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a case report

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Published in:
Journal of Medical Case Reports

DOI (link to publication from Publisher):
10.1186/s13256-025-05124-2

Publication date:
2025

Document Version
Publisher's PDF, also known as Version of record

Journal of
Medical Case Reports

CASE REPORT

Open Access

Autism spectrum disorder and 3p24.3p23 triplication: a case report

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Abstract

Background The role of copy number variants as genomic mutations causative of neurodevelopmental disorders has been recently established. They can act as risk factors of conditions with multifactorial etiopathogenesis and incomplete penetrance, such as nonsyndromic autism, and, in this case, are often inherited from an unaffected parent. Conversely, dominant syndromes, with high penetrance, can be caused by de novo occurring variants.

Case presentation We describe the clinical case, with a detailed characterization of the neuropsychiatric profile, of an almost 3-year-old white (Italian) male child with autism spectrum disorder, developmental delay, mild dysmorphic traits, and congenital anomalies (cardiac septal defects, gliotic changes, thinned corpus callosum, and arachnoid cyst), carrying a 13 Mb de novo 3p24.3p23 triplication.

Conclusion Our case suggests that the 3p24 chromosome region could be associated with a syndromic form of autism spectrum disorder and contribute to delineate its distinct clinical features. The extent of the de novo variant described herein is suggestive of pathogenicity, although the genes potentially responsible for the patient's phenotype are not easy to identify. We hypothesize that the dysregulation of *SATB1*, already associated to two syndromes (developmental delay with dysmorphic facies and dental anomalies and Den Hoed–De Boer–Voisin syndrome) with a phenotypic spectrum comparable to that of our patient, could be responsible for the clinical phenotype of this case, although the exact pathogenetic mechanism remains to be determined.

Keywords 3p triplication, 3p24.3p23, Autism, Neurodevelopmental disorder, Case report

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Background

Chromosomal copy number variations (CNVs) such as microdeletions and microduplications are a major cause of neurodevelopmental disorders (NDDs) and/or congenital defects (CDs), accounting for at least 15% of cases [1]. The primary mechanism by which CNVs can result in a pathogenic effect is the gene dosage alteration, when a CNV encompasses gene-dosage sensitive genes (haploinsufficient and triplosensitive genes; see Clingen; https://www.clinicalgenome.org/). Usually, the pathogenic contribution of a gain is more complicated to ascertain because the human genome is inherently more tolerant to dosage increase than to dosage reduction [2]. Finally, CNVs can sometimes exert a pathogenetic effect interfering with the spatial organization of the genomic region and/or disrupting proper interactions between genes and their regulatory elements [3]. Therefore, in some instances, gains—whether arranged in tandem or inserted elsewhere—can interfere with the genomic architecture of the insertion site and impact genic transcription in a way comparable to a gene loss of function. Conversely, a loss can act by producing a gain-of-function of a nearby gene, owing to topologically associating domains (TADs) fusion [4].

Several rare CNVs are associated with specific syndromic phenotypes transmitted in autosomal dominant fashion with a de novo occurrence [5]. Moreover, the application of genomic microarray analysis (CMA) in the last decade allowed for the identification of nonrecurrent CNVs in patients with NDDs/CDs with overlapping duplicated/deleted regions. This contributed to the defining of phenotype–genotype correlations and finally to the mapping of new disease-genes [6].

We describe the clinical case of a child diagnosed with a syndromic form of autism spectrum disorder (ASD) associated with global developmental delay (including motor, language, play, and social skills), carrying a de novo 3p triplication (3p24.3p23). To date, patients with syndromic forms of ASD displaying CNVs in the short arm of chromosome 3 have been frequently associated with the presence of microdeletion of the terminal cytoband of chromosome 3p, causing the 3pter-p25 syndrome (no. 613792). Within this region, *CHL1*, *CNTN6*, and *CNTN4* have been selected as likely NDDs candidate genes [7]. Very rarely, microduplications affecting the chromosomal region involved in the present case have been described [8]. The few published 3p duplications of different size in ASD-associated phenotypes suggest that a 3p chromosome region, more proximal and possibly restricted to 3p24, could be associated with NDDs (Supplementary Fig. S1). At the best of our knowledge, triplications of this chromosomal region have not yet been reported.

Case presentation

The child, an almost 3-year-old Italian male child, was referred to our child psychiatry unit to perform a clinical evaluation of language, motor, and sociocommunicative abilities.

The patient is the first child of a healthy white nonconsanguineous couple, born by vaginal delivery at 41 + 2 gestational weeks, after an uneventful pregnancy. At birth, his weight was 3490 g; height was 52 cm; head circumference was 35 cm; and Appearance, pulse, grimace, activity, and respiration (APGAR) score was 6 at the first minute and 8 at the fifth minute because of mild perinatal asphyxiation treated with manual ventilation. Micrognathia, strabismus, and neonatal jaundice (treated with phototherapy) were observed at birth.

The newborn immediately underwent a cardiology counseling, which displayed a slightly hypertrophic interventricular septum with false tendons and altered Doppler echocardiography velocity in the pulmonary artery. Furthermore, the otolaryngology analysis, including auditory brainstem response (ABR), did not reveal any anomalies.

At 20 days of life, a genetic consultation was performed and CMA requested. CMA was performed with an effective resolution of 75 Kb using a single nucleotide polymorphism (SNP)-array platform (CytoScan HD; Affimetrix, Santa Clara, CA, USA), which revealed a male genomic profile with a triplication of the short arm of chromosome 3 in the region 3p24.3p23, spanning approximately 13.4 Mb (arr[GRCh37] 3p24.3p23 (18093079_31485349) × 4). The segregation analysis by locus-specific fluorescent *in situ* hybridization (FISH), performed with labeled DNA extracted from clones included in the 32 K library (BACPAC Resources, Oakland, CA, USA), displayed the de novo origin of the triplication and allowed for the detection of the inverted configuration of the middle and the localization in tandem of the distal extra copy (Supplementary Fig. S1). The triplicated region includes 30 RefSeq genes, 15 Online Mendelian Inheritance in Man (OMIM), and 7 OMIM Morbid genes and was classified as likely pathogenic owing to the extension and de novo occurrence, according to the American College of Medical Genetics and Genomics (ACMG)/ClinGen guidelines [9].

The child showed a significant delay in developmental milestones: at 7 months, he held his head up, and at 12 months, he acquired trunk control. The standing position was possible at 12 months and independent walking at 24 months. Babbling was reported at 26 months, though first words did not occur yet. The sleep/wake cycle was characterized by difficulty in falling asleep, frequent awakenings, and motor restlessness. Feeding was

regular, although with some chewing difficulties; constipation was reported.

His parents reported deficits in social communication and social interaction, restrictive patterns of behavior, and strong sensory seeking, with notable atypical sensory processing characterized by marked visual and tactile self-stimulation in addition to hand mannerisms and body rocking.

At the age of 15 months, the child underwent his first neuropsychiatric assessment, which revealed a neurodevelopmental delay and social–relational difficulties. Physiotherapy intervention was prescribed. At 26 months, a new clinical evaluation was conducted, confirming the neurodevelopmental delay with the renovated prescription of physiotherapy in addition with speech therapy. In the context of this evaluation, the following instrumental investigations were performed: electroencephalogram (EEG; which did not reveal significant alterations) and brain magnetic resonance imaging (MRI; which showed the presence of gliotic changes, reduction in size of the thinned corpus callosum, and a retro-cerebellar arachnoid cyst in the left median-paramedian location). Family history was reported as negative for neurological and psychiatric diseases.

Neuropsychiatric assessment

The child referred to our child psychiatry unit at 28 months for an in-depth analysis of their developmental profile including communicative difficulties, motor abilities, social skills, and atypical patterns of behavior. To depict an accurate clinical picture and to evaluate the developmental trajectory of the child, we performed two clinical evaluations, the first one at 28 months of age and a follow-up after 6 months (34 months of age) (Table 1).

Table 1 Neuropsychiatric assessment

	Baseline assessment	Follow-up assessment
Age	28 months	34 months
Griffiths III (DE; DQ)		
Total	15; < 50	20; 50
Subscale A	12; 50	14; < 50
Subscale B	13; < 50	16; < 50
Subscale C	13; < 50	18; < 50
Subscale D	14; < 50	17; 50
Subscale E	19; 63	19; < 50
ABAS II *(composite score)*		
GAC	43	45
CAD	47	47
SAD	48	52
PAD	49	47
ADOS-2	SA = 20	SA = 16
	RRB = 6	RRB = 8
	Total score = 26	Total score = 24
	CSS = 10/10	CSS = 9/10
CBCL (*T* score)		
Internalizing problems	69	65
Externalizing problems	57	58
Total problems	63	63
SCQ—Last 3 months	27	24

The table includes all the clinical tests (scales and parental questionnaires) performed at baseline and follow-up evaluations

ABAS adaptive behavior assessment system, *GAC* general adaptive composite, *CAD* conceptual adaptive domain, *SAD* social adaptive domain, *PAD* practical adaptive domain, *ADOS-2* autism diagnostic observation schedule, second Edition; *SA* social affect, *RRB* restricted and repetitive behaviors, *CSS* calibrated severity score, *DE* developmental age, *DQ* development quotient, *CBCL* child behavior checklist, *SCQ* social communication questionnaire

First assessment

At 28 months of age, we carried out an assessment of his developmental level, adaptive skills, and sociocommunicative and behavioral profile, through the administration of standardized tools (Table 1).

At this age, the child was able to walk independently; however, first words had not occurred (he pronounced only sounds).

The child presented a development quotient (DQ) significantly under the norm (DQ < 50), as measured by the Griffiths Scale Third Edition [10]. Adaptive skills were assessed using the parent report questionnaire, Adaptive Behavior Assessment System (ABAS-II) [11], which showed an adaptive functioning below the average.

ASD symptoms were evaluated according to the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, Text Revision (DSM-5 TR) [12] criteria and through the administration of the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) [13], performed by a licensed clinician. Specifically, the child underwent the toddler module of the ADOS-2, suitable for children with a chronological age ranging from 12 to 30 months. The diagnostic algorithm is organized in two main areas: social affect (SA) and restricted and repetitive behavior (RRB). The total score obtained (26) was suggestive of a moderate risk for ASD.

In addition, an evaluation of problematic behaviors and sociocommunicative skills was performed through the following parental questionnaires. The Social Communication Questionnaire (SCQ) [14], investigating communicative, social and relational skills, showed a score of 27 (cut-off of 15), meaning that the parents had significant concerns regarding the social skills of the child. The Child Behavior Checklist (CBCL 1,

1/2–5) [15], displayed significant problematic behaviors in both internalizing (withdrawal) and externalizing domains (attention problems and aggressive behavior).

Furthermore, the clinical examination revealed facial dysmorphisms (Fig. 1): broad forehead, arched eyebrows, sunken eyes, long eyelashes, epicanthic folds, square-shaped nose with a broad root, absent columella, high-arched palate, small mandible (micrognathia), large ears with normal placement, and small and widely spaced teeth. Independent walking was present, although uncertain, and he had a widened base, external rotation of the feet, flat feet, sitting posture in kyphosis, and fair postural transitions. The neurological examination revealed muscle strength and trophism of upper and lower limbs ranged within normal limits, although hypertonia in the lower limbs was observed.

At the end of our clinical assessment, the diagnosis of developmental delay associated to the risk of ASD was assigned to the child, specifying the need of a second assessment after 6 months to better contextualize the atypical behaviors. We recommended continuing ongoing rehabilitation therapy and to begin applied behavioral analysis (ABA)—a behavioral intervention specifically recommended for autism symptoms [16]—in addition to the use of augmentative and alternative communication (AAC) techniques which improve the communication skills of children through the use of images. Furthermore, we prescribed the following instrumental examinations: abdominal ultrasound—which did not reveal anomalies of the urogenital system—and an otolaryngology examination, which did not show any hearing deficit.

Follow-up at 6 months distance

At the age of 34 months, to explore the child's developmental trajectory, we performed a new neuropsychiatric evaluation (Table 1). At this age, the child was still nonverbal.

The developmental delay was confirmed by the second assessment of the Griffith III scale. Even the adaptive skills (ABAS-II) verified a functioning below the average in all domains. In this follow-up evaluation, the child underwent Module 1 of the ADOS-2, suitable for children with a chronological age beyond 31 months. The total score obtained (24) exceeded the cut-off (9) for the diagnostic category of autism and, according to the ADOS-2 Calibrated Severity Score (CSS), was suggestive of a high level of ASD symptoms (CSS = 9/10). The parents were asked to fill in the same questionnaires completed during the previous assessment. The SCQ showed a clinically significant score of 24, the CBCL 1, 1/2–5 revealed significant scores in several domains, including "withdrawal" and "internalizing problems".

A conclusive diagnosis of ASD and developmental delay was finally performed. The family was recommended to continue the ongoing rehabilitation intervention (physiotherapy and parental training focused on the management of behavioral problems and the improvement of adaptive skills), reconfirming the need to begin the ABA intervention [16].

We prescribed a physiatric visit for the presence of flat feet/fallen arches with a subsequent prescription of proprioceptive plantar.

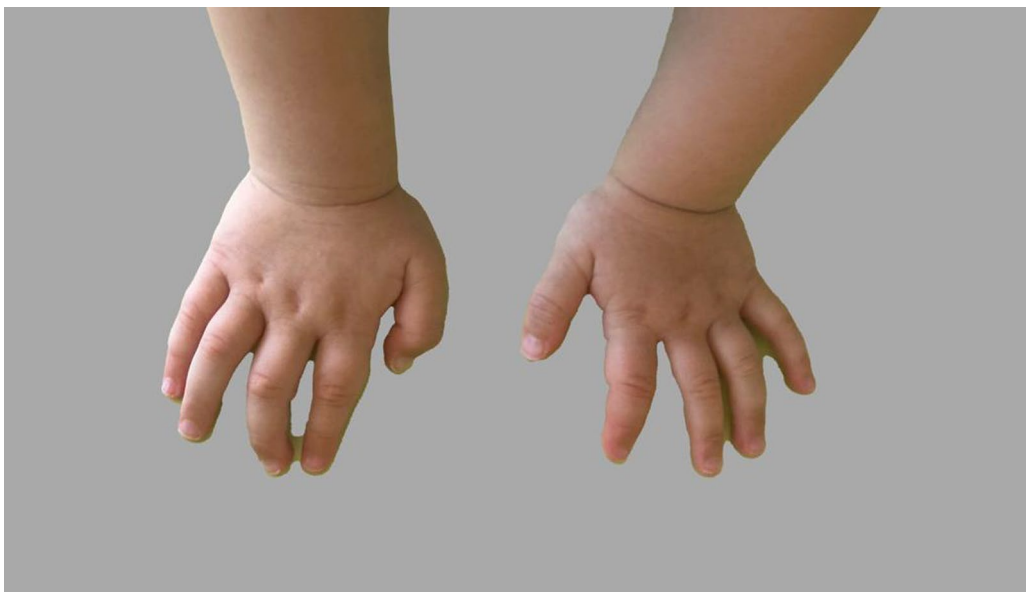

Fig. 1 Hands of the child carrying a de novo 3p triplication (3p24.3p23): brachydactyly more evident on the left hand

Discussion and conclusion

We report the first clinical description of developmental delay and autistic symptoms associated with a very rare genomic aberration: the 3p24.3p23 triplication. Our case report is unique from both a genetic and clinical point of view.

Regarding the clinical perspective, we provide an in-depth clinical assessment of a child characterized by a moderate developmental delay associated with adaptive skills under the norm, in addition to a severe level of ASD, depicting a clinical picture which implies several challenges especially in terms of intervention and long term outcome.

To the best of our knowledge, no previous studies have reported autistic symptoms examined through a standardized assessment in individuals with 3p duplication or triplication.

From a genetic point of view, the detection of a very large, de novo variant is suggestive per se of pathogenicity. While suspecting a causative role for this microtriplication, it is not easy to trace the pathogenic mechanism nor the genes potentially responsible for the patient's phenotype. To date, there are no genes assessed as triplosensitive in the triplicated region (Dosage Sensitivity Curations—ClinGen), even if there are some genes whose predictive scores suggest a possible dosage increase sensitivity (DECIPHER). Among them, *SATB1* (*602075) disregulation could be related to the proband's phenotype. SATB1, special AT-rich binding protein-1, is a chromatin organizer implicated in primary T cell development [17]. SATB1 contributes to epidermal morphogenesis and to cancerogenesis [18, 19]. More recently, it has also been described as a critical transcriptional regulator in cortex development and maturation of neurons and reported in OMIM database as causative gene of two distinct diseases: developmental delay with dysmorphic facies and dental anomalies (DEFDA; no. 619228) and Den Hoed–De Boer–Voisin syndrome (DHDBV; no. 619229), the former being associated with the loss-of-function variants and the latter caused by missense variants and phenotypically more severe. The phenotypic spectrum of both syndromes is broad and characterized by neurodevelopmental delay, intellectual disability, muscle tone abnormalities, cardiac anomalies, behavioral problems, and facial dysmorphisms. The missense mutations are predicted to cause the DHDBV syndrome by enhancing the binding of SATB1 to its target sequences. Therefore, we can hypothesize that the triplication reported in our patient, increasing SATB1 protein dosage, could shift SATB1 binding balance, resulting in a globally increased repressive effect on its target genes [2] and leading to a phenotypic effect resembling that of DHDBV syndrome. In contrast, *SATB1* is the gene closest to the distal edge of the amplificated region; therefore, we cannot exclude that it could undergo chromatin context variation related to the presence of a wide rearrangement and be affected by transcriptional interference. In fact, several papers show the complexity of transcriptional regulation of *SATB1* and the presence of several tissue specific enhancers even far away from the gene [20, 21]. In that case, the etiopathogenesis of this condition should be related to *SATB1* haploinsufficiency and therefore related to DEFDA syndrome. Both of our hypotheses are supported by the high phenotypic compatibility of our proband with both the clinical pictures associated with *SATB1* (Supplementary Table). In particular, the present patient shows some dysmorphic features reported in SATB1-related syndromes, such as the prominent forehead (DHDBV/DEFDA) and small chin, strabismus, broad nasal root, and small and widely-spaced teeth reported in DEFDA. The patient also shows a cardiac defect and brain anomalies (both described in DHDBV/DEFDA), as well as constipation (DEFDA). The neurologic and behavioural profile is very similar to that recorded in patients with *SATB1* mutations and includes global developmental delay, walk and language delay, sleep disturbances, and ASD with aggressive behavior. To the best of our knowledge, the only published case carrying a 3p24 microduplication including *SATB1* was described by Kaminsky and colleagues. Moreover, we selected from the DECIPHER database a further case with a pure gain overlapping the duplication of the current patient (patient no. 305061) that entirely includes *SATB1* and presented with short stature and learning disabilities. However, making genotype–phenotype correlations is difficult owing to the lack of accurate descriptions of these patients. In addition, our patient carries a triplication and may be subject to a more relevant dose increase.

Moreover, it cannot be excluded that the genomic rearrangement identified in the present case could interfere with the expression of other genes. The smallest overlapping region that we identified by comparing the duplicated genomic segments of all cases so far known includes the RefSeq gene *miR-4791* and the OMIM gene *KCNH8* (*608260). The latter is a member of the human Elk K^+ channel gene family, expressed mainly in the human nervous system. However, to date, it is not associated to pathology, and there is no data documenting its putative triplosensitivity (Supplementary Fig. S1).

In conclusion, the definition of a cognitive and behavioral clinical phenotype, in the context of genetic syndromes and genetic mutations, represents a key topic for both clinicians and families. In fact, awareness of a specific developmental and behavioral trajectory has notable therapeutical implications which can impact the outcome of the patient. Therefore, we recommend a

neuropsychiatric assessment in these conditions starting from early stages of development.

Further descriptions of the clinical profile of individuals carrying the same mutation will enable us to better delineate a specific neuropsychological profile and developmental trajectory of the genetic condition and could corroborate the role of the promising candidate genes located to this region, *SATB1* and *KCNH8*, in the etiology of ASD.

Website resources

DECIPHERhttps://www.deciphergenomics.org/

Dosage Sensitivity Curationhttps://dosage.clinicalgenome.org/

OMIMhttps://omim.org/

Abbreviations

ASD	Autism spectrum disorder
CNVs	Chromosomal copy number variations
NDDs	Neurodevelopmental disorders
CDs	Congenital defects
CMA	Microarray analysis
ABR	Auditory brainstem response
FISH	Fluorescent *in situ* hybridization
OMIM	Online inheritance in man
EEG	Electroencephalogram
MRI	Magnetic resonance imaging
DQ	Development quotient
ABAS-II	Adaptive behavior assessment system
DSM-5 TR	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, Text Revision
ADOS- 2	Autism Diagnostic Observation Schedule, second edition
SA	Social affect
RRB	Restricted and repetitive behaviors
SCQ	Social communication questionnaire
CBCL	Child behavior checklist
ABA	Applied behavioral analysis
AAC	Augmentative and alternative communication
CSS	Calibrated severity score

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13256-025-05124-2.

Additional file 1.

Acknowledgements
This work was supported by the Italian Ministry of Health with Current Research funds.

Author contributions
MS was responsible for the conceptualization, neuropsychiatric evaluation, and data curation and was a major contributor in writing, reviewing, and editing the final draft. MS and EC performed the neuropsychiatric evaluation and were major contributors in writing the original draft. GM and AS performed neuropsychiatric evaluation and were responsible for data collection and curation. LM, CG, and RM were major contributors in writing, reviewing, and editing the final draft. AP performed the genetic analyses and the genetic clinical evaluation. LB and MG performed the genetic analyses and were major contributors in writing, reviewing, and editing the final draft. All authors read and approved the final manuscript.

Funding
This work was supported by the Italian Ministry of Health with Current Research funds.

Availability of data and materials
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available owing to privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate
Ethical approval was not required for this case report, as it does not meet the definition of human research under our institution's guidelines.

Consent for publication
Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare they have no competing interests.

Received: 5 May 2024 Accepted: 31 January 2025
Published online: 10 March 2025

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