results, and interpretation. JL was involved in the care of the patient and completed the developmental assessments of the patient, as well as participated in the drafting and revising of the manuscript. TC was involved in the care of the patient, as well as drafting and revising the manuscript. CC was involved in the care of the patient, as well as drafting and revising the manuscript. JM was involved in the care of the patient, as well as drafting and revising the manuscript.

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