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Original paper

A 14q31.1-q32.11 deletion case: Genotype – Neurological Phenotype Correlations in 14q interstitial deletion syndrome

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Abstract Interstitial deletions involving the long arm of chromosome 14 are rare conditions that associate facial dysmorphism, neurological features such as seizures, motor and cognitive delay with speech problems and autistic traits. We report on an 11-year-old girl of Tatar origin with an interstitial deletion involving region 14q31.1-q32.11. The affected region encompasses 46 genes, including 19 Mendelian genes. Epilepsy, motor and cognitive delay and speech problems are the main neurological features identified in our patient. Through the accurate mapping of the deleted region and comparison with previously reported patients, we aim to expand the knowledge regarding genotype-phenotype correlations in 14q interstitial deletion cases.

Keywords aCGH, 14q31.1-q32.11 deletion, *NRXN3*, epilepsy, EEG abnormalities.

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Introduction

Establishing the genetic aetiology of rare conditions has a significant impact on the quality of life of the patients and their families (VEARS et al, 2015 [1]; LINGEN et al, 2016 [2]; JAITOVICH GROISMAN et al, 2019 [3]; TEDRUS et al, 2020 [4]; GABRIEL et al, 2020 [5]). The development and improvement of classical or new genomic technologies over the last two decades (SCHEFFER et al, 2011 [6]; MEFFORD, 2015 [7]; GONSALES et al, 2015 [8]; DOMINGUEZ-CARRAL et al, 2017 [9]; ORSINI et al, 2018 [10];OATES et al, 2018 [11]) offered valuable and complex data to be used in the genetic counselling of cases with congenital anomalies, intellectual disability, autism spectrum disorders or epilepsy(OLSON et al, 2014 [12]; NICITA et al, 2015 [13]; LOVREČIĆ et al, 2018 [14]; BĂNESCU 2019 [15]; COLLIVA et al, 2019 [16]; CAMPBELL et al, 2019 [17]). Chromosome 14 anomalies (both single-gene disorders and submicroscopic changes – deletion or duplication) are reported to be associated with: microcephaly, facial dysmorphic features, postnatal growth delay, pharmacoresistant seizures, autism, intellectual disability, cognitive delay with speech problems, vision loss and cerebral, heart, genitourinary or renal abnormalities (NICITA et al, 2015 [13]; MAURIN et al, 2006 [18]; CINGÖZ et al, 2011 [19]; TORGYEKES et al, 2011[20]; YOUNGS et al, 2012 [21]; ZOLLINO et al, 2012 [22]; OEHL-JASCHKOWITZ et al, 2014 [23]; RIEGEL et al, 2014 [24]). Genetic counselling of such cases is a complex process (GODARD et al, 2004 [25]; LESCA and DEPIENNE 2015 [26]; GIUSSANI et al, 2020 [27]) and requires specific and complete data regarding prognosis and long-term management (KALSER and CROSS, 2018 [28]). Genetic diagnosis through high-resolution chromosomal analysis has improved the detection and molecular characterisation of microdeletions and microduplications (OLSON et al, 2014 [12]; MAGALHÃES et al, 2019 [29]; ELLIS et al, 2020 [30]) involving the long arm of chromosome 14. Accurate mapping of the affected regions, as well as the continuously updated online literature (MYERS & MEDFORD, 2015 [31]) and medical databases, have contributed to a better insight of the genotype-phenotype correlation (AVANZINI et al, 2018 [32]).

Here, we report on a patient with a *de novo* 14q31.1-q32.11 interstitial deletion. We have identified gene content, characterized deletion breakpoints and compared the clinical traits of our patient with those described in other reported cases with 14q interstitial losses of different sizes.

Clinical Report

Our patient was born at 38-weeks after an uneventful pregnancy, to healthy and non-consanguineous parents of Tatar origin. Her birth weight was 2850 g (25th centile), length was 49 cm (50th centile), and head circumference was 35 cm (75th centile). The Apgar score was 8. There was no family history of genetic conditions or birth defects. Her neonatal course was without significant events. Motor development was almost normal, with a mild lag in reaching the sitting position (7 months old) and walking independently (1 year and 3 months old), while language acquisition was delayed. The patient had learning difficulties, poor concentration and social interactions and an IQ of 62 (mild intellectual disability). The patient has always been at the high point of the weight for age curve, with normal stature.

Figure 1. Clinical Phenotype: The patient at 11 years of age.

At the age of 5, she presented unprovoked generalized seizures. The electroencephalogram (EEG) evaluation showed bilateral centro-temporal discharges of spike-wave complexes, with maximal amplitude in the right derivations. Routine biochemical analysis, hormonal profile and electrocardiogram yielded normal results. Cardiac and abdominal ultrasound findings were unremarkable. The first MRI exam identified unspecific periventricular signal anomalies. The second MRI performed at 10 years old revealed normal results. Seizures were relatively well managed for 7 months with Oxcarbazepine. Upon reoccurrence of the seizures, Nitrazepam was added but it was later replaced by Clobazam due to side effects reported by parents (daytime drowsiness). The family reported increasing speaking difficulties, therefore Clobazam was also withdrawn.

The most recent follow-up was at 11 years old. Neurological examination revealed balance problems and walking difficulties, with poor expressive and receptive language skills. Her language and social skills have been constantly improved with specific therapies (speech therapy and cognitive-behavioral therapy). Seizures are controlled by Oxcarbazepine and Levetiracetam. EEG showed very rare discharges, predominantly during sleep. Physical examination revealed an overweight child, with an androgynous distribution of fatty tissue, particularly on the back of the neck and interscapulary, and with facial dysmorphism: upslanted palpebral fissures, round face, broad nasal bridge with mild hypertelorism (Figure 1). The patient has a hypopigmented macula on her torso, with a 5 cm diameter, present since birth. No other skin anomalies were identified. She has thoracic-cervical kyphosis and lumbar hyperlordosis.

Material and Methods

Blood was obtained from the patient after her parents had signed an informed consent. Genomic DNA was obtained from peripheral blood leukocytes, according to the protocol of the Wizard® Genomic DNA Purification Kit (Promega, Madison, WI, USA). Assessment of DNA

purity and concentration was performed through spectrophotometric measurements (Eppendorf Biophotometer).

High-resolution microarray (aCGH – comparative genomic hybridization) analysis was performed with Agilent SurePrint G3 CGH ISCA v2 8x60K microarrays, using commercially available male and female genomic DNA (Agilent Technologies, Human Reference DNA, Male and Female). All the procedures (restriction digestion, fluorescent labeling, purification of both patient and reference gDNA, hybridization, microarray wash and microarray scanning and analysis) were performed according to the manufacturer's protocol (Agilent protocol – Version 7.4 August 2015). The NimbleGen MS 200 Microarray Scanner (Roche) acquired the array images. Agilent Feature extraction software was used to data extraction. Copy number data was analyzed with Agilent Cytogenomics 5.0 software (Agilent Technologies Inc., US).

Results

The aCGH analysis revealed a loss of genomic material corresponding to an interstitial deletion on the long arm of chromosome 14, 14q31.1-q32.11 region, of approximately 11.4 Mb: Arr[GRCh37] 14q31.1-q32.11 (79843213 – 91261373)x1 (ISCN 2016), (Figure 2). No karyotype was performed before to the child. The parental cytogenetic analysis was normal. The deleted region encompasses 46 RefSeq genes, of which 18 OMIM genes (*NRXN3, DIO2, TSHR, GTF2A1, STON2, SEL1L, FLRT2, GALC, GPR65, KCNK10, TTC8, SPATA7, PTPN21, ZC3H14, FOXN3, TDP1, KCNK13, PSMC1, CALM1*).

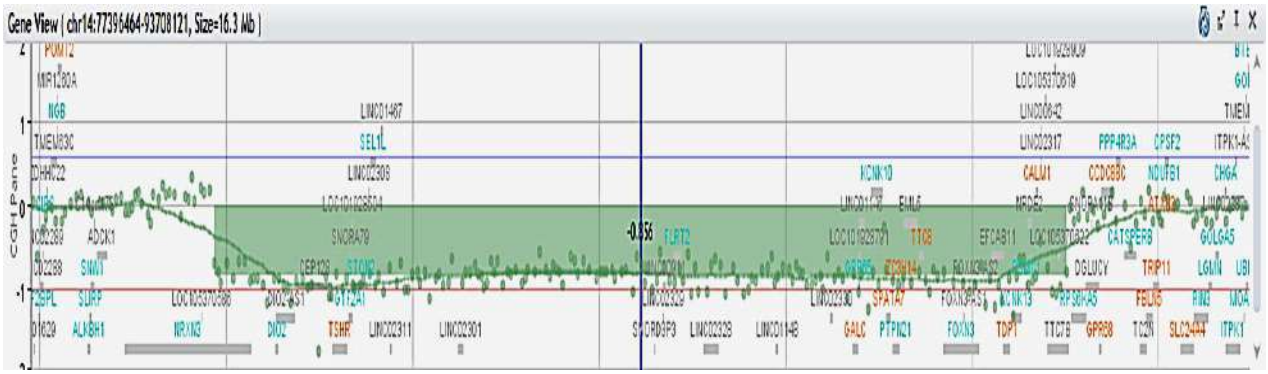

Figure 2. Chromosome 14 aCGH profile of the patient: detail of the 14q31.1-q32.11 region showing the deleted region of ~11, 4 Mb.

Table 1. Neurological features of the ten patients with 14q interstitial deletion containing the *NRXN3* gene

Patient	Deleted region	Deletion size	Seizures (age of onset; type)	EEG	MRI abnormalities
M, 11y – Kawamura et al, 1985	14q24.3-q32.1	NR	Single afebrile seizure at 11 y	No epileptic anomalies	NR
M, 2y - Ono et al, 1999	14q24.3-q32.1	NR	Simple FS at 13mo	Spikes in right O region	Frontal atrophy and delayed myelination
F, 5y - SchladeBartusiak et al, 2008 (HSC23984)	14q24.3-q32.1	18,5 Mb	Focal, 2y	T-O anomalies	Normal
M, 2y 1mo - Nicita et al, 2015	14q24.3-q31.1	5,5 Mb	9 mo; Focal	Spikes in bilateral C regions	Corpus callosum hypoplasia; enlargement of fronto-temporal sub-arachnoids spaces
M – Patient 332786 – Decipher Database	14q31.1	234,89 kb	seizures	NR	NR
M – Patient 332786 – Decipher Database	14q31.1	91,25 kb	Infantile spasms, seizures	NR	NR
F, 13y – Vlaskamp et al, 2017, patient 337	14q31.1	319 kb	Focal seizures, 3.5y	Focal sharp waves (occ.)	Megacisterna magna
F, 8y – Vlaskamp et al, 2017, patient 969	14q24.3-q31.1	3,2 Mb	Focal SE, focal seizures (2– 4/ month), 2–4 y	Normal	Normal
F, 11y - This report	14q31.1-q32.11	11,4 Mb	unprovoked generalized seizures, 5y	bilateral centro-temporal discharges of spike-wave complexes, with maximal amplitude in the right derivations	Normal

Discussion

In our study, we describe an 11-year-old girl presenting facial dysmorphism, seizures, epileptiform EEG activity, motor and cognitive delay with speech problems associated with a 14q interstitial deletion, extended from 14q31.1 to 14q32.11. In literature (both medical literature and online cytogenetics databases for unpublished patients – DECIPHER, ECARUCA, the Chromosome Anomaly Collection) there are 64 additional reported cases with interstitial 14q deletion syndrome which include our previously mentioned chromosomal region. 12 of these cases have inaccurate molecular characterization and a lack of breakpoints details, being reported before the era of high-resolution cytogenetics, when karyotype or FISH were the main diagnostic tools (TURLEAU et al,1984 [33]; YAMAMOTO et al, 1986 [34]; GORSKI et al, 1990 [35]; KARNITIs et al, 1992 [36]; Rivera et al, 1992 [37]; BYTH et al, 1995 [38]; ONO et al, 1999 [39]).

Patients with interstitial deletions of chromosome 14 usually share common clinical features like: facial dysmorphism, microcephaly, developmental and cognitive delay, seizures and speech problems (NICITA et al, 2015 [13]; CINGÖZ et al, 2011 [19]; TORGYEKES et al, 2011 [20]; OEHL JASCHKOWITZ et al, 2014 [23]; RIEGEL et al, 2014 [24]; PICCIONE et al, 2010 [40]; KAWAMURA et al, 1985 [41]). By comparing our patient with the previously published cases, common clinical features were found. Furthermore, the clinical picture of the patient herein reported showed important neurological impairment. She associated motor, cognitive and language delay with generalized seizures, abnormal EEG activity and mild intellectual disability. Thus, facial dysmorphism, motor, cognitive and language delay were described in almost all cases, while epilepsy and abnormal EEG activity were reported only in 8 patients with deletions located between 14q24.3 – q32.11 (NICITA et al, 2015 [13]; ONO et al, 1999 [39]; VLASKAMP et al, 2017 [42]; SCHLADE-BARTUSIAK et al, 2008 [43]). Seizure types, onset age, localization of epileptiform activity on EEG and MRI results for our patient and ones previously published in literature are compared in Table 1. The deletion size of the affected region (14q24.3 – q32.11) in these nine patients ranges from approximately 91,25 kb to 18,5 Mb. Comparative analysis of the array CGH results available only for seven patients revealed that the region of deletion overlap contains the *NRXN3* gene (*MIM 600567*), considered to be involved in the genetic etiology of bipolar pathology (HU et al, 2013 [44]) developmental delay (NOOR et al, 2014 [45]), intellectual disability, epilepsy and autism spectrum disordersn (YUAN et al, 2018 [46]; FAHEEM et al, 2015 [47]). The *NRXN3* gene encodes for neurexin III, a cell surface protein expressed in presynaptic terminals and required for synaptic cell adhesion and neurotransmission (NASEER et al, 2015 [48]; VAAGS et al, 2012 [49]; KASEM et al, [50]; RUDENKO et al, 2019 [51]; DAI et al, 2019 [52]). Thus, the clinical findings described in our case, together with the other eight reported cases, reinforce the idea that haploinsufficiency of *NRXN3* gene might cause epilepsy. Focusing on the entire gene content of the deleted region in our patient, aCGH revealed that the reported CNV contains other 13 MIM genes that could contribute and explain the entire clinical picture noticed in this case due to the role played by the encoded proteins.

Conclusions

In summary, our case shares a similar neurological picture characterized by seizures and EEG abnormalities with eight from the 64 previously reported cases, prompting us to sustain that NRXN3 might be a candidate gene for epilepsy. Confirmation of NRXN3 role in the etiology of epilepsy requires studies on larger cohorts and additional functional data. Furthermore, our case outlines that molecular assessment through aCGH can represent an important tool in the diagnostic work-up of epilepsy in children.

Abbreviations

EEG – electroencephalogram
MRI – magnetic resonance imaging
aCGH – comparative genomic hybridization
CNV – copy number variant

Conflict of Interest

The authors declare that they have no conflict of interests.

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