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CLINICAL REPORT

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Variable neurodevelopmental and morphological phenotypes of carriers with 12q12 duplications

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Abstract

Background: Variable size deletions affecting 12q12 have been found in individuals with neurodevelopmental disorders (NDDs) and distinct facial and physical features. For many genetic loci affected by deletions in individuals with NDDs, reciprocal duplications have been described. However, for the 12q12 region, there are no detailed descriptions of duplication cases in the literature.

Methods: We report a phenotypic description of a family with monozygotic twins diagnosed with NDDs, carrying a 9 Mb duplication at 12q12, and five other individuals with overlapping duplications ranging from 4.54 Mb up to 15.16 Mb.

Results: The duplication carriers had language delays, cognitive delays, and were diagnosed with autism spectrum disorder. Additionally, distinct facial features (e.g., high foreheads, deeply set eyes, short palpebral fissures, small ears, high nasal bridges, abnormalities of the nose tip, thin lips), large feet, and abnormalities in the digits were noted. We also describe incomplete penetrance of the NDD phenotypes among the individuals with 12q12 duplication.

Conclusion: This case series expands our knowledge on this rare genetic aberration and suggests that large 12q12 duplications may increase the risk for developing NDDs.

KEYWORDS
ADHD, autism spectrum disorder, chromosome 12, duplication, phenotype

1 | INTRODUCTION

Rare structural genetic variants, including copy number variation (CNV), have been identified in individuals with a variety of neurodevelopmental disorders (NDDs) such as autism spectrum disorders (ASD) and attention deficit hyperactivity disorders (ADHD) (Deshpande & Weiss, 2018;Lionel et al., 2011;Pinto et al., 2014). Additionally, rare CNVs have been shown to increase the risk for neurodevelopmental challenges, including ASD and ADHD, in the general population (Girirajan et al., 2011;Guyatt et al., 2018;Martin et al., 2019;Williams et al., 2012). Phenotypic descriptions of the carriers of the most recurrent and reciprocal CNV loci have emerged in the recent years (D'Angelo et al., 2016;Deshpande & Weiss, 2018;Hanson et al., 2015;Lowther, Costain, Baribeau, & Bassett, 2017). For clinicians involved in genetic counseling and for the affected families, it is important to expand the understanding, consequences, as well as the phenotypic spectrum associated with certain CNVs.

Previously, deletions affecting the 12q12 region have been published which delineate the associated phenotypes (Adam, Mehta, Knight, Hall, & Rossi, 2010;Carlsen, Frengen, Fannemel, & Misceo, 2015;Failla et al., 2008;Weng, Luo, & Hou, 2018). The 12q12 deletion carriers have been reported to present with intellectual disability (ID), growth restrictions, and distinctive physical features including broad forehead, low-set ears, strabismus, down-slanted palpebral fissures, broad or low nasal bridges, downturned corners of the mouth, small hands and feet, wide-spaced nipples, and testicular abnormalities (Carlsen et al., 2015;Weng et al., 2018). In individuals with NDDs, many genetic loci affected by deletions have reciprocal (or similar size and location) duplications that have been described. However, for the 12q12 region, no detailed descriptions of carriers of reciprocal duplications are currently found in the literature.

We recently characterized CNVs in a Swedish twin cohort, which included a monozygotic (MZ) twin pair with a large duplication affecting the 12q12 region (Stamouli et al., 2018). Here, we report additional findings in this MZ twin pair diagnosed with ASD, ADHD and language delay, as well as family segregation of the CNV. Additionally, assessment information from four other individuals identified with a similar size and location of duplication at 12q12 through the DECIPHER database, along information from the 17-year-old Croatian male patient from Wang et al. (2010), are also included for better characterization of phenotypic presentation of 12q12 duplication carriers.

2 | METHODS

2.1 | Ethical compliance

The overall study where the twin pair was identified was approved by the regional and national ethical boards in Sweden and informed consent was obtained from the various individuals and their parents included in this case series.

2.2 | Patients

We have earlier reported the MZ twin pair with a paternally inherited 9Mb duplication at 12q12 (genomic coordinates hg19, chr12:37995364–47072741) as part of the genetic study investigating CNVs in twin pairs (Stamouli et al., 2018) from the Roots of Autism and ADHD Twin Study in Sweden (RATSS; Bölte et al., 2014). The RATSS recruits twin pairs with NDDs, as well as typical development, and study procedures involve comprehensive data collection from twin pairs including medical and developmental history, physical assessments, and psychological and genetic testing (Bölte et al., 2014). A family history was collected through interview and a medical questionnaire. Carrier analyses of the additional family members were done using either quantitative polymerase chain reaction at the research laboratory or using chromosomal microarray at Sahlgrenska University Hospital. Here, we provide detailed information of the twin pairs' phenotypes and show segregation analysis in their family. Other duplication carriers were identified through the DECIPHER database and literature. The clinicians reporting these duplications were contacted to obtain any physical, medical, and behavioral findings and a consent from the individuals and/or families to be included in the study.

3 | RESULTS

3.1 | Detailed phenotypic description of the affected twin pair

3.1.1 | Obstetric data and early physical health

The twins were born at 37 weeks gestation via a planned cesarean section. Prenatally, excess amniotic fluid was present and Twin 1 was diagnosed with craniosynostosis. Following birth, Twin 1 underwent surgical intervention for

the synostosis with postoperative complications including a seizure, brain hemorrhage, and pneumonia. Twin 2 had no birth complications. At birth, Twin 1 was 2.710 g and 47 cm and Twin 2 was 3.060 g and 48 cm. The twins had minor health issues throughout childhood. Twin 1 had one reported febrile seizure, dust mite allergy, and vision problems and Twin 2 had pollen allergy. Karyotyping of the twins was performed during early childhood, but was reported to be without abnormalities.

3.1.2 | Behavioral assessments

Both twins had early developmental delays, primarily in the area of speech-language, fine motor, and cognitive skills. In their early years, the twins had limited spoken vocabulary and comprehension of words. The twins were assessed by psychologists at several points during their childhood, diagnosed formally with ADHD at age 3, and received special education services in school. Following the psychological assessments in RATSS at age 17, both twins were diagnosed with ASD, ADHD (combined presentation), and specific phobia of darkness. Additionally, both twins presented with learning difficulties and cognitive impairments (Table 1). Physical assessments of the twins were conducted by experienced clinical geneticists using an already published procedure (Myers et al., 2017).

3.1.3 | Morphological examination

Twin 1 presented at 17 years with a high, sloping forehead, and postsurgical scars on his head following earlier craniosynostosis surgery. Twin 2 presented with a triangular face and a high, bulging forehead. In addition, both had straight eyebrows, narrow, short palpebral fissures, deeply set eyes, small ears, high nasal bridges, narrow nose tips, thin upper lips, high, arched palates, broad distances between nasolabial ridges, and wore braces. The right helix on the ear of Twin 1 was overfolded (and had been operated on), while his left ear had a thin helix. Twin 2 had attached earlobes and had short digit II bilaterally on both fingers and toes. Both twins had large, wide feet (European size 48) with pes planus and a slight sandal gap. The twins had achieved full puberty at examination. Height, weight, length, and head circumference for both twins were within the normal ranges (Table 1 and Table S1).

3.1.4 | Segregation analysis and family history of affected twins

The duplication was paternally inherited and two additional family members (an older sister and her 5-year-old male child) were also identified as carriers of the duplication (Figure 1). None of the other carriers or noncarriers in the family had NDD diagnoses, nor reported neurodevelopmental challenges. No detailed morphological examination was performed on the other carriers in the family.

3.1.5 | Summary of all identified cases of 12q12 duplications

In addition to the affected twin pair and their family reported above, we identified five additional individuals through DECIPHER and a literature search, representing a total of seven individuals with a similar size and location of the duplication (Figure 2). From DECIPHER, four individuals were identified with duplications covering approximately 70% up 100% of the original duplication in the 12q12 region identified in the twin pair. Additionally, one individual was identified in a previous study on genetic variation in ASD by Wang et al. (2010) with a smaller duplication covering just under 50% of the same region as the duplication in the twins. The identified duplications range in size from 4.54 Mb in length to 15.16 Mb, with the minimum overlapping region spanning 3.9 Mb in size and containing 11 genes (Table 1, Figure 2). For two of the five individuals, only information related to the location and size of the duplication from DECIPHER is available as the patients moved or were unable to be contacted.

Six of the seven individuals with the duplication were males and ranged in age from 4 to 25 years at the most recent assessment. The duplications were reported to be of paternal inheritance in three individuals (including the twin pair) and maternal inheritance in one individual. In the prenatal and obstetric period, the carriers had reported intrauterine growth restriction ($n = 1$), failure to progress in delivery and poor fetal heart rate ($n = 1$), and excess amniotic fluid ($n = 2$) (see Table S1 for full details). All individuals were born at 37 weeks gestation or later. Two individuals were born vaginally, while three were born via cesarean section. Reported developmental issues included learning difficulties ($n = 5$), speech delay ($n = 5$), and cognitive impairment ($n = 5$), along with delays in fine ($n = 3$) and gross motor ($n = 3$) development (see Table 1 for further details). Four individuals (twin pair and two other individuals) either had a diagnosis of ASD or elements of autism-like behavior and the affected twins were both diagnosed with ADHD. Physical characteristics were reported in five of the individuals (Table 1, Table S1) and include anomalies in the facial region and toe digits.

4 | DISCUSSION

We provided a detailed phenotypic description of a male MZ twin pair carrying a rare 12q12 duplication together with a case series of five individuals with similar duplications. We show that

TABLE 1 The genetic, demographic, and phenotypic characteristics of participants with 12q12 duplications and presence of features in 12q12 deletion syndrome

Study site	Twin 1 RATSS, Sweden	Twin 2 RATSS, Sweden	Individual 1 Wang et al., 2010	Individual 2 Leeds (DECIPHER ID 280346)	Individual 3 Nantes (France) (DECIPHER ID 349,597)	Individual 4 Lille (France) (DECIPHER ID 254078)	Individual 5 DECIPHER ID 288184		
Genetic and demographic findings									
Size of aberration (bp)	9,077,378	9,077,378	4,538,000	6,191,135[a]	6,143,598	10,607,906	15,159,042		
Inheritance	Paternal	Paternal	NA	Paternal	Maternal	NA	NA		
Sex (M = Male, F = Female)	M	M	M	M	M	M	F		
Age at examination (years)	17	17	25	5.5	4	8	NR		
Weeks gestation	37	37	42	39	38	NA	NA		
								Count	Features in 12q12del
Selected morphological findings									
Abnormal head/facial shape	+	+	−	−	−	NA	NA	2/5	+
Deeply set eyes	+	+	−	−	−	NA	NA	2/5	
Abnormal palpebral fissures	+	+	−	+	+	NA	NA	4/5	+
Vision problems	+	−	−	−	+	NA	NA	2/5	+
Small ears	+	+	−	−	+	NA	NA	3/5	
Abnormal nasal bridge	+	+	−	−	−	NA	NA	2/5	+
Abnormality of nasal tip	+	+	−	−	+	NA	NA	3/5	
Highly arched palate	+	+	−	−	−	NA	NA	2/5	+
Thin upper lip vermillion	+	+	−	−	−	NA	NA	2/5	
Toe anomalies	−	+	−	−	+	NA	NA	2/5	+
Neurodevelopmental characteristics									
Delay in gross motor skills	+	+	NR	NR	+	NA	NA	3/3	
Delay in fine motor skills	+	+	+	NR	NR	NA	NA	3/3	
Cognitive impairments (including ID)	+	+	+	+	+	NA	NA	5/5	+
Speech/language delay	+	+	+	+	+	NA	NA	5/5	+
Autism/autistic behavior	+	+	+	−	+	NA	NA	4/5	+
Hyperactivity/ADHD	+	+	−	−	−	NA	NA	2/5	

Abbreviations: ADHD, attention deficit hyperactivity disorders; ID, Intellectual disability; NA, Not Available; NR, Not Reported; RATSS, Roots of Autism and ADHD Twin Study in Sweden; +, Feature Present; −, Feature Not Present.
[a]Minimum reported size.

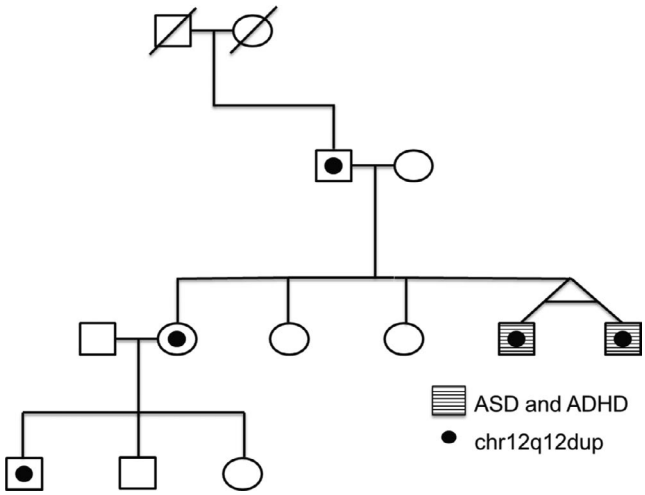

FIGURE 1 Three-generation pedigree of the twin pair showing duplication carriers and neurodevelopmental phenotypes

all cases with detailed information available had learning difficulties, cognitive disabilities, language delay, gross motor delays, and at least one NDD ranging from ID to ASD. However, we report incomplete penetrance of the duplication carriers, including the three-generation family of the MZ twin pair with nonsymptomatic carriers (Figure 1), which suggest that the affected family members potentially could be carriers of additional genetic risk variants or were exposed to environmental risk factors leading to more severe outcomes. Overall, we describe variability in the reported physical features and developmental issues among the carriers. In general, individuals with this duplication are primarily males with both maternal and paternal inheritance of the duplication. Potential morphological features associated with this duplication are primarily limited to those present in the twin pair with the most detailed examinations (Table 1, Table S1). However, two features, small ears and abnormality of the nasal tip, were described in one additional carrier.

Several reports have been published on phenotypic characteristics of individuals with 12q12 deletion syndromes (Adam et al., 2010;Carlsen et al., 2015;Failla et al., 2008;Weng et al., 2018). Phenotypic characteristics reported for individuals with 12q12 deletion in Adam et al. (2010) and Weng et al. (2018) were compared with the individuals in this case series (Table 1). In addition to the NDD diagnoses, physical features common to individuals with both deletions and those reported here with duplications in the 12q12 region include abnormalities in head shape, forehead, eyes, vision, ears, nose, oral-facial region, and toe digits. Chromosomal deletions result in haploinsufficency, while duplications may result in the production of excess proteins due to extra genes being present in the region (Clancy & Shaw, 2008). The resulting effects on protein production related to these aberrations may result in the similar, as well as different, phenotypic features found in 12q12 duplication and deletion carriers.

Prenatal and postnatal issues (e.g., excessive amniotic fluid in the twin pair, craniosynostosis in Twin 1, intrauterine growth restriction, etc.) may have been related to some of the phenotypic features found in individuals in this case series. For example, excessive amniotic fluid in the form of polyhydramnios can be caused by abnormal swallowing by the fetus in utero due to some type of genetic or central nervous system issue (Hara, Kikuchi, Miyachi, Sunagawa, & Takagi, 2006;Sandlin, Chauhan, & Magann, 2013). Meanwhile, craniosynostosis can lead to a variety of variations in physical appearance, including issues with eyes and digits, but these issues are generally present in syndromic craniosynostosis (Panigrahi, 2011). Meanwhile, intrauterine growth restriction

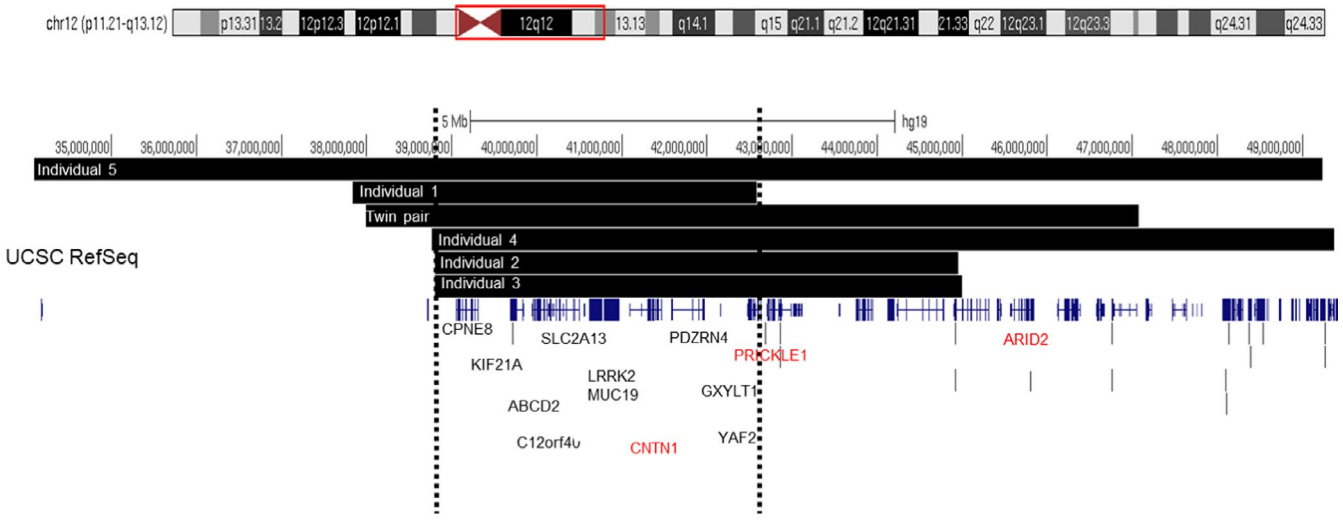

FIGURE 2 Schematic view of the 12q12 duplication region and the corresponding lengths of the duplications found in the twin pair and other five individuals described in the study, including area of minimal overlap (dashed lines) and selected genes. Gene symbols highlighted in red have been discussed in the paper

has been associated with the later presence of neurodevelopmental delays (Hartkopf et al., 2018;Sharma, Shastri, & Sharma, 2016).

The CNV region reported in this paper includes several protein coding genes, of which at least three (i.e., *CNTN1, ARID2,* and *PRICKLE1*), have been implicated previously in NDDs through multiple reports. *CNTN1* (*Contactin* 1, MIM 600016) is in the minimal overlap region for the carriers presented in this paper with 12q12 duplication, and is part of the contactin gene family from which multiple genes (i.e., *CNTN4*, *CNTN5*, and *CNTN6*) have been associated with the cases of ASD (Mercati et al., 2017;Zuko et al., 2013). Zuko et al. (2013) purport that contactins may play a critical role in normal brain development and individuals with mutations in these genes may present with a phenotype of ASD. *ARID2* (*AT-Rich Interaction Domain 2*, MIM 609539) plays a role in gene regulation through chromatin remodeling (Xu, Flowers, & Moran, 2012). Mutations affecting *ARID2* were found in four cases with Coffin-Siris syndrome 6 (MIM 617808) characterized by ID, speech delay, ADHD, and dysmorphic facial features (Shang et al., 2015). Additional reports have been published regarding individuals with *ARID2* mutations and all these reports describe the presence of ID and dysmorphic features (Bramswig et al., 2017;Gazdagh et al., 2018;Zahir et al., 2016). *PRICKLE1* (*Prickle Planar Cell Polarity Protein 1*-MIM 608500) is believed to play an important role in nervous system development and it has been linked to early-onset epilepsies, as well as some progressive neurological syndromes (Mastrangelo et al., 2018;U.S. National Library of Medicine, 2017). A study in mice found that mutations in *PRICKLE1* resulted in ASD-like behaviors (Paemka et al., 2013), as well as craniofacial abnormalities (Wan, Lantz, Cusack, & Szabo-Rogers, 2018). Later, genetic variants affecting *PRICKLE1* have been found in ASD cases (Cukier et al., 2014;Todd & Bassuk, 2018), demonstrating the potential role of the gene across NDDs.

In summary, we report here seven individuals with 12q12 duplication with variable NDDs along with abnormal physical features, of which some were common with the earlier described 12q12 deletion cases. There are multiple genes thought to be related to speech-language development, ID, and ASD in the largest region affected by the 12q12 duplications region that could be causal for the phenotypes seen in the duplication cases. Further cases are needed to confirm our physical and behavioral findings and possibly support a 12q12 duplication syndrome phenotype.

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AUTHOR CONTRIBUTIONS

LM and KT conceived and planned the study, and drafted the manuscript. MB, KM, DH, SP, JI, AN, MB, MV, SB, B-MA and KT acquired clinical phenotype data and/or analyzed genetic material. LM with help of AN, B-MA and KT did the final analyzes of the clinical data. All authors provided critical feedback on the analysis and manuscript, and approved the final version.

DATA AVAILABILITY STATEMENT

All available clinical data are shared in the article. The raw genetic data that support the findings of this study are available on request and clearance from the ethical board from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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