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O'Donnell-Luria-Rodan syndrome: description of a second multinational cohort and refinement of the phenotypic spectrum

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Abstract

Background—O'Donnell-Luria-Rodan syndrome (ODLURO) is an autosomal-dominant neurodevelopmental disorder caused by pathogenic, mostly truncating variants in *KMT2E*. It was first described by O'Donnell-Luria *et al* in 2019 in a cohort of 38 patients. Clinical features encompass macrocephaly, mild intellectual disability (ID), autism spectrum disorder (ASD) susceptibility and seizure susceptibility.

Methods—Affected individuals were ascertained at paediatric and genetic centres in various countries by diagnostic chromosome microarray or exome/genome sequencing. Patients were collected into a case cohort and were systematically phenotyped where possible.

Results—We report 18 additional patients from 17 families with genetically confirmed ODLURO. We identified 15 different heterozygous likely pathogenic or pathogenic sequence variants (14 novel) and two partial microdeletions of *KMT2E*. We confirm and refine the phenotypic spectrum of the *KMT2E*-related neurodevelopmental disorder, especially concerning cognitive development, with rather mild ID and macrocephaly with subtle facial features in most patients. We observe a high prevalence of ASD in our cohort (41%), while seizures are present in only two patients. We extend the phenotypic spectrum by sleep disturbances.

Conclusion—Our study, bringing the total of known patients with ODLURO to more than 60 within 2 years of the first publication, suggests an unexpectedly high relative frequency of this syndrome worldwide. It seems likely that ODLURO, although just recently described, is among the more common single-gene aetiologies of neurodevelopmental delay and ASD. We present the second systematic case series of patients with ODLURO, further refining the mutational and phenotypic spectrum of this not-so-rare syndrome.

INTRODUCTION

Large cohort studies of individuals with intellectual disability (ID) or autism spectrum disorder (ASD) first reported isolated individuals with de novo variants in the *KMT2E* gene starting in 2012.[1–5] Due to the nature of these studies, association of *KMT2E* variants with human neurodevelopmental disorders (NDDs) remained unclear until additional individuals could be identified and described in detail. In 2019, 38 patients (including previously described individuals) with a syndromic neurodevelopmental phenotype and heterozygous variants disrupting *KMT2E* were jointly reported in the seminal paper by O'Donnell-Luria and colleagues.[6] In this large cohort of patients, a recurring phenotype of generally mild ID (ranging from low-normal intelligence to moderate ID), macrocephaly (55%), ASD (26%) and epilepsy (15%) was observed. Further common features were a subtle facial gestalt and gastrointestinal symptoms, including vomiting or reduced bowel motility.

The phenotype was generally more severe in patients with missense changes compared with patients with null variants (including those predicted to escape nonsense-mediated decay (NMD)) and whole gene deletions. Rather than macrocephaly, two out of three patients carrying missense variants with a known head circumference showed microcephaly, the third had a low-normal head circumference. The authors hypothesised that the detected missense variants in *KMT2E* may cause this discordant phenotype due to a gain-of-function effect, rather than the assumed loss-of-function effect of the other described variants, but noted more data were needed.[6] Interestingly, there was a statistically significant sex bias in the

subgroup of patients carrying putative loss-of-function variants, with 24 out of 34 (71%) being male. Subsequently to this first systematic case series, another single family with three affected individuals carrying a frameshift variant has been reported in the literature with a detailed description of the patients' brain MRI findings. All three patients displayed a phenotype within the described clinical spectrum, but falling on the lower end of cognitive function with moderate and borderline severe ID.[7] Two patients with de novo missense variants in *KMT2E* were reported in a separate work. Both had microcephaly and moderate to severe ID, one had seizures.[8] Recently, two more patients were described, one carrying a de novo missense variant, the other carrying a synonymous variant predicted to impair normal splicing. The patient carrying the missense variant had microcephaly, profound ID and seizures. The patient carrying the predicted splice variant had mild ID, ASD and also suffered from seizures.[9]

The *KMT2E*-associated neurodevelopmental disorder has since been named O'Donnell-Luria-Rodan syndrome (ODLURO, OMIM #618512).

The *KMT2E* gene (lysine methyltransferase 2E) on chromosome 7q22.3 encodes an enzyme of the mixed lineage leukaemia/lysine N-methyltransferase 2 (KMT2) family. This gene family is involved in the transcriptional regulation of various genes through H3K4 methylation and chromatin remodelling, but KMT2E differs structurally from the other members of this family and seems to lack any methyltransferase activity.[10] Functional evidence suggests that the KMT2E protein is able to recognise and selectively bind to H3K4me3 and H3K4me2 methylated histones,[11] where it may regulate transcription factor binding or otherwise regulate transcription. Although it has been experimentally linked to the regulation of cell cycle progression and genomic stability,[10] and has been suggested to interact with NCOR2 and TBL1X in a repressor complex regulating cytokinesis-associated genes,[12] the precise function of KMT2E remains unclear to date. Many interactors of the NCOR1/2 nuclear corepressor complex, such as MECP2 (associated with Rett syndrome; OMIM #312750) or TBL1X/TBL1XR1 (associated with Pierpont syndrome and autosomal-dominant intellectual disability type 41; OMIM #602342 and #616944), among others, are known, when mutated, to be causative of ID and ASD.[13–18]

We report the second systematic case series of patients with ODLURO. With this study, we add an additional 18 multinational patients to the literature and increase the total number of known individuals with ODLURO to more than 60 patients worldwide. We confirm and further refine the phenotypic and mutational spectrum of ODLURO.

MATERIALS AND METHODS

Patient recruitment

The research in this study conforms to the Helsinki Declaration of ethical principles for medical research involving human subjects. Written informed consent for study participation and publication was obtained by the attending geneticist or the referring physician from the patients' legal guardian(s).

The cases included in this study were ascertained through GeneMatcher[19] and through personal correspondence between May 2018 and September 2020. All patients with the molecular genetic diagnosis of a *KMT2E*-associated neurodevelopmental disorder were included in this analysis, regardless of variant type.

Genetic testing

In all patients, variants and deletions disrupting *KMT2E* were detected either by chromosome microarray (CMA) or next-generation sequencing (NGS). For a description of CMA and NGS methodology, see the online supplemental methods.

Phenotypic features comparison

Phenotypic features were compared between this study's cohort and the cohort described by O'Donnell-Luria and colleagues[6] as reported in either that publication's main text or online supplemental table 2. Patients for whom specific feature information was missing (eg, no MRI was done) were not included in the respective totals, hence the group sizes differ between features.

Statistical analyses

Statistical tests were performed using Microsoft Excel. A p value of ≤0.05 was considered statistically significant.

Prediction algorithms

Splice predictions were calculated using the MaxEntScan algorithm.[20]

Variant reporting

All variants reported in this study refer to the *KMT2E* transcript NM_182931.2. Genomic coordinates refer to the hg19 human reference genome.

RESULTS

Molecular findings

In the 18 reported patients with heterozygous deleterious variants affecting *KMT2E*, four nonsense variants, seven frameshift variants, two single nucleotide substitutions affecting the canonical splice site, one multi-nucleotide deletion spanning the canonical splice site and one apparent synonymous variant that is predicted to generate a novel splice donor site were detected (see figure 1A). Two siblings carried the identical canonical splice site variant. Additionally, two microdeletions (one with a size of 711 kb encompassing ~98% of *KMT2E*'s coding sequence and the other one with a size of 61 kb encompassing ~75% of *KMT2E*'s coding sequence; figure 1B) were found. The larger heterozygous deletion contained two other known disease-associated genes, *PUS7* (OMIM*616261) and *RINT1* (OMIM*610089), both of which are currently associated exclusively with disorders that are inherited in an autosomal-recessive manner. Of all 17 variants, 13 were confirmed de novo, 2 were proven to be not inherited maternally and paternal samples were unavailable, one variant in two brothers and another variant in an unrelated patient were inherited

paternally. The fathers did not participate in clinical phenotyping and were not included in this study. But the father of patients 14 and 15 stated that he has difficulties in social interaction and the father of patient 6 attended a school for disabled children. Both fathers were not formally assessed for neurodevelopmental features. Only one of the detected variants had been previously described (c.4829dupT, reported in previous work[6]), all others were novel and all 17 were classified as likely pathogenic or pathogenic according to the revised ACMG (American College of Medical Genetics and Genomics) recommendations for the interpretation and reporting of sequence variations[21] or the ACMG/ClinGen technical standards for the interpretation of constitutional CNVs.[22]

Individual 13 carried a seemingly synonymous heterozygous variant c.264A>G (the translation impact is predicted as p.(Glu88=) but will subsequently be given as p.?) that is predicted to activate a cryptic donor splice site. The donor site MaxEntScore at this position was calculated to increase from 3.93 to 8.99, signifying a very strong splice site prediction. The SpliceAI[23] prediction algorithm similarly predicted a donor site gain with a score of 0.74. The variant was confirmed de novo in the patient.

For a more detailed description of the detected pathogenic variants, see table 1.

Phenotypic findings

From the 18 patients in our cohort carrying putative loss-of-function variants in *KMT2E*, 14 are boys and 4 are girls. The age at the most recent clinical assessment ranged from 1 to 16 years. Pregnancy and birth history were generally uncomplicated for these patients, except for the youngest patient of our cohort (patient 2). The boy was born prematurely at 26 weeks of gestation. He had a large ventricular septal defect which was closed operatively, developed a retinopathy of prematurity and shows recurrent apparent life-threatening events and brief resolved unexplained events.

All but one patient (94%) showed speech developmental delay and 13 (72%) presented with global developmental delay. In one boy and one girl, developmental regression was observed regarding speech development with a loss of previously learnt vocabulary starting at 14 months in the girl, and at 18 months in the boy. These two patients were also diagnosed with ASD. It is unclear if the observed language regression occurred in the context of their ASD.

Intellectual function was assessed in 12 patients, with 6 having intellectual disability. In two patients, the degree of ID could be specified; their respective IQ measurements lay in the upper range of mild ID to low normal intelligence at 65/71 (performance and verbal IQ; patient 7) and 63/71 (performance and verbal IQ; patient 17). One boy (patient 10) had a below average IQ of 83, while both parents were tested to have above average IQs of 125 and 134. A speech disorder with dysphasia, but without intellectual disability was present in another boy (patient 3).

Of the tested patients, 41% (7/17) met the criteria of ASD based on the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria and assessment by an expert clinician, with 6 (86%) of these individuals being male. Two of the patients (patient 14 and 15) with high-functioning ASD are brothers and inherited the familial

KMT2E canonical splice site variant from their father. In more than half of our cohort, other behavioural problems were reported, especially sleep disturbances (47%) and less frequently repetitive (33%) and self-injurious (11%) behaviour.

The reported sleep disturbances in our cohort consisted of frequent awakening and difficulty falling asleep with prolonged sleep latency. Sleep disorders are commonly seen in patients with ASD,[24] although in our cohort, sleep disorders were also reported in 3 out of 10 patients (30%) without an ASD diagnosis, the oldest of whom being 9 years and 4 months when last examined.

One patient was diagnosed with attention deficit hyperactivity disorder (ADHD) and another one with sensory integration disorder.

Clinically recurrent dysmorphic features were macrocephaly (10 patients, up to +3.5 SD) and subtle facial features, especially a large forehead, deep-set eyes and full cheeks (see figure 2). In our cohort, the more common presentation of macrocephaly was that of a high-normal occipitofrontal circumference (OFC) at birth, crossing the 97th percentile within the first year of life, although this was not universal and we also observed macrocephaly in infancy normalising to a high-normal OFC by age six in one patient (patient 17).

Muscular hypotonia (eight patients; 44%) and non-specific radiographic signs on brain MRI were also seen frequently. Fourteen patients had a brain MRI, seven (50%) with non-specific findings. The described recurrent central nervous system features were corpus callosum hypoplasia (patients 2, 4, 9), ventriculomegaly (patients 1, 9), cerebral cysts (patients 2, 3, 17) and delayed myelination (patients 1, 2, 4, 6). The following changes on brain MRI were described for only single patients, respectively: mega cisterna magna, reduced brain volume, pachygyria, and multiple ependymal nodules and small pituitary (patient 2, born prematurely).

Half of the patients reported gastrointestinal symptoms, most frequently constipation (eight individuals). Interestingly, no patient in our cohort was diagnosed with epilepsy so far. Only two unrelated patients had recurrent febrile seizures without complications.

For a summary of the phenotypical findings and a comparison with the original ODLURO publication, see table 2. A detailed phenotypical description for each patient listing additional non-recurrent findings is available in online supplemental table S1.

Together with the original cohort,[6] eight patients have been described carrying nonsense and frameshifting variants that are predicted to escape NMD. Regarding quantitative traits like OFC and IQ, and the prevalence of recurring *KMT2E*-associated features, we detected no significant phenotypic differences between these patients and patients carrying variants that are predicted to lead to NMD.

Additional molecular findings

In one patient (patient 3), exome sequencing additionally identified the maternally inherited heterozygous variant c.2021G>A; p.(Arg674Gln) in *MYH8* (NM_002472.2), causative of a known familial trismus-pseudocamptodactyly syndrome (distal arthrogryposis type 7,

DA7; OMIM #158300) as an independent genetic condition. Patients with DA7 may also present with macrocephaly and difficulties with speech articulation; however, developmental delay and cerebral cysts, as observed in this patient, are not typically associated with this condition. Whether the patient's dysphasia is caused by ODLURO or DA7 remains unclear, we assume that both pathologies cause a hybrid phenotype in this case.

In another patient (patient 4), the heterozygous nonsense variant c.3340G>T; p.(Glu1114*) in the *CHD8* gene (NM_001170629.1) in addition to a heterozygous nonsense variant in *KMT2E* was detected. Both variants were confirmed de novo (maternity and paternity confirmed). Nonsense variants in *CHD8* have been robustly associated with mild to moderate ID and ASD susceptibility.[25 26] Additionally, a large proportion of patients display overgrowth with increased height and/or macrocephaly.[27] Again, corpus callosum hypoplasia, delayed myelination and developmental regression—as present in patient 4—are not typical features of the *CHD8*-associated neurodevelopmental phenotype and likely represent an added phenotypical component caused by disruption of *KMT2E*.

In patient 14, the homozygous well-known pathogenic[28] variant c.109G>A; p.(Val37Ile) in *GJB2* (NM_004004.5) was detected, causative of the patient's mild to moderate sensorineural hearing impairment. This variant is exceedingly common in Southeast Asia (carrier frequency of 8.4%) and the most common cause of monogenic mild hearing impairment in this population. It is not associated with a neurodevelopmental disorder.

DISCUSSION

In this case series, we present 18 individuals with ODLURO, refining the phenotypic spectrum of this recently described[6 7 9] syndrome.

As in the initial cohort, we also see a male bias in our cohort (male/female 14:4). Combined with the other patients published so far,[6 7 9] this sex distribution of 41 males to 15 females with putative loss-of-function variants (excluding 7 patients carrying missense variants with a suspected gain-of-function[6 8 9]) is significantly biased towards affected males (binomial test: $p<0.001$ vs ~1:1 sex distribution in the general population). A male preponderance has been described in various NDDs and especially in ASD.[29] Even in monogenic NDD caused by pathogenic variants in autosomal genes, a sex-dependent penetrance has been observed,[30 31] being for some genes lower in males, and lower in females for others. Intriguingly in the context of *KMT2E*, post-translational histone modification profiles in the brain show sex differences in mice[32] and humans,[33] and may influence differences in brain development and behaviour, although we reiterate that the precise nature of the interaction between histones and KMT2E is still uncertain. Another gene in the KMT2 family, *KMT2A* (coding for a functional histone lysine methyltransferase) shows a higher expression in the female prefrontal adult human brain.[34] In summary, many studies on the topic of sexual dimorphism in neurodevelopmental disorders exist and suggest complex (epigenetic) developmental interactions as one important factor; however, the precise mechanisms for the sex-specific variable penetrance in some disorders remain unclear at present.

Our study confirms the originally described ODLURO phenotype with mostly speech developmental delay and variable, but generally mild, ID and/or ASD. In the cohort of O'Donnell-Luria *et al*,[6] 8 out of 31 patients (26%) carrying loss-of-function variants were diagnosed with ASD, while in our cohort, we observed a somewhat higher rate at 7 out of 17 (41%). This difference is not significant (Fisher's exact test: p=0.34). In both studies, one additional patient, respectively, showed characteristics of a sensory integration disorder. The additionally reported behavioural concerns were similar in both case series. However, we report a high prevalence (47%) of sleep disturbances among affected individuals. Sleep disturbances have so far not been explicitly reported to be associated with ODLURO, although one patient carrying a missense *KMT2E* variant in the original publication was described as lacking normal sleep (patient 34 from previous work[6]). We propose that sleep disturbances, including frequent awakening and difficulties falling asleep, may be a recurring feature in ODLURO.

We observed previously described features like macrocephaly, muscular hypotonia and gastrointestinal symptoms like constipation at comparable frequencies to the original ODLURO publication.[6]

Patients presented with a subtle facial gestalt including a prominent forehead, epicanthal folds, full cheeks and deep-set eyes. It remains to be seen if, combined with other phenotypic features, ODLURO can be specifically recognised in the clinical setting.

In both ours and the original case series, various non-specific, but partly recurring abnormalities were detected in more than half of the conducted brain MRIs. About 28% of studied patients had corpus callosum hypoplasia, cerebral cysts or both. These findings substantiate the important role of *KMT2E* in structural brain development. Interestingly, it has been shown that *KMT2E* is highly expressed in the brain during fetal development[35] and remains highly expressed even in the adult brain (Human Protein Atlas[36]; https://www.proteinatlas.org—accessed 28 July 2020).

In the subgroup of patients carrying intragenic truncating variants in *KMT2E* described in the original ODLURO publication,[6] only 4 out of 26 (15%) had epilepsy, but 3 out of 4 (75%) of the patients with microdeletions and 4 out of 4 (100%) of the patients carrying missense variants did. Three out of the four microdeletion carriers from the original cohort had large deletions affecting multiple genes, between 1.9 and 2.9 megabases in size. No patients in our cohort— including two patients with microdeletions at 5 and 9 years old —have been diagnosed with epilepsy so far. Larger cohorts will be needed to elucidate the suggested, but presently unclear genotype–phenotype correlation regarding intragenic *KMT2E* truncating variants and microdeletions. As only two patients of our cohort and four patients of the originally described cohort carry microdeletions containing the *KMT2E* gene either partially or fully, the information regarding this subgroup of patients is still very limited. It is worth noting that those two patients in our cohort with microdeletions show a generally similar phenotype to those with intragenic loss-of-function variants, consistent with haploinsufficiency as a common disease mechanism.

When comparing the symptoms of our patients carrying null variants in *KMT2E* with the previously reported patients carrying missense variants,[6 8 9] we again see a notably different and generally milder phenotype in our patients with null variants.

We did not detect a significant phenotypic difference between patients carrying variants predicted to lead to NMD, and patients carrying nonsense and frameshift variants in the last exon of *KMT2E* predicted to escape NMD.

The additional phenotypic features that are described only in one or two ODLURO patients to date will need to be studied in future larger cohorts in order to correctly recognise their association, or lack thereof, with ODLURO. Identifying additional clinical hints could be helpful in the diagnosis of patients and eventually in optimising the clinical care of affected patients. Since there is so far only a smaller number of reports on teenagers and adults (10 patients in total, including the father/daughter/son trio in previous work[7]), conclusions about patients' long-term development and possible late-onset health problems in adulthood remain speculative at best.

Three patients in our cohort carried pathogenic variants in one other gene, respectively, associated with a monogenic disorder. Two of these conditions (distal arthrogryposis type 7 and the *CHD8*-associated neurodevelopmental disorder) had some clinical overlap with ODLURO. As such, the respective contribution of these variants to the phenotypes in these two patients remains unclear. But it seems likely that the patients have two genetic conditions causing blended, partly overlapping phenotypes.

With the description of ODLURO, all members of the *KMT2* gene family have now been associated with autosomal-dominant NDDs (see table 3). Common features of these disorders appear to be variable ID, seizures, ASD and gastrointestinal symptoms, but these show incomplete penetrance to varying degrees. The ODLURO phenotypic spectrum has a considerable overlap with these disorders, which may suggest an underlying pathomechanistic similarity.

In the STRING database of protein–protein association networks,[37] among KMT2E's top 20 highest-confidence interactors are KMT2A, KMT2B, KMT2C, KMT2D, SETD1A and SETD1B, but also the histone acetyltransferase EP300, and SIN3A, which is part of a histone deacetylase complex. These proteins are associated with the autosomal-dominant phenotypes of Rubinstein-Taybi syndrome type 2 (OMIM #613684) and Witteveen-Kolk syndrome (OMIM #613406), respectively. Both phenotypes are not dissimilar to the KMT2-associated phenotypes summarised above (table 3) with variable ID, ASD, seizures, short stature and constipation. Future research will need to examine whether these phenotypic parallels have a biological basis, representing a 'histone modification disease network', or are coincidental.

A weakness of our study is the missing formal intelligence tests in most patients, partly due to the young age of many patients. A midterm or long-term follow-up with formal development testing in the future could further substantiate our observations in this cohort so far.

Shortly after the systematic description of ODLURO in 2019, our report now brings the number of known patients to 63.[6–9] This suggests that among the more than 2500 currently known or suspected ID and ASD-associated genes,[38–41] deleterious variants in *KMT2E* are a more common aetiology for developmental delay, ID and ASD than presently thought. We recommend that *KMT2E* be included in the routine NGS testing in patients with global developmental delay, ID or ASD, especially in the presence of macrocephaly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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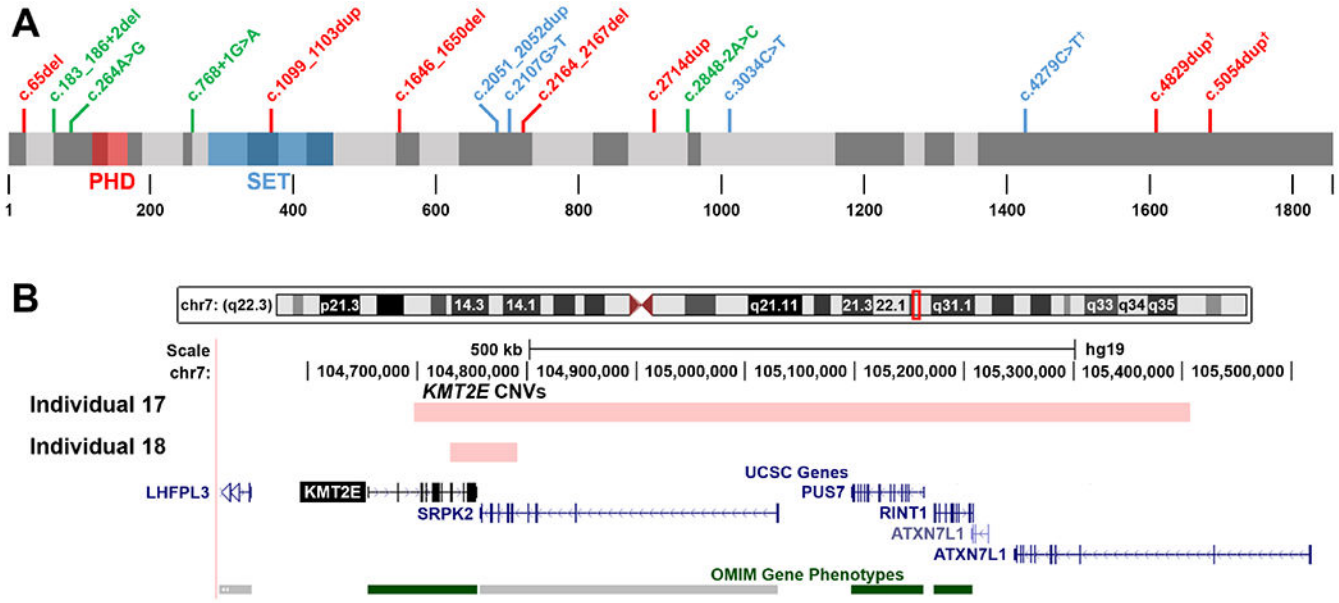

Figure 1.

(A) Localisation of *KMT2E* variants reported in this study at the protein level. Exon regions are depicted with alternating grey shading, the first coding exon in NM_182931.2 is exon 3. Frameshifting variants are written in red, nonsense variants in blue and (putative) splice variants in green. The c.65del (p.(Gly22Valfs*7)) variant represents the earliest truncating variant in *KMT2E* published to date. PHD, PHD zinc finger domain; SET, SET domain; †, variants predicted to escape nonsense-mediated decay. (B) Genomic locations of the CNVs reported in individuals 17 and 18.

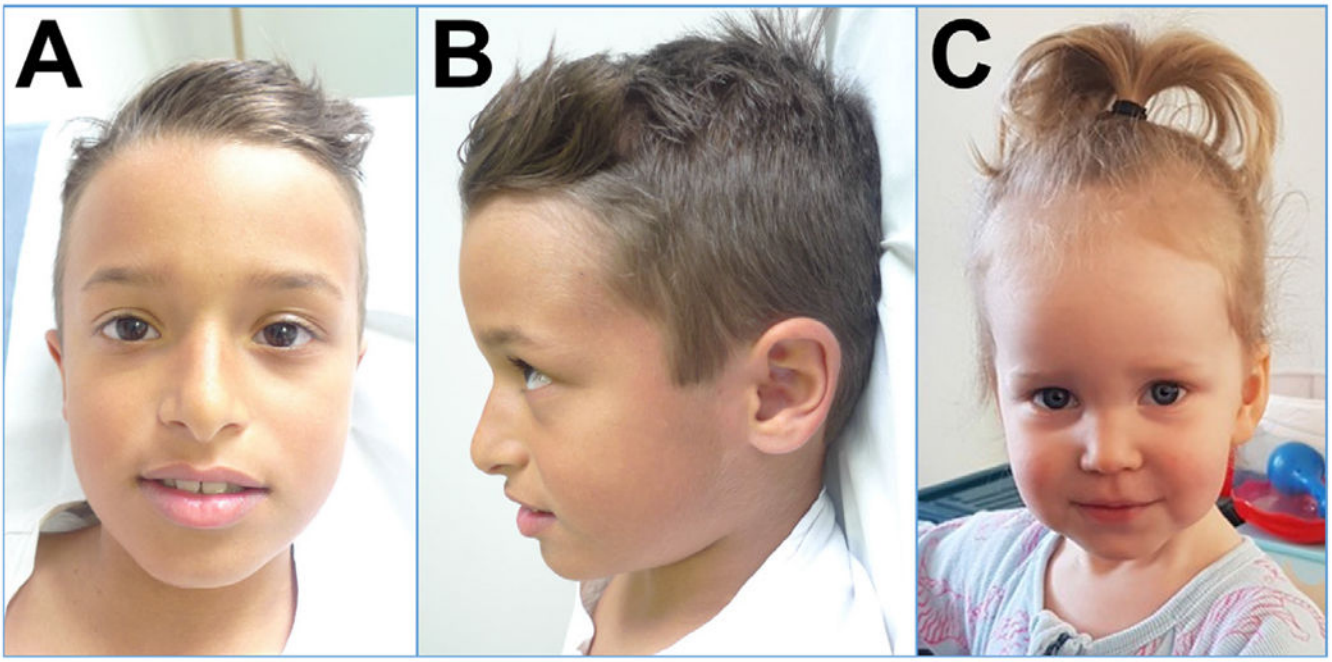

Figure 2.
Facial photographs of two patients reported in this study: (A) patient 17 frontal; (B) patient 17 profile; (C) patient 8 frontal.

Table 1

KMT2E mutational findings in the study cohort

Individual	Variant	Translation impact	Variant type	Inheritance	ACMG
1	c.2051_2052dup	p.(Glu685*)	Nonsense	De novo	P
2	c.2107G>T	p.(Glu703*)	Nonsense	De novo	P
3	c.3034C>T	p.(Gln1012*)	Nonsense	De novo	P
4	c.4279C>T	p.(Gln1427*)	Nonsense†	De novo	LP
5	c.65del	p.(Gly22Valfs*7)	Frameshift	n/a*	LP
6	c.1099_1103dup	p.(Glu369Serfs*25)	Frameshift	Paternal	LP
7	c.1646_1650del	p.(Ile549Argfs*6)	Frameshift	De novo	P
8	c.2164_2167del	p.(Lsy722Valfs*17)	Frameshift	De novo	P
9	c.2714dup	p.(Met906Tyrfs*15)	Frameshift	De novo	P
10	c.4829dup	p.(Leu1610Phefs*259)	Frameshift†	De novo	LP
11	c.5054dup	p.(Pro1686Serfs*183)	Frameshift†	De novo	LP
12	c.183_186+2del	p.?	Splice	De novo	LP
13	c.264A>G	p.?	Splice	De novo	LP
14	c.768+1G>A	p.?	Splice	Paternal	LP
15	c.768+1G>A	p.?	Splice	Paternal	LP
16	c.2848-2A>C	p.?	Splice	n/a*	LP
17	arr(hg19)7q22.3 (104,696,686–105,407,628) x1	p.?	Gross deletion	De novo	P
18	arr(hg19)7q22.3 (104,730,300–104,791,108) x1	p.?	Gross deletion	De novo	P

*The mother was tested negative, the father not available for testing.

†Variant predicted to escape NMD.

ACMG, American College of Medical Genetics and Genomics classification; LP, likely pathogenic; NMD, nonsense-mediated decay; P, pathogenic.

Table 2

Cohort overview and summary of phenotypic findings

	This study	O'Donnell-Luria *et al*,[6] excl. missense variants	Combined
Sex			
Male	14/18 (78%)	24/34 (71%)	38/52 (73%)
Female	4/18 (22%)	10/34 (29%)	14/52 (27%)
Age at last examination	7.2±4.5 years	8.9±5.7 years	–
(Mean±SD (range))	(1–16 years)	(1.5–24 years)	
Dysmorphic features			
Macrocephaly	10/18 (56%)	18/33 (55%)	28/51 (55%)
Dolichocephaly	2/17 (12%)	*n/q*	–
Large forehead	10/17 (59%)	*n/q*	–
Epicanthal folds	7/17 (41%)	*n/q*	–
Deep-set eyes	7/17 (41%)	*n/q*	–
Prominent nasolabial folds	3/17 (18%)	*n/q*	–
Full cheeks	9/17 (53%)	*n/q*	–
Small ears	4/17 (24%)	*n/q*	–
Clinodactyly	4/17 (24%)	*n/q*	–
Neurodevelopmental features			
Motor delay	13/18 (72%)	18/27 (67%)	31/45 (69%)
Speech delay	17/18 (94%)	21/28 (75%)	38/46 (83%)
Regression	2/18 (11%)	4/33 (12%)	6/51 (12%)
Autism spectrum disorder	7/17 (41%)	8/31 (26%)	15/48 (31%)
Intellectual disability	6/12 (50%)	17/20 (85%)	23/32 (72%)
Mild ID	*2/6* (*33%*)	*6/17* (*35%*)	*8/23* (*35%*)
Moderate ID	*0/6* (*0%*)	*6/17* (*35%*)	*6/23* (*26%*)
Not specified	*4/6* (*67%*)	*5/17* (*29%*)	*9/23* (*39%*)
Epilepsy	0/18 (0%)	7/30 (23%)	7/48 (15%)
Febrile seizures	2/18 (11%)	*n/s*	–
Muscular hypotonia	8/18 (44%)	15/27 (56%)	23/45 (51%)

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	This study	O'Donnell-Luria *et al*,[6] excl. missense variants	Combined
Behavioural features			
ADHD	1/18 (6%)	2/34 (6%)	3/52 (6%)
Stereotypical behaviour	6/18 (33%)	3/34 (9%)	9/52 (17%)
Self-injurious behaviour	2/18 (11%)	1/34 (3%)	3/52 (6%)
Aggressive behaviour	1/18 (6%)	2/34 (6%)	3/52 (6%)
Sleep disturbances	8/17 (47%)	*n/s*	–
CNS features			
Corpus callosum hypoplasia	3/14 (21%)	4/22 (18%)	7/36 (19%)
Ventriculomegaly	2/14 (14%)	3/22 (14%)	5/36 (14%)
Cerebral cysts	3/14 (21%)	4/22 (18%)	7/36 (19%)
Delayed myelination	4/14 (29%)	1/22 (5%)	5/36 (14%)
GI features			
Constipation	8/18 (44%)	5/27 (19%)	13/45 (29%)
Gastro-oesophageal reflux	1/18 (6%)	2/27 (7%)	3/45 (7%)
Vomiting	3/18 (18%)	1/27 (4%)	4/45 (9%)

Features that were present in more than one individual or were previously reported to be associated with ODLURO are listed. From the original publication, only patients with putative loss-of-function variants (including those predicted to escape NMD) and microdeletions are compared, as the patients carrying missense variants displayed a notably different phenotype, suggesting a different mutational pathomechanism.

ADHD, attention deficit/hyperactivity disorder; CNS, central nervous system; GI, gastrointestinal; ID, intellectual disability; NMD, nonsense-mediated decay; n/q, feature noted but not quantified; n/s, feature not specified.

Table 3

Disorders associated with genes in the *KMT2* gene family and common recurring phenotypic features

Gene	OMIM phenotype	DD	ID	ASD	Sleep	Sz	GI	SS	Scol	OFC
KMT2A	Wiedemann-Steiner syndrome	+	+	+		+	+	+		↓
KMT2B	Dystonia 28, childhood-onset	+	+			+		+	+	↓
KMT2C	Kleefstra syndrome 2	+	+	+	+	+	+	+	+	↓
KMT2D	Kabuki syndrome 1	+	+			+	+	+	+	↓
KMT2E	O'Donnell-Luria-Rodan syndrome	+	+	+	+	+	+			↑
SETD1A	NDD with speech impairment and dysmorphic facies	+	+	+	+	+	+			–
SETD1B	ID with seizures and language delay	+	+	+		+				–
ASH1L	Autosomal dominant ID 52	+	+	+	+	+	+			↑

ASD, autism spectrum disorder; DD, developmental delay; GI, gastrointestinal symptoms (eg, constipation, reflux, gastrointestinal malformation); ID, intellectual disability; NDD, neurodevelopmental disorder; OFC, occipitofrontal circumference; Scol, scoliosis; Sleep, sleep disturbances; SS, short stature; Sz, seizures.