Case Report
De Novo Mutation in KMT2C Manifesting as Kleefstra Syndrome 2: Case Report and Literature Review

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Abstract: Diagnosis of pediatric intellectual disability (ID) can be difficult because it is due to a vast number of established and novel causes. Here, we described a full-term female infant affected by Kleefstra syndrome-2 presenting with neurodevelopmental disorder, a history of hypotonia and minor face anomalies. A systematic literature review was also performed. The patient was a 6-year-old Caucasian female. In the family history there was no intellectual disability or genetic conditions. Auxological parameters at birth were adequate for gestational age. Clinical evaluation at 6 months revealed hypotonia and, successively, delay in the acquisition of the stages of psychomotor development. Auditory, visual, somatosensory, and motor-evoked potentials were normal. A brain MRI, performed at 9 months, showed minimal gliotic changes in bilateral occipital periventricular white matter. Neuropsychiatric control, performed at 5 years, established a definitive diagnosis of childhood autism and developmental delay. Molecular analysis of the exome revealed a novel KMT2C missense variant: c.9244C > T (p.Pro3082Ser) at a heterozygous state, giving her a diagnosis of Kleefstra syndrome 2. Parents did not show the variant. Literature review (four retrieved eligible studies, 10 patients) showed that all individuals had mild, moderate, or severe ID; language and motor delay; and autism. Short stature, microcephaly, childhood hypotonia and plagiocephaly were also present. Conclusion. Kleefstra syndrome 2 is a difficult diagnosis of a rare condition with a high clinical phenotypic heterogeneity. This study suggests that it must be taken in account in the work-up of an orphan diagnosis of intellectual disability and/or autism spectrum disorder.

Keywords: KMT2C; Kleefstra syndrome 2; intellectual disability

1. Introduction

Intellectual disability (ID) disorder is a composite group of disorders characterized by significantly damaged intellectual functioning and adaptive behaviors deficiency [1]. About 1–3% of the western population are affected and characterized by genotypes and phenotypes which are highly heterogeneous [2]. The etiological factors of ID are very varied and in many children the cause of ID is still unknown [2]. Genetics plays a relevant role in its development; indeed, advanced sequencing methods have identified mutated genes in intellectual disability, autism, and other disorders [3]. For instance, a recent study stressed the importance of rare heterozygous de novo mutations as a cause of undiagnosed developmental disorders [4]. Developmental disorders caused by de novo mutations have
an average prevalence of 1 in 213 to 1 in 448 births in relation to parental age and globally account for about 400,000 affected children born annually [4].

In the last few years, use of diagnostic whole exome sequencing for undetermined neurodevelopmental disorders identified de novo KMT2C mutations.

In this paper we report a novel patient with ID, autism, and minor facial dysmorphisms displaying a missense heterozygous mutation in KMT2C, compatible with diagnosis of Kleefstra syndrome 2 (KLEFS2). A systematic literature review of other cases of KLEFS2 was also performed.

2. Methods

2.1. Literature Review

We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the literature search results. We consulted the PubMed, Scopus and Chocorane Library academic medical databases. Our search strategy was based on the terms “KMT2C” and “Kleefstra syndrome 2”. Systematic search of the literature databases was performed with no language restrictions, and it considered publications from January 2000 to February 2021. To be suitable for inclusion, studies had to describe a case of KLEFS2. Three authors took part. They had separately selected articles and took a stepwise approach, first by regarding the title, then by reviewing the abstract, and, as a third step, by revising the full text, where appropriate (Figure S1). Finally, four studies were selected. All the details about the articles included and excluded has reported in Supplementary Figure S1.

2.2. Material and Methods WES

Library elaboration and whole exome capture were performed by using the Twist Human Core Exome Kit (Twist Bioscience) according to the manufacturer’s protocol. The sequencing was carried out on the Illumina NovaSeq 6000 platform. The BaseSpace pipeline (Illumina) and the TGex software (LifeMap Sciences) were employed for the calling- and annotating variants, respectively. Sequencing data were aligned to the hg19 human reference genome. A minimum depth coverage of 30× was considered eligible for analysis, according to the guidelines of the American College of Medical Genetics and Genomics. Variants were analyzed for coverage and Qscore (minimum threshold of 30), and visualized by the Integrative Genome Viewer (IGV).

3. Case Presentation

The proband was a 6-year-old Caucasian female referred to our center for neurodevelopmental disorder, history of hypotonia, and minor face anomalies. The family history was negative for intellectual disability or genetic conditions. She was born to non-consanguineous parents at 39 weeks of gestation after a normally conducted pregnancy until the seventh month when there was an onset preeclampsia, and a caesarian section was performed. She was deemed adequate for her gestational age: birth weight was 3460 g (75th percentile), length 50 cm (50–75th percentile) and head circumference 35 cm (75–90th percentile). The Apgar score at 1 and 5 min was 8/9. Clinical evaluation at 6 months revealed hypotonia and, successively, delay in the acquisition of the stages of psychomotor development. Auditory, visual, somatosensory, and motor evoked potentials were normal. A brain MRI, performed at 9 months, showed minimal gliotic changes in bilateral occipital periventricular white matter. Control MRI, performed a year later, showed improvement of the alteration of the posterior periventricular signal in relation to myelination phenomena, low-signal stria in the supratrigonal area from a likely vascular element, and modest ectasia of the regional perivascular spaces. The childhood neurological and neuropsychiatric visits ended with psychomotor delay and general developmental disorder characterized by the absence of language, a tendency to isolation, with little interest and inconsistent visual engagement. Autistic traits characterized by poor participation, repetitive behaviors, unusual interest in objects, symptoms that resemble attention deficit hyperactivity disorder and mild macrocrania, motor stereotypies, and
KMT2C mutations cause Kleefstra syndrome 2 (OMIM 617768), a neurodevelopmental disorder characterized by delayed psychomotor development, intellectual disability, and mild dysmorphic features. Inheritance is autosomal dominant.

KMT2C maps to chromosome 7q36 and is highly expressed in the cerebellum of the developing and adult human brain [6,7]. This gene encodes histone-lysine N-methyltransferase 2C, an enzyme that monomethylates lysine 4 of histone H3 (H3K4me1) thus leading to chromatin structure changes that cause transcriptional activation which regulates gene expression.
transcription [8]. Genes encoding regulators of H3K4 methylation are known to be among the strongest genetic risk factors for intellectual disability and autism spectrum disorders, having been associated with monogenic forms of neurodevelopmental disease [8]. It is interesting to note that one reported individual has hypoplasia of the cerebellar vermis [9], which is absent in the others.

KMT2C gene constitutes the core of nuclear regulatory structures together with the KMT2D gene, called the KMT2C/D COMPASS complex (complex of proteins associated with Set1). Over the past two decades, mutations in five core genes of the COMPASS complex have been associated with three known human syndromes: Kabuki syndrome type 1 and 2 (KMT2D, KDM6A), Rubinstein-Taybi syndrome type 1 and 2 (CBP, EP300), and type 2 Kleefstra syndrome (KMT2C). Phenotypic similarities and differences can be found between the members of this new family of diseases [10].

Recently, a KMT2C gene mutation has been identified as a cause of familial nonsyndromic primary teeth retention, suggesting that KMT2C is also involved in the physiological eruption of permanent teeth, without other phenotypic abnormalities [11]. However, there is no history of this disorder both in our case and in the other description patients.

The novel variant found is not reported in the public databases of mutations/polymorphisms. According to the criteria of the American College of Medical Genetics and Genomics (ACMG) for the interpretation of variants, this can be classified as likely pathogenic. The identification of this novel mutation, with the review of previously published cases, allows us to better define the clinical phenotype related to KMT2C mutations (Table 1). As shown in Table 1, all reported cases had ID, ranging from mild to severe, developmental delay, and autism or autistic spectrum disorders such as pervasive developmental disorder (PDD). Other recurrent clinical features were short stature (5/11), microcephaly (5/11), childhood hypotonia (4/11), and plagiocephaly (3/11). Kleefstra-like facial dysmorphisms are variables as shown in Table 2.
Table 1. Clinical and genetic characteristics of affected individuals with KMT2C mutation.

| Reference            | Total Cases | Sex/Age | KMT2C Gene Mutations Additional De Novo Mutation | Growth | Development | Neurological | Other | MRI |
|----------------------|-------------|---------|--------------------------------------------------|--------|-------------|--------------|-------|-----|
|                      |             |         | Chromosome Position (Hg19) cDNA Change Amino Acid Change Deletion H. (SD) W. (SD) H.C. (SD) I.D. L.D. M.D. |        |             |              |       |     |
| Kleefstra et al. [12] (2012) | 1           | F/15 years | g.151891591G > A c.4441 C > T p.(Arg 1481*) - 2.5 0 2 Moderate IQ 35 Yes | hyperactivity, aggressiveness. Hypotonia | - | N.R. |
| Koemans et al. [13] (2017) | 5           | M/29 years | g.151880108del c.5216 del p.(Pro 1739Leufs*2) - 1.7 +0.6 -0.5 Moderate Yes | Autistic-traits. Epilepsy PKU, RRI | N.R. |
|                         |             | M/31 years | g.151874988G > C c.7550C > G p.(Ser 2517*) - 0.5 -1.5 -0.5 Mild Yes | Autism | Strabismus, cryptorchidism | N.R. |
|                         |             | F/7 years | g.151859847_151859850del c.10812_10815del p.(Lys 3605Glufs*24) -3 -1.5 -2.25 Mild IQ 63 Yes | Autism, sleeping disorder RRI, dry skin, hoarse voice | | Normal |
|                         |             | F/10 years | - - - - | 7q36.1 (151,858,920–152,062,163) ×1 | N.R. | -2.5 -2 | Severe Yes | Automutilation Hypotonia. Epilepsy | - | Non-progressive enlarged extracerebral space |
| Faundes et al. [9] (2018) | 3           | F/17 years | 7:151,884,849 c.4744 G > T p.(Gly 1582*) -2.1 -2.7 -2.42 Severe N.R | Elective mutism | Delayed puberty | N.R. |
|                         |             | F/4 years | 7:151,873,688-151,873,689 c.8849 G 8850 delAT p.(His 2950 Arg5*17) -2 -2 -1.97 Severe | Mild | - | Hydrocephalus hypoplasia of cerebellar vermis |
|                         |             | F/5 years | 7:151,836,279 c.14526dupG p.(Pro 4843Alafs*12) 0.4 0.18 -1 Severe N.R. | Autistic traits, developmental regression, insensitivity to pain and abnormal gait | Constipation | N.R. |
| Schoch et al. [14] (2020) | 1           | F/6 years | - - - - | 7q36.1 (151,839,151–151,965,981) ×1 | N.R. | N.R +2 | Mild IQ 81 Yes | N.R. | Torticollis | N.R. |
Table 1. Cont.

| Reference          | Total Cases | Sex/Age | KMT2C Gene Mutations | Growth | Development | Neurological | Other | MRI |
|--------------------|-------------|---------|----------------------|--------|-------------|--------------|-------|-----|
|                    |             |         | Additional De Novo Mutation |        |             |              |       |     |
|                    |             |         | Chromosome Position (Hg19) | cDNA Change | Amino Acid Change | Deletion | H. (SD) | W. (SD) | H.C. (SD) | I.D. | L.D. M.D. |
| Our case           | 1           | F/6 years | - | c.9294 C > T | p.Pro3082Ser | - | +0.67 | +0.67 | +0.67 | Severe | Yes | slight telelia, ligamentous hyperlaxity |

Abbreviations: H.: height. W.: weight. H.C.: head circumference. N.R.: not reported. I.D.: intellectual disability. L.D.: language delay. M.D.: motor delay. PKU: phenylketonuria; RRI: recurrent respiratory infections. *: International nomenclature of mutations

Table 2. Facial dysmorphisms and other physical characteristics of affected individuals with KMT2C mutation.

| Features                          | Kleefstra et al. [12] (2012) | Koemans et al. [13] (2017) | Faundes et al. [9] (2018) | Schoch et al. [14] (2020) | Our Case |
|-----------------------------------|------------------------------|-----------------------------|---------------------------|---------------------------|----------|
| Features                          | Sex            | F  | M  | M  | F  | F  | F  | F  | F  | F  | F  | F  |
|                                   | Age            | 15 Years | 29 Years | 31 Years | 15 Years | 7 Years | 10 Years | 17 Years | 4 Years | 5 Years | 6 Years | 6 Years |
| Microcephaly                     | +              | -  | -  | -  | -  | -  | -  | +  | +  | +  | +  | +  |
| Macrocephaly                     | -              | +  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| Brachycephaly                    | +              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| Plagiocephaly                    | -              | -  | -  | -  | -  | -  | -  | +  | -  | +  | +  | +  |
| Coarse facies                    | +              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| Broad and rounded forehead       | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | +  | +  |
| Deep set eyes                    | -              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| Marked infra-orbital creases     | -              | -  | -  | -  | -  | -  | -  | +  | -  | -  | -  | -  |
| Midface hypoplasia               | +              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| Flattened midface                | -              | +  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| Hypertelorism                    | +              | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | +  |
| Features                                      | Kleefstra et al. [12] (2012) | Koemans et al. (2017) [13] | Faundes et al. [9] (2018) | Schoch et al. [14] (2020) | Our Case |
|----------------------------------------------|------------------------------|--------------------------|---------------------------|--------------------------|-----------|
| Sex                                          | F M                           | M M                       | F F                        | F F                       | F F       |
| Age                                          | 15 Years                      | 29 Years                  | 31 Years                   | 15 Years                  | 7 Years   |
|                                              | 10 Years                      | 17 Years                  | 4 Years                    | 5 Years                   | 6 Years   |
|                                              | 6 Years                       |                           |                           |                           |           |
| Down-slanting palpebral fissures             | − − − − − − + +              | − − − − − − − − − −       | +                         | +                        | − − −     |
| Palsy                                         |                             |                           |                           |                           |           |
| Synophrys                                     | + − − − − − − + +            | +                         | − − − − − − − − − −       | +                        | − − −     |
| Arched eyebrows                               | − − − − − − − − − −          | +                         | − − − − − − − − − −       | +                        | − − −     |
| Prominent eyebrows                           | − − − − − − − − − −          | +                         | − − − − − − − − − −       | +                        | − − −     |
| Short nose                                    | − − − − − − − − − −          | +                         | − − − − − − − − − −       | +                        | − − −     |
| Nose with saddle bridge and bulbous tip      | − − − − − − − − − −          | +                         | − − − − − − − − − −       | +                        | − − −     |
| Narrow philtrum                              | − − − − − − − − − −          | +                         | − − − − − − − − − −       | +                        | − − −     |
| Tented and cupid-bowed upper lip             | + − − − − − − − − − −        | +                         | − − − − − − − − − −       | +                        | − − −     |
| Thick and everted lower lip                  | + − − − − − − − − − −        | +                         | − − − − − − − − − −       | +                        | − − −     |
| Thin upper lip, down-turned mouth,            | − − − − − − − − − −          | +                         | − − − − − − − − − −       | +                        | − − −     |
| and misaligned teeth                          | − − − − − − − − − −          | +                         | − − − − − − − − − −       | +                        | − − −     |
| High palate                                   | − − − − − − − − − −          | +                         | − − − − − − − − − −       | +                        | − − −     |
| Pointed chin                                  | + − − − − − − − − − −        | +                         | − − − − − − − − − −       | +                        | − − −     |
| Dysplastic ear helices                        | + − − − − − − − − − −        | +                         | − − − − − − − − − −       | +                        | − − −     |
| Preauricular tag                              | − − − − − − − − − −          | +                         | − − − − − − − − − −       | +                        | − − −     |
| Duplicated right Thumb and left               | − − − − − − − − − −          | +                         | − − − − − − − − − −       | +                        | − − −     |
| Hearing loss (sensorineural)                  | − − − − − − − − − −          | +                         | − − − − − − − − − −       | +                        | − − −     |
| Scoliosis                                     | − − − − − − − − − −          | +                         | − − − − − − − − − −       | +                        | − − −     |
| Thoracic kyphosis                            | − − − − − − − − − −          | +                         | − − − − − − − − − −       | +                        | − − −     |
5. Conclusions

Kleefstra syndrome 2 is a rare condition, and its diagnosis is arduous principally due to high clinical phenotypic heterogeneity. With this report we suggest considering Kleefstra syndrome 2 as an etiological cause of autism with unknown pathogenesis and report the novel c.9244C > T (p.Pro3082Ser) variant as causative of this condition. A specific diagnosis has a critical role for management of the disease, prediction of possible problems, prognosis, and prenatal or preimplantation diagnosis, and may participate in the advance of eventual future therapies. Finally, this report summarizes previously reported clinical manifestations of Kleefstra syndrome 2, comparing them with these present in our patient and provide a guidance for better counseling of future Kleefstra syndrome 2 patients and their families.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pediatric14010019/s1, Figure S1. Flowchart of literature search results.

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