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Case Report
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Laryngeal Cleft as Presentation of a 4q13.1q21.23 Deletion

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Abstract

Objective: We present the first case of bronchial anomalies and laryngomalacia in a patient with a large 4q13.1q21.23 deletion and a review of the literature.

Case Report: Our patient was born after a pregnancy that was complicated by fetal growth restriction at 30 weeks gestational age. His birth weight was below the 3rd percentile (-2 SD). He had multiple facial dysmorphisms. An inspiratory stridor was noted and deep desaturations for which he was referred to the neonatal intensive care unit. He was started on continuous positive airway pressure. Laryngo- and bronchoscopy showed a laryngeal cleft grade I, a functional relevant laryngomalacia, a right sided tracheal bronchus and very proximal branching in the major bronchi. A CT thorax confirmed the abnormal branching of the bronchi. Cerebral ultrasound revealed a mega cisterna magna and partial atresia of the corpus callosum. The trio WES analysis in the patient revealed a 24.1 Mb *de novo*, interstitial deletion in 4q13.1q21.3 of the paternal allele of chromosome 4 (GRch37: chr4:62,383,011-86,491,865), encompassing more than a hundred protein-coding genes and including the 1.37 M critical region of the 4q21 microdeletion syndrome. In literature no other patients with a 4q deletion have been described with bronchial abnormalities.

Conclusion: We present a patient with a 4q13.1q21.23 deletion and severe respiratory disease due to laryngomalacia and a tracheal bronchus. The respiratory anomalies in our patient add to the phenotypic spectrum of deletions in this region. Unexplained respiratory symptoms in patients with a 4q deletion could point to tracheal anomalies, suggesting that respiratory imaging could be indicated.

Keywords: 4q deletion; 4q microdeletion syndrome; Laryngeal cleft; Laryngomalacia; Bronchial anomaly

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Introduction

A laryngeal cleft is a rare congenital abnormality caused by a failure of posterior cricoid lamina fusion or incomplete tracheoesophageal septum development. The majority of patients have an additional congenital abnormality. Recognizable syndromes in which laryngeal clefts are reported include syndromes caused by a chromosomal aneuploidy, 22q11.2 deletion syndrome, Opitz/BBB syndrome, Pallister Hall syndrome, CHARGE syndrome and VACTERL association. Recurrence in families has been reported [1,2]. In many patients, however, an underlying genetic cause cannot be identified. The 4q21 microdeletion syndrome (OMIM: #613509) was first described by Bonnet et al. [3] in 2010 after identifying a commonly deleted critical interval of 1.37 Mb in nine unrelated patients with differently sized, overlapping, *de novo* deletions in 4q21. Patients with this syndrome have distinctive facial features (frontal bossing, hypertelorism, short philtrum), severely delayed speech development, intellectual disability, neonatal hypotonia and a postnatal growth delay with a (relatively) normal head circumference. Since Bonnet's publication in 2010 [3], 22 patients have been described in the literature [4-13] and 78 are reported in DECIPHER, including a patient [14] with *de novo* loss of 19.5 Mb that completely falls within the deleted region in this patient. We present a newborn with a *de novo* 4q13.1q21.23 deletion who suffered from severe respiratory insufficiency due to a laryngeal cleft, laryngomalacia and an atypical bronchial tree. To our knowledge, laryngomalacia, a laryngeal cleft or atypical development of the bronchial tree have not been described before in patients with a deletion in the proximal long arm of chromosome 4.

Clinical Presentation

Our patient was born as the second son of non-consanguineous parents with an unremarkable medical history. He was conceived naturally. The pregnancy was complicated by fetal growth restriction at 30 weeks gestational age whereas normal growth was observed at 20 weeks of gestation. The delivery was complicated by prolonged rupture of membranes and a postpartum rupture of a notably thin umbilical cord; which was clipped immediately after birth. His Apgar scores were 8/8 at 1- and 5-min post-partum with points withdrawn for color and reactivity. His birth weight was below the 3rd percentile (-2 SD), his height was -1.5 SD and his head circumference was +1.5 SD. His physical exam showed low set ears, a wide frontal fontanel, broad nasal bridge, frontal bossing, hypertelorism, hypospadia and hypotonia. He was admitted to the neonatal ward for intravenous treatment of hypoglycemia, which was noted during routine glucose screening for children small for gestational age. An inspiratory stridor was noted as well as deep desaturations for which he was referred to the neonatal intensive care unit. He was started on continuous positive airway pressure. Laryngo- and bronchoscopy showed a laryngeal cleft grade I, a functional relevant laryngomalacia, a right sided tracheal bronchus and very proximal branching in the major bronchi. A CT thorax confirmed the abnormal branching of the bronchi. Cerebral ultrasound revealed a mega cisterna magna and partial atresia of the corpus callosum. Cardiac and renal ultrasound showed no abnormalities. Multiple attempts to wean from respiratory support failed over a prolonged period. This was due to severe incidents with airway collapse when positive pressure support was weaned. This continuing dependency on respiratory support led to discussions on the proportionality of long-term invasive respiratory therapy. After much deliberation care was withdrawn (Figure 1).

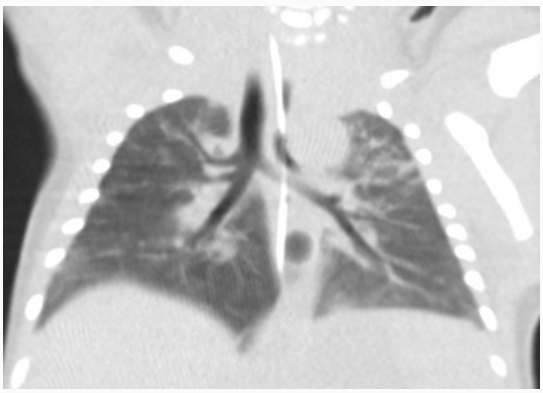

Figure 1: Atypical bronchial tree (right sided tracheal bronchus).

Materials and Methods

Genetics

Whole Exome Sequencing (WES) was performed with a trio-based approach on genomic DNA extracted from blood leukocytes of the patient and his parents. Exomes were captured and enriched using the Agilent SureSelect Human All Exon V5 Kit, according to manufacturer's instructions (Agilent Technologies, Santa Clara, California, USA). Sequencing was performed using a NovaSeq Sequencer (Illumina, San Diego, California, USA). Read alignment to the human reference genome (GRCh37/hg19) and variant calling was performed using the BWA and GATK software, respectively. Variant annotation was performed using a custom designed in-house annotation and variant prioritization pipeline. Copy Number Variation analysis was performed using CoNIFER software and annotated using an in-house strategy. Patient-parents trio analysis of the WES data was done using a gene panel of 3,741 genes associated with Mendelian inherited disorders (version DG-2.16).

Database search

DECIPHER was consulted June 2022 to identify additional cases of laryngeal clefts, laryngomalacia or tracheal bronchus (https://decipher.sanger.ac.uk/).

Results

The trio WES analysis in the patient revealed a 24.1 Mb *de novo*, interstitial deletion in 4q13.1q21.3 of the paternal allele of chromosome 4 (GRch37: chr4: 62,383,011-86,491,865), encompassing more than

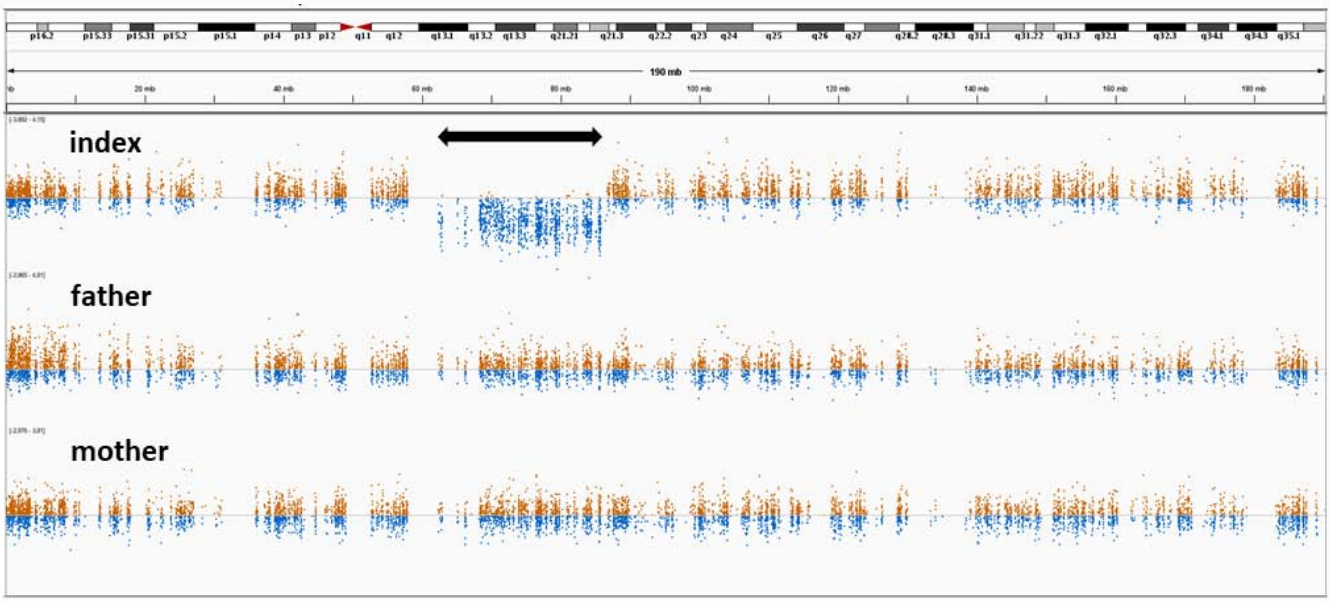

Figure 2: Screenshot of the integrative genome viewer [15] showing a multidisplay view of the CNV in exome data of the index patient and his parents for chromosome 4. The double headed black arrow indicates the *de novo*, interstitial loss of 24.1 Mb in 4q13.1q21.23 (Chr4:62,383,011-86,491,865 (hg19)).

a hundred protein-coding genes and including the 1.37 M critical region of the 4q21 microdeletion syndrome. No other clinically relevant copy number or nucleotide variants were identified (Figure 2). No patients with a tracheal bronchus are reported in DECIPHER [15]. Seven other patients are listed in DECIPHER with a laryngeal cleft, none of them have overlapping deletions with our patient. Laryngomalacia was described in 127 other patients; however, none of these patients had an abnormality of chromosome 4. DECIPHER reports 134 patients with (partly) overlapping deletions that are smaller than the deletion identified in our patient and one patient with a larger deletion. One patient [16] with a deletion of 3.3 Mb that completely falls within the deleted region in our patient had a laryngeal stenosis. No other laryngeal or bronchial abnormalities are described in this cohort.

Discussion

Over a hundred patients are reported with a deletion that is partly overlapping with the deletion in our patient. Overlapping clinical features are abnormalities of the corpus callosum, frontal bossing, neonatal hypotonia and growth delay with relative brain sparing. Laryngeal cleft with laryngomalacia and a tracheal bronchus are symptoms that have not previously been linked to the 4q13.1q21.23 region. Bonnet et al. [3] report on a patient with laryngeal diplegia. Others have reported on midline defects and 4q21 deletions such as a cleft palate [9]. Bronchial abnormalities have not been described in the literature in relation with deletions in the long arm of chromosome 4. In many patients with 4q abnormalities, however, no additional imaging of the thorax was performed. This could imply that more patients with 4q chromosomal deletions could have an abnormal bronchial tree. Therefore, we propose/suggest that in case of unexplained respiratory symptoms laryngeal and bronchial architecture should be evaluated in these patients.

Conclusion

We present a patient with a 4q13.1q21.23 deletion and severe respiratory disease. The identification of a de novo deletion 4q13.1q21.23 with a poor developmental prognosis played an important role in the decision making. This illustrates the usefulness of early genetic testing in severely ill newborns. The respiratory anomalies in our patient add to the phenotypic spectrum of deletions in this region.

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