European Journal of Medical Genetics 60 (2017) 285–288

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Clinical research

Wiedemann-Steiner syndrome: Novel pathogenic variant and review of literature

Anjali Aggarwal*, David F. Rodriguez-Buritica, Hope Northrup

Division of Medical Genetics, Department of Pediatrics, McGovern Medical School, University of Texas Health Science Center at Houston, 6431 Fannin Street, Houston, TX 77030, United States

ARTICLE INFO

Article history:
Received 10 August 2016
Received in revised form
30 January 2017
Accepted 15 March 2017
Available online 27 March 2017

Keywords:
Wiedemann-Steiner syndrome
KMT2A
Novel pathogenic variant

ABSTRACT

Wiedemann-Steiner syndrome (WDSTS) is a very rare genetic disorder characterized by short stature, intellectual disability and distinctive facial appearance. We present a five-year-old boy who was diagnosed with WDSTS based on identification of a novel *de novo* pathogenic variant in the *KMT2A* gene (OMIM: 159555) by Whole Exome Sequencing and supported by some characteristic clinical features. Genotype and phenotype of the patient is compared with the earlier reported patients in the literature, in an attempt to broaden our knowledge of this rare syndrome.

1. Introduction

Wiedemann-Steiner Syndrome (WDSTS) is a rare autosomal dominant disorder first described by Wiedemann et al. in 1989 who reported a Caucasian boy with pre- and postnatal growth deficiency, psychomotor delay, and a round and flat face, short nose, widely spaced eyes, long philtrum, short palpebral fissures, low-set ears, and high-arched palate. Other findings included an alternating convergent squint, dilatation of the renal calyces, and short and thick limbs.

Over the next decade, more authors described patients with similar clinical features (MacDermot et al., 1989, Flannery et al., 1989, and Edwards et al., 1994). In 2000, Steiner et al. described an 8-year-old girl with growth deficiency, mental retardation, unusual facies and hypertrichosis and compared with the one described by Wiedemann et al. Additional authors including Visser at al., 2002; Polizzi et al., 2005; Koc et al., 2007 and Koenig et al., 2010 reported children with WDSTS since that time. WDSTS appears to be present among all populations, affecting males and females equally, typically arising from a *de novo* occurrence.

The genetic underpinning of WDSTS was identified in 2012, when Jones et al. performed whole-exome sequencing in four patients with Wiedemann-Steiner syndrome and identified heterozygous *de novo* truncating pathogenic variants in the *MLL* gene in three of the four patients. They concluded that haploinsufficiency of *MLL* (now known as *KMT2A*) causes WDSTS and pathogenic variants were *de novo* in occurrence.

KMT2A (Lysine Methyltransferase 2A) encodes a histone methyltransferase that has been demonstrated to regulate chromatin-mediated transcription and is widely expressed in most human tissues. Pathogenic variants in *KMT2A* lead to defects in chromatin remodeling (Milne et al., 2002) and are thought to result in global changes in gene expression throughout development leading to abnormalities in multiple body systems. *KMT2A* contains 36 exons and has three known mRNA isoforms.

To the best of our knowledge, less than 30 *KMT2A* pathogenic variant-positive patients have been reported in WDSTS literature. Complete phenotype and genotype-phenotype correlation is not fully understood. We discuss the clinical features and genetic findings in our patient in comparison to the earlier reported patients with a limited attempt at the genotype-phenotype correlation.

1.1. Case report

We report a five-year-old boy who was born to a 28-year-old gravida 3 mother and nonconsanguineous 24-year-old father. Family history is significant for 2 maternal half siblings with history of attention deficit disorder. There were no known exposures during pregnancy. Pregnancy was uncomplicated and the antenatal

* Corresponding author.
E-mail address: Anjali.Aggarwal@uth.tmc.edu (A. Aggarwal).

http://dx.doi.org/10.1016/j.ejmg.2017.03.006
1769-7212/

ultrasounds were normal. Baby was born at 39 weeks gestation via vaginal delivery. Birth weight was 2.8 kg (3rd– 10th percentile), length was 47.6 cm (3rd-10th percentile), and head circumference was 31.5 cm (<3rd percentile; −2.5SD). APGAR scores were 8 and 9 at 1 and 5 min, respectively. Neonatal course was uneventful and he was discharged home on third day of life.

Around the age of seven months he started falling off the growth charts for both height and weight. Because of loss of growth velocity, he was evaluated for endocrine and gastroenterological problems. Upon testing, subclinical hypothyroidism was detected. A bone age performed at three years was normal. He was on appropriate nutrition supplementation. He crawled at the age of nine months, and walked at fifteen months old. His parents did not recognize any speech issues until attempted enrollment into a day school. Evaluators at school suggested speech therapy. The patient has difficulty with expressive and receptive language, and was noted to have mild learning disability. No formal IQ test was performed. He was toilet trained at five years old.

Bilateral ptosis (left> right) was noted since birth and he underwent ptosis surgery at the age of four years. He underwent adenoidectomy for snoring and obstructive sleep apnea at the age of four years. He was referred for Genetics evaluation due to history of developmental delay and poor growth. At five years of age, weight was 13.6 kg (<5th percentile; −2.5SD), height 90.7 cm (<5th percentile; −3.8 SD), and head circumference 51 cm (25-50th percentile). Physical examination demonstrated mild bilateral ptosis, downslanting palpebral fissures, long eyelashes, long philtrum, and downturned corners of mouth (Fig. 1a). Hirsutism was noted throughout back (Fig. 1b). He is in pre-kindergarten currently and making progress with appropriate assistance and therapies. He is noted to be sensitive to excessive noise and gets easily frustrated, but has no attention deficit or hyperactivity.

Chromosomal microarray was normal. The patient was further investigated with whole exome sequencing (WES) that was performed as a clinical test using a trio approach. Genome DNA was fragmented by using sonicating genomic DNA and ligating to multiplexing PE adaptors. The adaptor-ligated DNA was then PCR amplified using primers with sequencing barcodes. For target enrichment/exome capture procedure, the pre-capture library is enriched by hybridizing to biotin labelled VCRome 2.1 in-solution exome probes at 47° C for 64–72 h. Additional probes for over 3600 Mendelian genes were also included in the capture in order to improve the exome coverage. For massively parallel sequencing, the post capture library DNA was subjected to sequence analysis on Illumina HiSeq platform for 100 bp paired-end results. The output data from Illumina HiSeq were converted from bcl file to FastQ file by Illumina CASAVA 1.8 software, and mapped by BWA program to the reference haploid human genome sequence. The variant cells were performed using the Atlas-SNP and Atlas-indel developed in −house by HGSC. The variant annotations were performed using in-house developed software: HGSC-SNP anno and HGSC-indel-anno. WES revealed a Sanger validated novel *de novo* frameshift pathogenic variant: NM_001197104 (KMT2A_v001):c.152_186del (p. Pro51Argfs*84). No additional variants were identified.

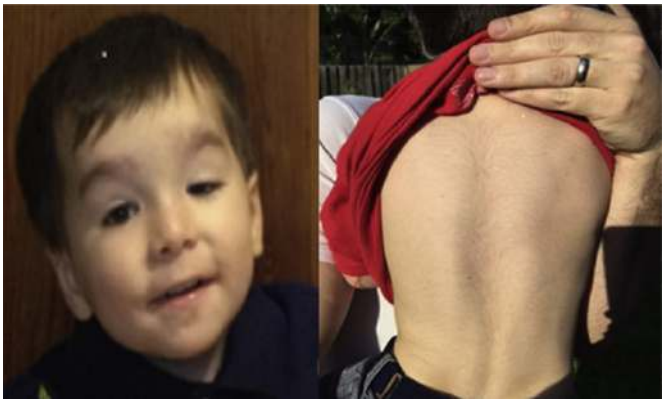

Fig. 1. (a): Front profile at the age of 3 years showing long philtrum, low set ears, widely spaced eyes, strabismus, bilateral ptosis (left > right), epicanthal folds, narrow palpebral fissures, downslanting palpebral fissures, thick eyebrows, broad nose and thin upper lip. **(b)**: Back showing hypertrichosis which is more prominent along the midline.

2. Discussion

The constellation of clinical features described in WDSTS is broad and the clinical diagnosis is often challenging. Characteristic clinical findings in pathogenic variant positive patients with WDTS reported in the literature (including currently reported patient) is shown in Table 1.

As seen in the currently reported patient, the clinical phenotype of WDSTS includes a variable degree of prenatal and postnatal growth restriction as well as unusual facial features including: flat face, low set and dysmorphic ears, widely spaced eyes, synophrys, long eyelashes, broad nose, long philtrum, thin upper lip, high arched palate and micrognathia. The facial features become more pronounced with age (Koenig et al., 2010). Described dental abnormalities include hypodontia, premature dental eruption and widely spaced teeth. Skin findings can include sacral dimple, localized or generalized hypertrichosis. Hypertrichosis cubiti has been regarded as the most prominent but not a universal feature of this syndrome.

Neuropsychiatric manifestations include variable degree of intellectual disability, developmental delay that can improve over time, epilepsy, wide-based gait, absent corpus callosum, aggressive behavior, autistic features, hyperactivity and poor sleep (Vissers et al., 2016). Musculoskeletal features including short stature, thin built, delayed or advanced bone age, short and tapering fingers, clinodactyly, syndactyly, hypotonia and pectus excavatum have been described. Currently reported patient has speech delay and learning issues.

Failure to thrive is an important symptom in the first few years. Constipation and feeding difficulty have been reported in some patients. Three patients have been described to have urinary problems (Wiedemann et al., 1989; Mendelsohn et al., 2014; Dunkerton et al., 2015). Cardiac abnormalities that have been noted include patent ductus arteriosus and atrial septal defect in one patient each (Jones et al., 2012).

Table 1
Frequency of clinical features in the *KMT2A* pathogenic variant positive patients with WDSTS in literature (including currently reported patient).

Clinical feature	(n = 26)	Percentage (%)
Developmental delay	23	88
Post-natal growth retardation	22	85
Hypertrichosis (generalized/localized)	21	81
Thick eyebrows	16	62
Long eyelashes	16	62
Wide nasal bridge	16	62
Downslanting palpebral fissures	15	58
Narrow palpebral fissures	14	54
Hypertelorism	12	46
Broad nasal tip	12	46
Thin vermilion border	12	46
Thick hair	11	42
Feeding problems	9	35
5th finger clinodactyly	9	35

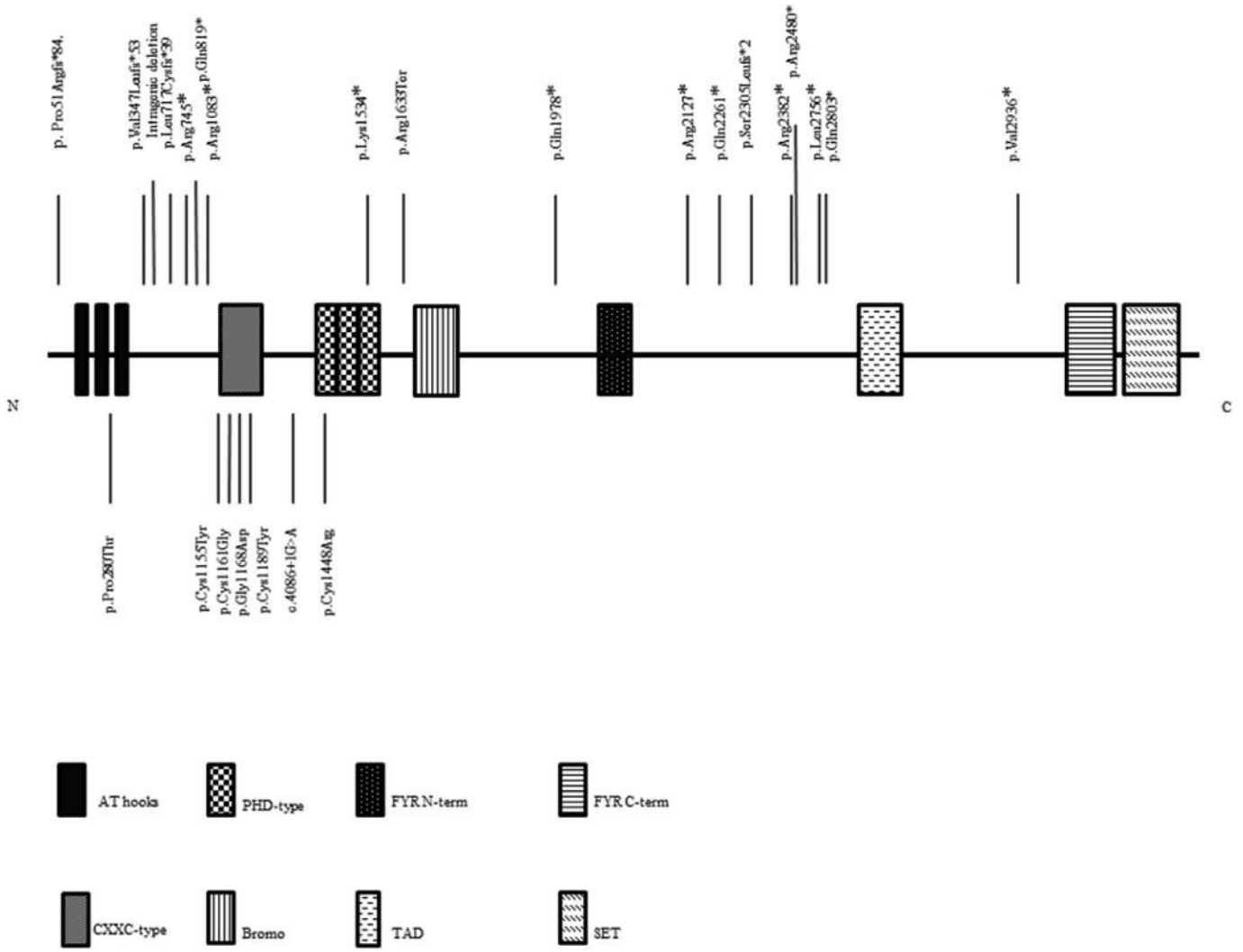

Fig. 2. *KMT2A* protein structure and location of *KMT2A* reported in literature (including the currently reported patient). The upper panel shows nonsense pathogenic variants and the lower panel shows missense pathogenic variants. Domain key has been shown in the lower half of the figure. Refer to the supplementary table for details of the published pathogenic variants.

Pathogenic variants have been described in WDSTS literature since 2012. Pathogenic variants causing WDSTS appear to be distributed along the entire gene. Among the 26 patients described, most pathogenic variants causing WDSTS (7 patients) were clustered in exon 27, which can be considered a pathogenic variant hotspot. Five patients each had a pathogenic variant in exon 3 and 5. Identical twins reported by Dunkerton et al. had a pathogenic variant in exon 4. One patient each harbored a pathogenic variant in intron 8, exon 11, 13, 15 or 26. The patient described by Mendelsohn et al. had an intragenic deletion involving exons 2–10. Majority of these pathogenic variants in *KMT2A* results in a null allele/loss-of function (18/25) (Fig. 2).

The identical twins described above were found to have small kidneys with normal function (Dunkerton et al., 2015). The patient with an intragenic deletion involving exons 2–10 had recurrent urinary tract infections, unilateral ureterocele and grade IV vesicouretral reflux (Mendelsohn et al., 2014). The renal ultrasound in currently reported patient (pathogenic variant in exon 1) revealed a unilateral mild left hydronephrosis and mild right pelviectasis with the plan being to monitor with a repeat renal ultrasound in a year.

All three of the patients with renal manifestations had pathogenic variants involving earlier exons of the *KMT2A*. Since the number of reported patients with WDSTS is small, it is difficult to draw a statistically significant genotype-phenotype correlation. With the available information and small number of individuals with WDSTS identified so far, we suggest a screening renal ultrasound in all WDSTS patients. With increasing awareness about this rare disorder and wider availability of genetic testing, we anticipate additional reports of WDSTS patients. Further study of individuals with *KMT2A* pathogenic variants will be needed to fully understand the phenotypic spectrum and draw more discrete genotype-phenotype correlations.

Conflict of interest disclosures

None.

Acknowledgement

We would like to thank the family for their participation in this study. The novel variant has been submitted to the Leiden Open Variation Database (LOVD). Individual #00089138.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmg.2017.03.006.

References

Dunkerton, S., Field, M., Cho, V., Bertram, E., Whittle, B., Groves, A., Goel, H., 2015 Sep. A de novo mutation in KMT2A (MLL) in monozygotic twins with Wiedemann-Steiner syndrome. Am. J. Med. Genet. A 167A (9), 2182–2187.

Edwards, M.J., Crawford, A.E., Jammu, V., Wise, G., 1994 Oct 15. Hypertrichosis 'cubiti' with facial asymmetry. Am. J. Med. Genet. 53 (1), 56–58.

Flannery, D.B., Fink, S.M., Francis, G., Gilman, P.A., 1989 Apr. Hypertrichosis cubiti. Am. J. Med. Genet. 32 (4), 482–483.

Jones, W.D., Dafou, D., McEntagart, M., Woollard, W.J., Elmslie, F.V., Holder-Espinasse, M., Irving, M., Saggar, A.K., Smithson, S., Trembath, R.C., Deshpande, C., Simpson, M.A., 2012 Aug 10. De novo mutations in MLL cause Wiedemann-Steiner syndrome. Am. J. Hum. Genet. 91 (2), 358–364.

Koc, A., Karaer, K., Ergun, M.A., Cinaz, P., Percin, E.F., 2007. A new case of hairy elbows syndrome(hypertrichosis cubiti). Genet. Counsel. 18 (3), 325–330.

Koenig, R., Meinecke, P., Kuechler, A., Schäfer, D., Müller, D., 2010 Sep. Wiedemann-Steiner syndrome: three further cases. Am. J. Med. Genet. A 152A (9), 2372–2375.

MacDermot, K.D., Patton, M.A., Williams, M.J.H., Winter, R.M., 1989 Jun. Hypertrichosis cubiti (hairy elbows) and short stature: a recognisable association. J. Med. Genet. 26 (6), 382–385.

Mendelsohn, B.A., Pronold, M., Long, R., Smaoui, N., Slavotinek, A.M., 2014 Aug. Advanced bone age in a girl with Wiedemann-Steiner syndrome and an exonic deletion in KMT2A (MLL). Am. J. Med. Genet. A 164A (8), 2079–2083.

Milne, T.A., Briggs, S.D., Brock, H.W., Martin, M.E., Gibbs, D., Allis, C.D., Hess, J.L., 2002. MLL targets SET domain methyltransferase activity to Hox gene promoters. Mol. Cell. 10, 1107–1117.

Polizzi, A., Pavone, P., Ciancio, E., La Rosa, C., Sorge, G., Ruggieri, M., 2005 Oct. Hypertrichosis cubiti (hairy elbow syndrome): a clue to a malformation syndrome. J. Pediat. Endocr. Metab. 18 (10), 1019–1025.

Visser, R., Beemer, F.A., Veenhoven, R.H., De Nef, J.J.E.M., 2002. Hypertrichosis cubiti: two new cases and a review of the literature. Genet. Counsel. 13 (4), 397–403.

Vissers, L.E., Gilissen, C., Veltman, J.A., 2016 Jan. Genetic studies in intellectual disability and related disorders. Nat. Rev. Genet. 17 (1), 9–18. http://dx.doi.org/10.1038/nrg3999. Epub 2015 Oct 27.

Wiedemann, H.R., Kunze, J., Grosse, F.-R., Dibbern, H., 1989. A syndrome of abnormal facies, short stature, and psychomotor retardation. In: Atlas of Clinical Syndromes: A Visual Aid to Diagnosis for Clinicians and Practicing Physicians, second ed. Wolfe Publishing Ltd., London, pp. 198–199.

Further reading

Bo, Yuan, Davut, Pehlivan, Ender, Karaca, Nisha, Patel, Wu-Lin, Charng, Tomasz, Gambin, Claudia, Gonzaga-Jauregui, Reid, Sutton V., Gozde, Yesil, Sevcan Tug, Bozdogan, Tulay, Tos, Asuman, Koparir, Erkan, Koparir, Beck Christine, R., Shen, Gu, Huseyin, Aslan, Ozge Ozalp, Yuregir, Khalid Al, Rubeaan, Dhekra, Alnaqeb, Alshammari Muneera, J., Yavuz, Bayram, Atik Mehmed, M., Hatip, Aydin, Bilge, Geckinli B., Mehmet, Seven, Hakan, Ulucan, Fenercioglu, Elif, Mustafa, Ozen, Shalini, Jhangiani, Muzny Donna, M., Eric, Boerwinkle, Tuysuz, Beyhan, Alkuraya Fowzan, S., Gibbs Richard, A., Lupski James, R., 2015 Feb 2. Global transcriptional disturbances underlie Cornelia de Lange syndrome and related phenotypes. J. Clin. Invest. 125 (2), 636–651.

Bramswig, N.C., Lüdecke, H.J., Alanay, Y., Albrecht, B., Barthelmie, A., Boduroglu, K., Braunholz, D., Caliebe, A., Chrzanowska, K.H., Czeschik, J.C., Endele, S., Graf, E., Guillén-Navarro, E., PÖ, Kiper, López-González, V., Parenti, I., Pozojevic, J., Utine, G.E., Wieland, T., Kaiser, F.J., Wollnik, B., Strom, T.M., Wieczorek, D., 2015 Jun. Exome sequencing unravels unexpected differential diagnoses in individuals with the tentative diagnosis of Coffin-Siris and Nicolaides-Baraitser syndromes. Hum. Genet. 134 (6), 553–568.

Calvel, P., Kusz-Zamelczyk, K., Makrythanasis, P., Janecki, D., Borel, C., Conne, B., Vannier, A., Béna, F., Gimelli, S., Fichna, P., Antonarakis, S.E., Nef, S., Jaruzelska, J., 2015. A case of Wiedemann-Steiner syndrome associated with a 46,XY disorder of sexual development and gonadal dysgenesis. Sex. Dev. 9 (5), 289–295.

Ko, J.M., Cho, J.S., Yoo, Y., Seo, J., Choi, M., Chae, J.H., Lee, H.R., Cho, T.J., 2017 Feb. Wiedemann-steiner syndrome with 2 novel *KMT2A* mutations: variable severity in PsychomotorDevelopment and musculoskeletal manifestation. J. Child. Neurol. 32 (2), 237–242. http://dx.doi.org/10.1177/0883073816674095. Epub 2016 Oct 24.

Miyake, N., Tsurusaki, Y., Koshimizu, E., Okamoto, N., Kosho, T., Brown, N.J., Tan, T.Y., Yap, P.J., Suzumura, H., Tanaka, T., Nagai, T., Nakashima, M., Saitsu, H., Niikawa, N., Matsumoto, N., 2016 Jan. Delineation of clinical features in Wiedemann-Steiner syndrome caused by KMT2A mutations. Clin. Genet. 89 (1), 115–119.

Steel, D., Salpietro, V., Phadke, R., Pitt, M., Gentile, G., Massoud, A., Batten, L., Bashamboo, A., Mcelreavey, K., Saggar, A., Kinali, M., 2015 Dec. Whole exome sequencing reveals a MLL de novo mutation associated with mild developmental delay and without 'hairy elbows': expanding the phenotype of Wiedemann-Steiner syndrome. J. Genet. 94 (4), 755–758.

Stellacci, E., Onesimo, R., Bruselles, A., Pizzi, S., Battaglia, D., Leoni, C., Zampino, G., Tartaglia, M., 2016 Sep. Congenital immunodeficiency in an individual with Wiedemann-Steiner syndrome due to a novel missense mutation in *KMT2A*. Am. J. Med. Genet. A 170 (9), 2389–2393. http://dx.doi.org/10.1002/ajmg.a.37681. Epub 2016 Jun 20.

Strom, S.P., Lozano, R., Lee, H., Dorrani, N., Mann, J., O'Lague, P.F., Mans, N., Deignan, J.L., Vilain, E., Nelson, S.F., Grody, W.W., Quintero-Rivera, F., 2014 May 1. De Novo variants in the KMT2A (MLL) gene causing atypical Wiedemann-Steiner syndrome in two unrelated individuals identified by clinical exome sequencing. BMC Med. Genet. 15, 49.

Sun, Yu, Hu, Guorui, Liu, Huili, Zhang, Xia, Huang, Zhuo, Yan, Hui, Wang, Lili, Fan, Yanjie, Gu, Xuefan, Yu, Yongguo, 2016 Oct 19. Further Delineation of the Phenotype of truncating *KMT2A* mutations: the extended Wiedemann–Steiner syndrome. Am. J. Med. Genet. A. http://dx.doi.org/10.1002/ajmg.a.38025 ([Epub ahead of print]).