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CASE REPORT Open Access

A new association between Kleefstra syndrome and Panayiotopoulos epilepsy

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Abstract

Background Kleefstra syndrome is a rare genetic disorder attributed to loss of function of *EHMT1*, either due to a point mutation or a microdeletion in the chromosome region 9q34.3. This gene encodes an enzyme that modifies histone function and is essential for normal development. Individuals with Kleefstra syndrome typically present intellectual disability (from moderate to severe), language delay, autism spectrum disorders, generalized hypotonia, and distinctive facial dysmorphic features. Additional manifestations in children may include cardiac defects, renal and urological malformations, genital anomalies, respiratory infections, epilepsy (including febrile seizures), and psychiatric disorders. Panayiotopoulos syndrome is a specific type of epilepsy, usually presenting in early to mid-childhood with benign focal seizures. These seizures are characterized by primarily autonomic symptoms, abnormal EEG findings showing shifts or multiple seizure foci (often located in occipital lobe), and other autonomic manifestations such as pallor, redness or cyanosis, mydriasis or miosis, heart and breathing problems, thermoregulatory changes, urinary and/or fecal incontinence, hypersalivation, and altered gut motility.

Case presentation We present the case of a child with Kleefstra syndrome and Panayiotopoulos epilepsy. The patient is a 12-year-old male born from a full-term pregnancy to non-consanguineous healthy parents with a family history of neurodevelopmental disorders. At birth, he presented dysmorphic facial features including receding forehead, low-set ears and lingual protrusion. From 6 months of age, he manifested predominantly axial and lower limb hypotonia, associated with a delay in acquiring psychomotor developmental milestones. Genetic counseling was requested, and array-CGH was then performed. Molecular analysis detected a 9q34.3 microdeletion which included the *EHMT1* gene, leading to Kleefstra syndrome diagnosis. From the age of 6 years, he began experiencing seizures with features typical of Panayiotopoulos epilepsy and started treatment with valproic acid.

Conclusions We highlight the association between Panayiotopoulos epilepsy and Kleefstra syndrome, which has not been previously reported in the literature. Although this kind of epilepsy is quite frequent in pediatric age and the possibility of a casual co-occurrence should be considered, however in Kleefstra syndrome patients carrying 9q34.3 microdeletion a potential additional role of genetic (besides *EHMT1*) and epigenetic factors in developing seizures cannot be excluded. The present data expand the genomic and phenotypical features of the syndrome, providing new insights about research, which are useful to achieve genotype/phenotype correlations and better management of affected subjects.

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Keywords Panayiotopoulos, Kleefstra syndrome, Seizures, EHMT1, CACNA1B-*AS*– a-CGH

Background

Kleefstra syndrome, also called 9q34.3 microdeletion syndrome (9qSTDS), is a very rare genetic syndrome first identified in 1993 [1, 2]. Main features include moderate or severe intellectual disability, severe delay in the development of language, mainly on the expressive side, autism spectrum disorder (ASD), generalized hypotonia, and dysmorphic facial features. Additionally, individuals may experience renal/urological and genital defects, increased susceptibility to respiratory infections, epileptic seizures (including febrile ones), and psychiatric disorders, apathy or catatonia which can develop after puberty. Rare cases of patients with mild intellectual disability or borderline or normal cognitive function are also described [1, 2]. The majority of the clinical features in KS can be attributed to loss of function of *EHMT1*, either due to a point mutation or a microdeletion in the chromosome region 9q34.3, leading to the loss of the entire gene. This gene encodes an enzyme that modifies histone function and is essential for normal development. The diagnosis of Kleefstra syndrome is confirmed by genetic testing that reveals a heterozygous deletion on chromosome 9q34.3, including at least part of the *EHMT1* gene, in addition to other variants of *EHMT1*. Kleefstra syndrome is estimated to affect 1: 25,000 to 1: 35,000 individuals. However, the actual prevalence may be higher due to underdiagnosis [1].

Panayiotopoulos syndrome is a common idiopathic disorder, characterized by seizures, often prolonged, with predominantly autonomic symptoms, and an EEG showing shifts and/or multiple foci, often with occipital predominance. Autonomic manifestations which usually precede other symptoms, primarily consist of episodes of vomiting. Others include pallor, mydriasis, cardiorespiratory and thermoregulatory changes, urinary and/or fecal incontinence, hypersalivation, and changes in bowel motility. The child, who was initially fully conscious, may become confused and unresponsive. Deviation of eyeballs may also occur. Only half of the seizures ends with brief hemiconvulsions or generalized convulsions. Ictal syncope and, exceptionally, cardiorespiratory arrest may occur. Convulsive *epilepticus status* is extremely rare. Two-thirds of seizures occur during sleep [3]. Panayiotopoulos syndrome is specific to childhood and does not occur in adults [3]. It affects 13% of children aged 3–6 years who have had 1 or more non febrile seizures, and 6% in the age group 1–15 years. In this report we will describe the first case of association between Kleefstra syndrome and Panayiotopoulos disease.

Case presentation

The proband, a 12-year-old boy, was born from a second high-risk pregnancy considered at high-risk due to maternal glucose intolerance and threatened preterm birth starting from the seventh month. The delivery occurred at 41 + 1 weeks by cesarean section for breech presentation. Apgar score was 9 and 10 at 1 and 5 min, respectively. Birth weight was 4,050 g– 92th centile, length 52 cm– 75th centile and head circumference 36 cm– 84th centile, calculated by INES chart scale [4, 5]. His parents are unrelated Italians with normal cognitive, social, and academic functioning. His family history is notable for neuropsychiatric disorders, with his older sister experiencing speech delay. Feeding was reported to be varied in terms of food types and textures. Due to mild generalized hypotonia and dysmorphic facial features, the patient underwent genetic counseling. Array Comparative Genomic Hybridization (a-CGH) analysis identified a deletion of approximately 830 Kb (GRCh37, resolution of approximately 1 Kb) on the long arm of chromosome 9, within the 9q34.3 region. The deletion involved 19 genes, including *EHMT1*, leading to the diagnosis of Kleefstra syndrome.

At the age of 5 months and 10 days, physical examination revealed a head circumference of 41.2 cm (15th percentile according with WHO growth chart) [6]; dysmorphic facial features were also present, including receding forehead, short palpebral fissures, and low-set ears (Fig. 1).

At the age of 6 months, he was evaluated at our Child Neuropsychiatric Department. On examination, his head circumference was 42 cm (15th percentile for the WHO growth chart). The anterior fontanel was not closed, it was neither tense nor pulsating. In the supine position, his head was mobile in all directions, and he maintained a stable, symmetrical median posture with spontaneous and lively movements. Mild hypotonia of the lower limbs and mild ligamentous laxity were also noted. Head control was good, but trunk control was not yet present. In the prone position, he could lift his head from the support plane to reach the puff position. Osteotendinous reflexes were normal and symmetrical. Trophism was normal and plantar grasp present.

At 9 months, a reduction in head circumference growth was observed (42 cm, 1st percentile), along with lingual protrusion and orobuccal automatisms. In the supine position, there was a reduction in spontaneous movement, and he tended to keep his hands closed in fists. Visual and auditory evoked potentials were normal. Two months later, an EEG in sleep state showed normal patterns. Conversely, brain magnetic resonance imaging

Fig. 1 Receding forehead, short palpebral fissures, and low-set ears

(MRI) revealed hypoplasia of the corpus callosum with a squat appearance and reduced thickness, especially of the rostrum and splenium. (Fig. 2)

From the age of 6 years, he developed seizures that occurred in full well-being and in apyrexia. These seizures were characterized by deviations of the eyeballs, initially to the right and sometimes to the left, accompanied by prominent vomiting, gastralgia, and prolonged loss of consciousness. An EEG performed during sleep showed left-sided high-voltage spikes, predominantly in the occipital region (Fig. 3). This profile was consistent with Panayiotopoulos syndrome (precedently said early onset benign occipital epilepsy and currently renamed by ILAE as Self-limited epilepsy with autonomic seizures). Therefore, treatment with sodium valproate was initiated which has provided good seizure control until now.

At the age of 9 years and 2 months, anthropometric measures were as follows: weight 56 kg (>99th percentile), height 137 cm (69th percentile), and head circumference 51.5 cm (4th percentile). No cardiac or renal problems were present, but micropenis and dental problems, including caries and prognathism, were noted. Deambulation occurred with feet in external rotation. Generalized hypotonia and fine and gross motor coordination disorders were also observed. On psychological evaluation, severe intellectual disability was assessed with WISC-IV scale. (WISC IV) [7, 8]. The patient is currently enrolled in a multidisciplinary follow-up program.

Discussion and conclusion

Kleefstra Syndrome typically presents the following main features, moderate to severe intellectual disability, autism spectrum disorders, sleep disturbances, delayed motor development, sensorial defects, congenital heart disease, facial dysmorphic features (brachy-microcephaly, broad forehead, unusual shape of the eyebrows [arched or straight with synophrys], slightly oblique palpebral fissures, median retrusion of the face, thickened ear helices, short nose with anteverted nostrils, fleshy vermilion, everted lower lip and exaggerated Cupid's bow or "tent" appearance of the vermilion of the upper lip, protruding tongue), and obesity. Minor features are genitourinary

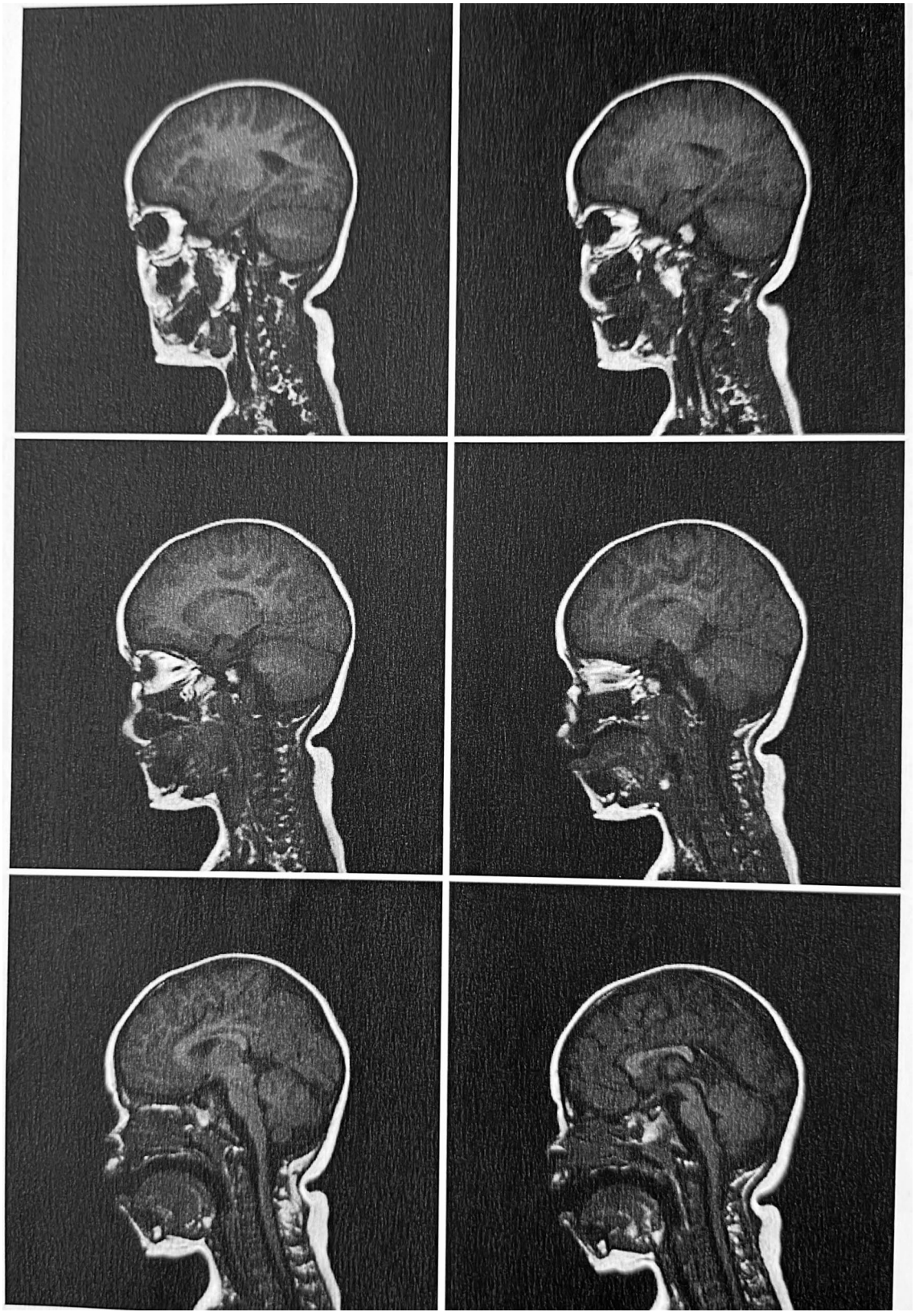

Fig. 2 Brain MRI revealed hypoplasia of the corpus callosum with a squat appearance and reduced thickness, especially of the rostrum and splenium

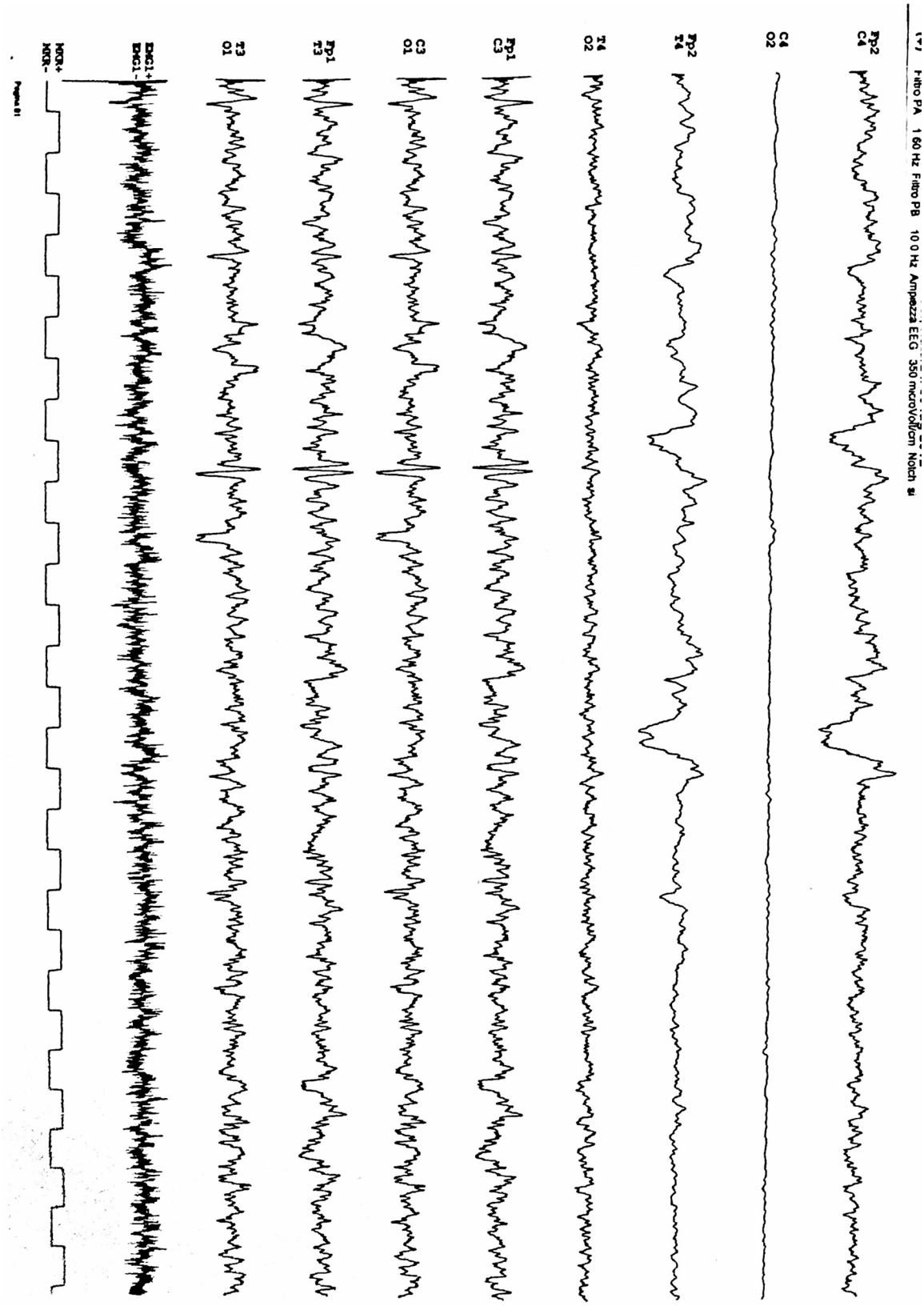

Fig. 3 The Patient's EEG presents high voltage spikes in the left hemisphere with prevalence in occipital region

anomalies, including hypospadias, cryptorchidism and micropenis, mild intellectual disability, epilepsy, clubfoot, epigastric hernia with gastroesophageal reflux, tracheo/bronchomalacia and pulmonary atresia leading to frequent lung infections and respiratory failure. Psychiatric disorders, nonspecific brain anomalies like corpus callosum and cortical hypoplasia or white matter defects, can also be seen. Our patient presents most of the mentioned clinical features reported in Kleefstra Syndrome, such as facial dysmorphic features (protruding tongue, prognatism, unusual shape of the eyebrows, broad forehead), obesity, micropenis and brain anomalies. Literature studies report many types of epileptic seizures associated with Kleefstra syndrome. However, an association with Panayiotopoulos-type seizures has never been found before [9–15]. Table 1 summarizes the seizures and genomic profiles present in literature in subjects with Kleefstra syndrome.

Giacomini et al. described eight patients whose most common seizures were focal motor, infantile spasms, tonic seizures and bilateral tonic-clonic ones [16]. Conversely, our patient showed an electroclinical pattern compatible with Panayiotopoulos syndrome. Additionally, the genetic profile revealed a deletion on chromosome 9, in the 9q34.3 region. The deletion regards approximately 19 genes, including some of those deleted in 9q subtelomeric deletion syndrome (*EHMT1* and *NELFE*). Most of these genes, if overexpressed, are oncogenic and related to many types of tumor. Conversely, four of them are related to neurodevelopmental disorders, e.g. *EXD3* (exonuclease 3'-5' domain containing 3, 140,201,348 – 140,317,614), a ubiquitous gene, whose mutation is linked with increased risk of depression, suicidal ideation, post-traumatic stress disorders and suicide attempts [17–19]; *NSMF*, (NMDA receptor synaptic nuclear signaling and neuronal migration factor, MIM:#608137), related to idiopathic hypogonadotropic hypogonadism (IHH); *EHMT1* (euchromatic histone lysine methyltransferase 1, MIM:#607001) probably involved in the silencing of MYC- and E2F-responsive genes and in the G0/G1 cell cycle transition, related to Kleefstra syndrome, and *CACNA1B-AS*, (CACNA1B antisense RNA 1), expressed in brain and peripheral nervous system involved in regulating neuropathic pain and in cell proliferation and apoptosis, and related, if mutated, to epilepsy - dyskinesia (bi-allelic loss of function), myoclonus-dystonia or development of gliomas [20–22] (Fig. 4). *EHMT1* plays an important role in the development of the cortical neuronal network. In a study conducted by Martens et al. on mice, it was observed that *EHMT1* deficiency results in impaired neuronal network activity during the transition from unrelated background action potential firing to synchronized network bursting. The spontaneous burst and the excitatory synaptic currents in a deficit condition are reduced, while the excitatory postsynaptic currents are not affected. Furthermore, in the long term, the loss of *EHMT1* function ultimately leads to reduced neuronal network connections and less regular bursts. This suggests that the developmental disorders observed in *EHMT1*-deficient networks may result in a temporal misalignment between activity-dependent developmental processes, thus contributing to the pathophysiology of Kleefstra syndrome [23, 24]. Another study, carried out in 2018, also demonstrated that *EHMT1* and its paralogue *EHMT2* are responsible for the deposition of dimethylated H3K9 (H3K9me2). Through this study it was discovered that the epigenome of the adult Ehmt1+/- mouse brain shows a marked increase in H3K9me2/3 which correlates with an altered expression of protocadherins, main regulators of neuronal diversity. This, from birth, causes the formation of aberrant methylation patterns and consequently the evolution of cognitive deficit [25, 26]. Mutations like deletion of *EHMT1* are related in 30% of cases to seizures, and this relationship may be even more marked in the compresence of mutation in *CACNA1B-AS* which can be related to epilepsy - dyskinesia.

In this study we argue that deletion mutation in *EHMT1* may contribute to Panayiotopoulos epilepsy through pathogenetic mechanism of epileptogenesis. Then, clinicians might consider in such patients, among epileptic seizures, the occurrence of Panayiotopoulos disease. This may be relevant to avoid unsuitable treatment, as well as to improve the quality of life of affected subjects and their families. These data expand the genomic and phenotypical features of the syndrome, providing new insights about research, which are useful to achieve genotype/phenotype correlations and better management of patients.

Table 1 Type of seizures and genetical findings in Kleefstra syndrome patients. - Comparison among seizures and genomic profiles of our patient and those with Kleefstra syndrome described in the literature

Authors	Iwakoshi et al. [15]	Kleefstra et al. [13]	Kleefstra et al. [12]	Kleefstra et al. [11]	Noruzinia et al. [10]	Okur et al. [9]	Giacomini et al. [16]	Our patient
Year	2004	2005	2006	2009	2017	2018	2023	2024
Number of patients	3	1	5	22	1	3	8	1
Patients with seizure	2	1	2	6	1	1	8	1
Genetical Findings	9q34.3 terminal deletion and unbalanced translocation involving 9q34.3-qter monosomy and 6p25-pter trisomy	*de* novo balanced translocation t(X;9)(p11.23;q34.3)	Deletion of the exons 1–6 of *CACNA1B*; *de novo* nonsense mutation in exon 24 of *EHMT1*	Intragenic *EHMT1* mutation and submicroscopic 9q deletions of variable size, including 7 interstitial deletions. Other mutations comprised nonsense changes, c.778 C.T and c.1717 C.T (p.Arg260X, p.Gln573X), deletion (c.1440_1443del (p.Asp481fs), and *de novo* splice site variants (c.2775-1G.A and c.2100-1G.C)	heterozygous *de novo* 9q34.3 microdeletion	1.24 Mb unbalanced translocation between the long arm of chromosome 9 and short arm of chromosome X: arr[hg19]9q34.3(139,776,707 – 141,020,389)x1, Xp22.33p22.2(169,921 – 13,409,172)×3 46, XX der(9)t(X;9)(p22.2;q334.3)	9q34.3 microdeletion, 9q deletion, translocation (9q34:16q24 [46,xyish der(9)t(9;16)(9pter-9q34.3:16q24.3-16qter)]) and two *EHMT1* variants: NM_024757.5:c.3046 C > T(p.Arg1016*),NM_024757.5:c.1790 C > T(p.Ala597Val)	arr[hg19] 9q34.3 microdeletion (140188317 × 2, 140188572–141020389 × 1) of 830 Kb = about 19 genes
Type of seizure	Febrile and generalized seizures	NA	In the first case not available the description of seizures; in the last case, severe myoclonus epilepsy of infancy	Different type of seizures such as absences, generalized tonic-clonic seizure, complex and focal	NA	NA	Focal motor; epileptic spasms; tonic; bilateral tonic-clonic seizures	Panayiotopoulos epilepsy

NA = not available

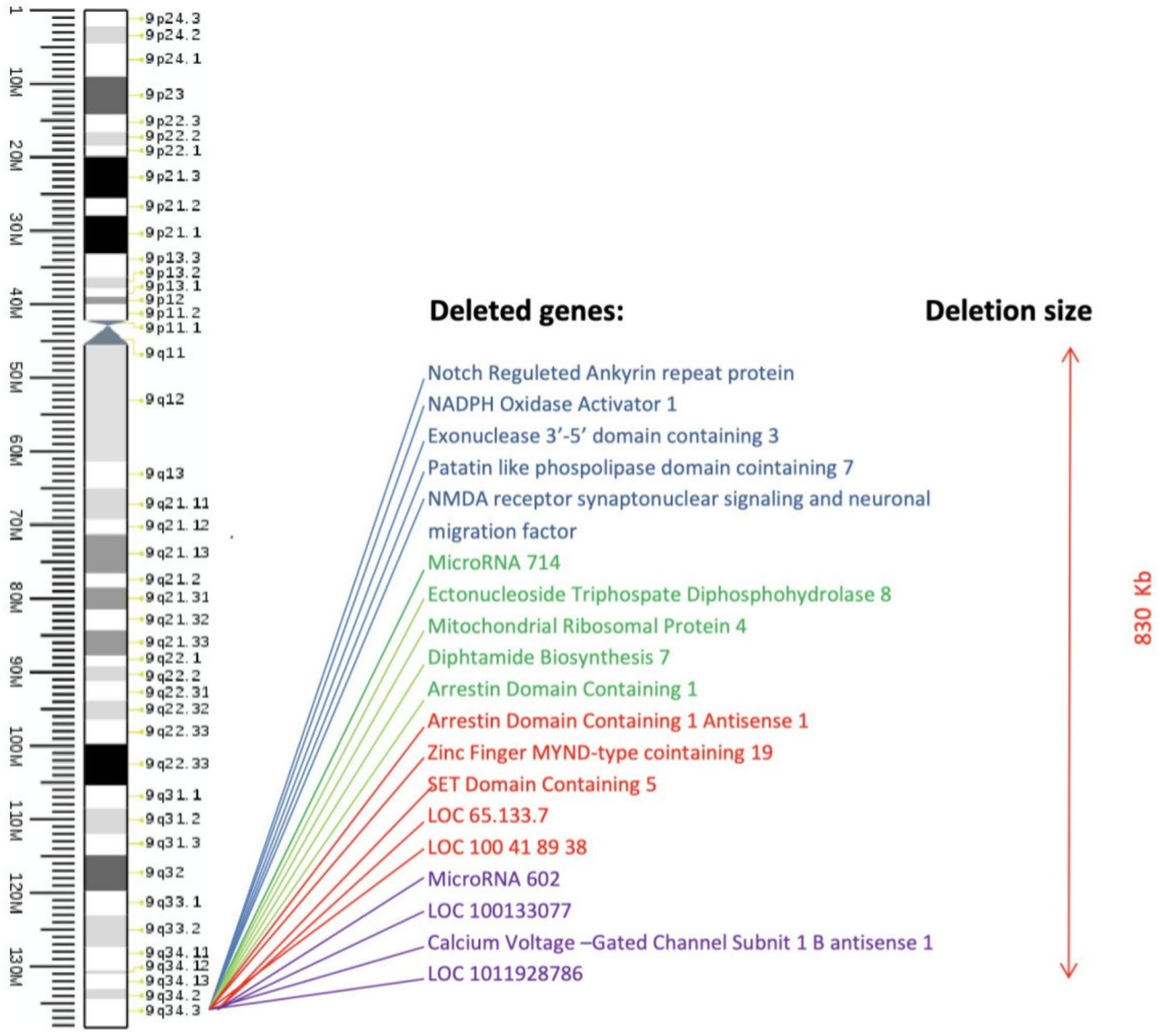

Fig. 4 Overview of the 9q34.3 region and its gene content, showing present patient's microdeletion spanning about 830 Kb of genomic DNA, from the position 140,188,572 to 141,020,389, according to DECIPHER Genome Browser (GrCh37/hg19 assembly)

Abbreviations

a- CGH	Array comparative genomic hybridization
ASD	Autism spectrum disorder
CC	Cranial circumference
MRI	Magnetic resonance imaging
OCF	Occipito-frontal circumference

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Author contributions
AG conceptualized the report, collected genetical data and drafted the first version of the manuscript first in Italian. SG, AF, YC AND MR made the final revision of the manuscript. RN is the chief of the department and contributed in drafting the manuscript and took care of the patient. GS performed the genetical assessment. All authors approved the final manuscript as submitted.

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Data availability
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from parents at admission of their child. All procedures performed in this report were in accordance with the ethical standards of the institutional and national research committee, and with the 1964 Helsinki declaration and its later amendments, or comparable ethical standards. The study was approved by the ethics committee Palermo 1 of "Paolo Giaccone" University Hospital.

Consent for publication
Written informed consent for publication was obtained.

Competing interests
The authors declare that they have no competing interests. Furthermore, they declare that the author Gregorio Serra has the role, within Italian Journal of Pediatrics, as Associate Editor.

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