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CASE REPORT

10q distal trisomy and 15q monosomy as a rare genetic cause for intellectual disability

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ABSTRACT

Intellectual disability (ID) is defined as a neurodevelopmental disorder. The prevalence is 1% to 3%. Genetic factors strongly contribute to the etiology of ID; however, the origin remains unknown in up to 60% of the cases. De novo mutations are a common genetic cause in sporadic cases of ID. This report describes the cases of 2 siblings with distinctive phenotypical features and neurodevelopmental disorders with an unbalanced translocation, (46,XX,der[15]t[10;15][q24.3;26.1]mat), resulting in trisomy of the long arm of chromosome 10 and monosomy of the long arm of chromosome 15. The cases are thought to be associated with distal trisomy 10q syndrome and monosomy 15q syndrome. Both trisomy 10q and monosomy 15q syndromes are rare diseases with distinctive clinical profiles.

Keywords: Developmental delay, genetic syndrome, intellectual disability, translocation

INTRODUCTION

Intellectual disability (ID) is defined as a neurodevelopmental disorder characterized by delayed acquisition of developmental milestones in early childhood, resulting in impairments in social, practical, and conceptual domains, and has a prevalence of 1% to 3% (1). Genetic factors contribute strongly to the etiology of neurodevelopmental diseases and the underlying genetic mechanisms have been shown to be complex and vary from one individual to another (2-5). Although significant progress has been made in ID genetics as a result of advances in molecular analysis technology over the past decades, the precise etiology of ID remains unknown in up to 60% of cases (6). De novo mutations represent a common genetic cause in sporadic cases of ID and account for most severe cases (7). A detailed molecular analysis and systematic breakpoint mapping of identified de novo chromosomal arrangement abnormalities may shed further light on our understanding of the genomic and molecular architecture of ID (7). Described here are 2 siblings with shared cognitive and clinical phenotypic findings with an unbalanced chromosomal translocation, resulting in trisomy of the long arm of chromosome 10 and monosomy of the long arm of chromosome 15 (46,XX,der[15]t[10;15][q24.3;26.1]mat). The phenotypic features as well as the neurodevelopmental pathologies of these patients are thought to be associated with distal trisomy 10q and monosomy 15q syndromes. A number of researchers have reported on both trisomy 10q and monosomy 15q syndromes and the clinical consequences (8).

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CASE 1

A 33-month-old girl was referred to our clinic by the hospital genetics department for a developmental evaluation. Her father reported concerns with his daughter's development. She was delivered at term via spontaneous vaginal delivery without complication and her prenatal history was remarkable for intrauterine growth retardation. The developmental history indicated that she rolled at 20 months, independently sat at 30 months, and had not yet begun to crawl. Hypotonia and muscle stiffness were present, and she had difficulty acquiring gross motor milestones. She was also delayed in reaching language, fine motor, and social developmental domain milestones. She did not speak her first words until 30 months of age and had 3 words at the time of presentation. Her parents reported no behavioral disturbances since birth. No evidence of neglect or abuse was detected. Clinical assessment observations included cooing and bubbling without meaningful words, she was able to sit without support, and she was able to grasp an object but not pass it to the other hand. She was alert to environmental stimuli and able to respond to her name, and smiled back in interactions with good eye contact. Dysmorphic features, including microcephaly, microphthalmia, a flat face with a large forehead, a small nose with a depressed nasal bridge, and low-set ears were noted in the physical examination. The family reported that she had undergone orthopedic surgery for hip dysplasia at the age of 2 years. Her parents had a non-consanguineous marriage and there were no previously identified cases of neurodevelopmental disorders, including ID, in the extended family of either parent. Genetic analyses of the parents revealed a balanced translocation of t(10;15)(q24.3;26.1) in the mother. The Denver Developmental Screening Test II was applied to the child and the results indicated a personal-social domain score level of 10-11 months, a fine motor and adaptive domain score of 10-12 months, a language domain score of 8-9 months, and a gross motor domain score of 6.5-8 months of age. The gross motor delay was more prominent than other aspects of development. A diagnosis of global developmental delay was made following the clinical examination and developmental assessment. No psychiatric comorbidities were found during the examination. Psychoeducation was provided to the parents about developmental milestones and the diagnosis of ID, including counseling about how to improve the child's skills. Education designed for ID in a special education institution was planned.

CASE 2

Case 2, the elder sibling of the first patient was an 11-year-old girl. She was delivered at term without complication by spontaneous vaginal delivery and her prenatal history was remarkable for intrauterine growth retardation, like her sister. She had delays in multiple areas of development, including motor and language skills. Her parents reported that they were first concerned about their daughter's development at 12-18 months of age. She had exhibited delays in acquiring developmental skills, similar to those of her sibling. She did not speak her first words until age 3, started putting words together at age 6, and at the time of presentation, could still not put 3 words together; she expressed herself to her parents through gestures. She was diagnosed with global developmental delay at the age of 4 and had been in special education classes for students with ID since the initial diagnosis. She had received physical therapy for orthopedic problems for 2 years. She started to walk at age 10. She started goverment elementary school in inclusive settings at age 8, and she was in her fourth year of primary education. Her academic achievements were significantly behind her peers. She could not yet read or write. No psychiatric comorbidity had been detected in the past or at presentation. No medication had been administered. During the clinical assessments, she rarely expressed herself verbally, using one-word answers and a vocabulary of approximately 20 words. She pointed to what she wanted and shook her head to express herself. Poor fine motor control was observed. She did exhibit understanding of instructions, such as responding to requests to demonstrate main body parts on a doll. Her phenotypic appearance was very similar to that of her sibling. A mental status examination indicated that while she was cooperative and oriented, her thought content was poor. The Stanford-Binet psychometric test yielded an IQ score of 38, and the evaluation was moderate ID. The diagnosis and clinical consequences were evaluated and discussed with the family, including expectations for development and counseling on improving the child's skills. Special education was to be continued and follow-up examinations were planned.

DISCUSSION

This report describes a rare genetic variant in 2 siblings with similar cognitive and clinical phenotypes. Both girls had the same unbalanced translocation, the karyotype 46,XX,der(15) t(10;15)(q24.3; q26.1)mat.

Balanced translocations occur when pieces of 2 chromosomes break off and switch places, creating an altered but balanced set of chromosomes. Carriers of a balanced translocation may not have any pathological condition; however, in their offspring, the altered set of chromosomes may yield extra and/or missing genetic material in certain locations, known as an unbalanced translocation. Congenital abnormalities are usually associated with unbalanced translocations (8,9). In our cases, the children had extra material on chromosome 10q and missing material on chromosome 15q, stemming from a maternal balanced translocation of chromosomes 10 and 15. In the literature, several phenotypical characteristics, including a dysmorphic appearance and distinct neurocognitive profiles, have been associated with distal trisomy of chromosome 10q and with monosomy of 15q (9). Distal trisomy of 10q is commonly the result of an unbalanced parental reciprocal translocation with another autosomal chromosome or pericentric inversion. The terminal end of the chromosome is typically the duplicated region, with proximal breakpoints ranging from 10q22.3 to 10q26.3 (9). In the present cases, the location of the proximal breakpoints was q24.2. More than 50 cases of distal trisomy of 10q have been identified in the literature with distinctive craniofacial findings (a flat face with a large, prominent forehead, a small nose with a depressed nasal bridge, highly arched eyebrows, short and narrow palpebral fissures, telecanthus), and pre- and post-natal developmental problems, including ID, autism spectrum disorder, and prenatal growth retardation (9-11). Our patients' phenotypes were consistent with the literature. The diagnosis of the first case was global developmental delay, which is defined as significant (2 or more standard deviations below the mean) delay in at least 2 developmental domains: gross and fine motor, speech and language, cognition, personal and social development, and activities of daily living. The second patient's developmental history was also consistent with global developmental delay; she was diagnosed with moderate ID. Musculoskeletal abnormalities such as hypotonia, abnormal laxity of the joints and other malformations of the extremities may also be seen, along with abnormalities of other systems, such as the renal, respiratory, and cardiac systems (8). In our cases, the lack of involvement of the internal organs may be explained by previous findings suggesting that the phenomenology and the severity of symptoms may vary among individuals, probably depending on the length of the duplicated region (9). Monosomy of 15q, however, is a rare chromosomal abnormality associated with pre- and post-natal growth defects, developmental delay, and craniofacial findings similar to those seen in our cases, including microcephaly, a broad nasal bridge, and low-set ears (12-14). It is thought that the loss of 1 copy of the gene responsible for encoding insulin-like growth receptor 1 accounts for the growth retardation seen during both the intrauterine period and post-natal development (12,15).

In conclusion, trisomy of chromosome 10q and monosomy of chromosome 15q are rare chromosomal rearrangement abnormalities that are associated with distinct phenotypical findings. The co-existence of these 2 genetic variations may be even rarer and may be associated with a poorer prognosis. Clinicians should consider that patients with ID may also have a comorbid genetic syndrome. This could permit an early diagnosis and enable necessary interventions. Further exploration of genomic alterations within these chromosomal regions and the identification of genes contributing to the molecular mechanisms of ID may be helpful to determining a prognosis, as well as developing molecular targets for intervention.

Contribution Categories		Author Initials
Category 1	Concept/Design	C.U., A.A., A.K.
	Literature review	C.U., A.A.
	Data analysis/Interpretation	C.U., A.A., A.K.
	Case follow-up (if applicable)	C.U.
Category 2	Drafting manuscript	C.U.
	Critical revision of manuscript	A.A., A.K.
Category 3	Final approval and accountability	A.A., A.K.
Other	Technical or material support	C.U., A.A.
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