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CASE REPORT

Phenotypic characterization of a boy with 4q duplication associated with anorectal anomaly: case report.

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Abstract

Duplications of 4q represent rare chromosomal abnormalities of variable clinical features, these being directly related to the size of the duplicated segment, and whether the change was isolated or with translocation of another chromosome. Anorectal anomalies are present in a wide spectrum of birth defects, and can be isolated or syndromic, with about 60% of affected patients also having other anomalies. We present in this report a case of anorectal anomaly diagnosed at birth associated with microcephaly, facial dysmorphisms and neuropsycho-motor developmental delay. It has a normal karyotype and with the aid of the CGH-array technique it was possi-ble to diagnose this case and expand the clinical phenotype of dup4q to include the association with anorectal anomaly.

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INTRODUCTION

First described by Yue and colleagues in 1970, chromosome 4q duplication (dup4q) is a rare disorder, generally formed due to unbalanced parental translocations with rare *de novo* occurrences.[1]

Anorectal anomalies comprise a wide spectrum of congenital defects ranging from mild anal anomalies to complex cloacal malformations.[2] The main chromosomal disorders associated with them are trisomy 21, 22q duplication, and 13q microdeletion; dup4q is not strongly associated with these anomalies.[3]

The present study describes a rare case of a patient with partial 4q duplication (4q34.1q35.2) and anorectal anomaly.

CASE REPORT

A 12-year-old boy, the first child of a young, healthy, non-consanguineous couple, without complications in prenatal care, was born from a cesarean section due to breech presentation. He had APGAR scores of 8/9 and did not require neonatal resuscitation. He weighed 2,230g (2.9th percentile) at birth. Physical examination revealed the presence of anal imperforation, for which he was referred to a public tertiary pediatric hospital in the State of Ceará.

Physical examination performed on admission showed the patient was in fair general condition, with pallor +/4 and jaundice 2+/4. Findings included microcephaly, coarse facies, short palpebral fissures, epicanthus inversus, a flat nasal base, a smooth nasal philtrum, protruding ears, and a short neck. The abdomen was distended with visible bowel loops. He also had bilateral thumb subluxation, lateralized legs, and bilateral hydrocele.

Microcephaly and global developmental delay were noted during outpatient follow-up after surgery. The ophthalmological evaluation revealed he had convergent strabismus, lens opacity, and normal findings on fundoscopy. The use of an eye patch followed by surgery was recommended.

Tests showed no karyotype changes. He also had a normal ultrasound of the abdomen and urinary tract. Computed tomography scans of the head showed supratentorial ventricular dilation. Molecular tests using the microarray comparative genomic hybridization technique (aCGH) demonstrated the presence of a partial duplication of the long arm of chromosome 4 - arr(GRCh37)4q34.1q35.2 (175461388_190896674)x3.

Currently, the patient has microcephaly and mild intellectual disability. He can form sentences and walk without support but needs help to carry out activities of daily living. He is in the 4th grade and has had trouble at school. He has also had hetero-aggressive outbursts and a low frustration threshold. He can feed orally and does not need a ventilator or oxygen therapy. The patient is being monitored by a multidisciplinary team and is on clonidine, risperidone, and aripiprazole to control aggression, with good therapeutic response. Genetic counseling sessions were held and the parents were advised to undergo karyotyping, which they have not done to date. (Figure 1)



Figure 1. Patient at 12 years old.

DISCUSSION

4q duplications are rare.[1] An isolated 4q duplication is uncommon. When the chromosomal disorder involves only chromosome 4, the affected region generally ranges from q12-q35,[1] with the most common breakpoints in 4q duplication occurring between 4q21-q28[4]. Associations between dup4q and other chromosomal alterations are rare, however, the literature contains reports of associations with deletion 7q[1.5], Xp[5] duplication, monosomy 13q[6,] monosomy 9q[7], and trisomy 21q[8].

Cytogenetic tests based on the analysis of lymphocyte chromosomes obtained from peripheral blood samples can identify large chromosomal anomalies with the aid of light microscopy, which include translocations, deletions, and aneuploidies; in turn, aCGH, using molecular biology techniques, identifies microdeletions or microduplications by comparing the genetic material of the specimen under study with healthy controls.[5] Our patient was diagnosed based on aCGH.

Patients with dup4q syndrome present various signs and symptoms.[4] The most common clinical presentation

includes intellectual and growth deficiency, microcephaly, nasal bridge anomalies, hearing loss, auricular dysplasia, dental anomalies, congenital heart defects, renal hypoplasia, and thumb anomalies.[4,9] Cryptorchidism, umbilical hernia, and epilepsy are less common.[4,9] Case reports also indicate an association with choanal atresia, parkinsonism, and immunodeficiency.[7,10,11]

Anorectal anomalies comprise a wide spectrum of congenital defects with varying degrees of severity, present in around one in every 3,000 live births.[2] About 60% of affected patients also present other anomalies of the urinary tract, cardiovascular system, central nervous system, or skeleton.[12] The etiology of these anomalies is based on genetic and environmental factors, although the precise origin is not yet completely known.[3]

Anorectal anomalies can be isolated or non-isolated. Non-isolated anomalies are associated with chromosomal alterations and monogenic syndromes. Chromosomal or monogenic alterations occurring in combination with intellectual disability and/or dysmorphism are indicative of a syndrome.[13] About ten percent of these syndromes involve chromosomal alterations or monogenic conditions that manifest with anorectal anomalies. These changes generally occur due to de novo genetic mutations, which are present in patients but not in their parents.[12] Studies looking into isolated anorectal anomalies were unable to identify the genomic alterations causing this phenotype, suggesting a certain level of genetic heterogeneity, which means that the same condition can be caused by mutations in more than one gene.[2] (Table 1)

Table 1. Genetic etiologies of anorectal anomalies

ANORECTAL ANOMALY		
ISOLATED	**NON-ISOLATED**	
Non-syndromic:	**- Chromosome mutations:**	**Monogenic syndromes:**
De novo mutations	Trisomy 21	- Townes-Brocks
	22q duplication	- Duane-radial ray
	13q microdeletion	- CHARGE
	4q duplication	-Currarino
		- Pallister-Hall
		- Opitz G/ BBB

Adapted from Dworschak[2]

Findings involving the gastrointestinal system are uncommon in dup4q. Egritas O, et al. reported the case of a 15-day-old patient with idiopathic neonatal cholestasis.[14] In the literature, the association between dup4q and anorectal anomaly was reported only in a single case of an 18-week fetus.[15]

The patient described in this report presented with a severe phenotypic alteration. He was diagnosed based on the association between neurological alterations and anorectal anomaly. This paper contributed to the dissemination of information about the syndrome's phenotype. It is the second report in the literature describing the association between anorectal anomaly and dup4q.

CONCLUSION

Dup4q is a rare, poorly characterized genetic disease, described only in case reports. Our report described an unusual phenotypic association with anorectal anomaly, the first case featuring a living patient on outpatient follow-up, and stressed the importance of performing genetic tests to elucidate the etiology of anorectal anomalies.

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