Case Report: Wiedemann-Steiner syndrome with a new frameshift mutation in KMT2A

Jun He[1], Aimin Deng[1], Ying chen[1], Shuyuan Yan[1], yanling wang[1], Tuanmei Wang[1], and Xiangwen Peng[1]

[1]Hunan Normal University

April 05, 2024

Abstract

Here we report a 5 year old girl with a new frameshift mutation (c.2318dup:p.S774Vfs*12) in the KMT2A gene.The patient's clinical manifestations: postnatal growth retardation, early teething, rapid tooth replacement,dysplasia of dentition; wide eye spacing; generalized hirsutism; stubby fingers; low muscle tension and retarded mental development.

Introduction

Wiedemann-Steiner syndrome (WDSTS, OMIM 605130) is a Rare autosomal dominant genetic disease[1; 2; 3], this is the first time Wiedemann et al. described it in 1989, and more than 20 papers later reported on WDSTS[2; 4; 5; 6; 7; 8; 9; 10; 11; 12; 13; 14; 15; 16; 17; 18; 19; 20; 21]. Wiedemann-Steiner syndrome is mainly manifested as: intellectual disability, wide eye distance, abnormal teeth, high palate, thin upper lip, inner canthal epidermis, long middle and low ears, wide nose bridge, sunken nasal tip, wide nose, strabismus, down Oblique palpebral fissure, long eyelashes, aggressive behavior, language development delay, tapered fingers, seizures, hypotonia, general developmental delay, inability to grow, short toes, constipation, wide base gait, delayed bone maturation, little finger flexion Deformed, short stature, flat face[1; 10; 22]. Here we report a case of KMT2A frameshift mutation, the girl's parents are wild type. Our research has enriched our knowledge of KMT2A mutations and suggested that proper prenatal genetic screening is also necessary.

Case report

A 5 years and 7 months old girl was admitted to Changsha Hospital for maternal&Child Health care. The clinical features of the patient included postnatal growth retardation, early teething, rapid tooth replacement, dysplasia of dentition; wide eye spacing; generalized hirsutism; stubby fingers; a distinctive facial appearance, low muscle tension of the lower limbs and retarded intellectual development. Using whole-exome high-throughput sequencing detection technology and whole-genome copy number variation (CNV-seq) detection technology, using Berry Gene's Verita Trekker® variant site detection system and Enliven® variant site annotation interpretation system Data is analyzed. One mutation of the gene KMT2A was detected in the sample of the subject. It is suggested that the c.2318dup mutation of gene KMT2A is a pathogenic mutation site (Fig1.A), which causes changes in the open reading frame of the gene, leading to changes in protein function; and the autosomal dominant genetic disease Wiedemann-Steiner and it was judged to be pathogenic. The clinical features consistent with the phenotype of this case are intellectual disability, wide eye distance, and abnormal teeth. Subsequently, the first-generation sequencing verification results showed that the proband had a heterozygous mutation of c.2318dup in gene KMT2A, and neither father nor mother had mutations. Genome copy number variants (CNVs) of unexplained clinical significance above 100Kb were detected in the sample of the subject: seq[hg19]dup(11(q24.3q25)chr11:g.130420000_131280000dup11 chromosome q24.3-q25 repeated 0.86Mb region (Fig1.B). After querying DGV, DECIPHER, OMIM, ClinGen,

UCSC, gnomAD and PubMed public database resources, no clear pathogenic information and literature reports related to the fragment were found.

Discussion

With the development of genetic technology, more and more genetic diseases have been diagnosed. So far, more than 83 WDSTS patients have confirmed KMT2A gene mutations, most of which share similar clinical features, such as elbow or back hirsutism, growth retardation, cognitive impairment, prenatal and postnatal growth retardation and unique The appearance of the face: eyelid cracks, downward slope, wide nose bridge, wide nose, long eyelashes, thick eyebrows[3; 15]. In addition to low muscle tone, peculiar facial features, and intellectual disability, the frameshift mutation we discovered also has a new feature: early teething, fast tooth replacement, and dysplasia of axons.

There are currently more than 20 papers reporting new mutations in the KMT2A gene. The Clinvar database reports nearly 100 mutations and small indels[3; 20], classified as pathogenic, of which 43 are frameshift small indels, 39 are missense mutations and 4 are splicing mutations, nearly 60% are located in exons 3 and 27 mutations[5]. The mutation in this case is also located in exon 3.

Genetic diseases have experienced long-term socio-psychological and economic burdens. Benefiting from the development of genetic technology, WES not only has a higher genetic diagnosis rate, but also considerable cost savings. The diagnostic cost of WES is getting lower and lower. Perhaps the use of WES for prenatal diagnosis is an economically feasible and effective means to reduce birth defects caused by genetic mutations.

CONCLUSION To our knowledge, this is a new mutation that causes the child's intellectual disability, but the parents do not have this gene mutation. In summary, our findings extend the WDSTS genetic and phenotypic spectrum.**DATA AVAIL ABILITY STATEMENT** The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent has been obtained from the minor's parents, and all the data in the article have been approved.

Author contributions

HJ and XWP conceptualized and drafted the initial manuscript and reviewed and revised the manuscript. HJ, AMD, YC, SYY, YLW, JZX and TMW collected data and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Reference

[1] J. Min Ko, J.S. Cho, Y. Yoo, J. Seo, M. Choi, J.H. Chae, H.R. Lee, and T.J. Cho, Wiedemann-Steiner Syndrome With 2 Novel KMT2A Mutations. Journal of child neurology 32 (2017) 237-242.

[2] A.J.S. Chan, C. Cytrynbaum, N. Hoang, P.M. Ambrozewicz, R. Weksberg, I. Drmic, A. Ritzema, R. Schachar, S. Walker, M. Uddin, M. Zarrei, R.K.C. Yuen, and S.W. Scherer, Expanding the neurodevelopmental phenotypes of individuals with de novo KMT2A variants. NPJ genomic medicine 4 (2019) 9.

[3] A. Aggarwal, D.F. Rodriguez-Buritica, and H. Northrup, Wiedemann-Steiner syndrome: Novel pathogenic variant and review of literature. European journal of medical genetics 60 (2017) 285-288.

[4] S. Baer, A. Afenjar, T. Smol, A. Piton, B. Gerard, Y. Alembik, T. Bienvenu, G. Boursier, O. Boute, C. Colson, M.P. Cordier, V. Cormier-Daire, B. Delobel, M. Doco-Fenzy, B. Duban-Bedu, M. Fradin, D. Genevieve, A. Goldenberg, M. Grelet, D. Haye, D. Heron, B. Isidor, B. Keren, D. Lacombe, A.S. Lebre, G. Lesca, A. Masurel, M. Mathieu-Dramard, C. Nava, L. Pasquier, A. Petit, N. Philip, J. Piard, S. Rondeau, P. Saugier-Veber, S. Sukno, J. Thevenon, J. Van-Gils, C. Vincent-Delorme, M. Willems, E. Schaefer, and G. Morin, Wiedemann-Steiner syndrome as a major cause of syndromic intellectual disability: A study of 33 French cases. Clinical genetics 94 (2018) 141-152.

[5] L. Jinxiu, L. Shuimei, X. Ming, L.C. Jonathan, L. Xiangju, and D. Wenyuan, Wiedemann-steiner syndrome with a de novo mutation in KMT2A: A case report. Medicine 99 (2020) e19813.

[6] D. Ramirez-Montano, and H. Pachajoa, Wiedemann-Steiner syndrome with a novel pathogenic variant in KMT2A: a case report. Colombia medica 50 (2019) 40-45.

[7] H.R. Feldman, S.R. Dlouhy, M.D. Lah, K.K. Payne, and D.D. Weaver, The progression of Wiedemann-Steiner syndrome in adulthood and two novel variants in the KMT2A gene. American journal of medical genetics. Part A 179 (2019) 300-305.

[8] X. Wang, G. Zhang, Y. Lu, X. Luo, and W. Wu, Trio-WES reveals a novel de novo missense mutation of KMT2A in a Chinese patient with Wiedemann-Steiner syndrome: A case report. Molecular genetics & genomic medicine 9 (2021) e1533.

[9] L. Hirst, and R. Evans, Wiedemann-Steiner syndrome: A case report. Clinical case reports 9 (2021) 1158-1162.

[10] A. Grangeia, M. Leao, and C.P. Moura, Wiedemann-Steiner syndrome in two patients from Portugal. American journal of medical genetics. Part A 182 (2020) 25-28.

[11] M. Chen, R. Liu, C. Wu, X. Li, and Y. Wang, A novel de novo mutation (p.Pro1310Glnfs*46) in KMT2A caused Wiedemann-Steiner Syndrome in a Chinese boy with postnatal growth retardation: a case report. Molecular biology reports 46 (2019) 5555-5559.

[12] E. Stellacci, R. Onesimo, A. Bruselles, S. Pizzi, D. Battaglia, C. Leoni, G. Zampino, and M. Tartaglia, Congenital immunodeficiency in an individual with Wiedemann-Steiner syndrome due to a novel missense mutation in KMT2A. American journal of medical genetics. Part A 170 (2016) 2389-93.

[13] V. Arora, R.D. Puri, S. Bijarnia-Mahay, and I.C. Verma, Expanding the phenotypic and genotypic spectrum of Wiedemann-Steiner syndrome: First patient from India. American journal of medical genetics. Part A 182 (2020) 953-956.

[14] R. Nardello, G.D. Mangano, A. Fontana, C. Gagliardo, F. Midiri, P. Borgia, F. Brighina, V. Raieli, S. Mangano, and V. Salpietro, Broad neurodevelopmental features and cortical anomalies associated with a novel de novo KMT2A variant in Wiedemann-Steiner syndrome. European journal of medical genetics 64 (2021) 104133.

[15] J.L. Wang, K. Huang, W. Wu, M.Q. Zhu, H. Lin, D.W. Wu, G.P. Dong, and J.F. Fu, [A case of Wiedemann-Steiner syndrome caused by a novel variation of the KMT2A gene]. Zhonghua er ke za zhi = Chinese journal of pediatrics 59 (2021) 516-518.

[16] H. Xue, Y. Feng, C. Zhang, L. Ma, J. Wu, Q. Li, T. Gao, and Z. Cao, [Wiedemann-Steiner syndrome due to novel nonsense variant of KMT2A gene in a case]. Zhonghua yi xue yi chuan xue za zhi = Zhonghua yixue yichuanxue zazhi = Chinese journal of medical genetics 38 (2021) 138-140.

[17] T. Enokizono, T. Ohto, R. Tanaka, M. Tanaka, H. Suzuki, A. Sakai, K. Imagawa, H. Fukushima, A. Iwabuti, T. Fukushima, R. Sumazaki, T. Uehara, T. Takenouchi, and K. Kosaki, Preaxial polydactyly in an individual with Wiedemann-Steiner syndrome caused by a novel nonsense mutation in KMT2A. American journal of medical genetics. Part A 173 (2017) 2821-2825.

[18] B.A. Mendelsohn, M. Pronold, R. Long, N. Smaoui, and A.M. Slavotinek, Advanced bone age in a girl with Wiedemann-Steiner syndrome and an exonic deletion in KMT2A (MLL). American journal of medical genetics. Part A 164A (2014) 2079-83.

[19] S. Dunkerton, M. Field, V. Cho, E. Bertram, B. Whittle, A. Groves, and H. Goel, A de novo Mutation in KMT2A (MLL) in monozygotic twins with Wiedemann-Steiner syndrome. American journal of medical genetics. Part A 167A (2015) 2182-7.

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

[21] H. Zhang, B. Xiang, H. Chen, X. Chen, and T. Cai, A novel deletion mutation in KMT2A identified in a child with ID/DD and blood eosinophilia. BMC medical genetics 20 (2019) 38.

[22] Y. Sun, G. Hu, H. Liu, X. Zhang, Z. Huang, H. Yan, L. Wang, Y. Fan, X. Gu, and Y. Yu, Further delineation of the phenotype of truncating KMT2A mutations: The extended Wiedemann-Steiner syndrome. American journal of medical genetics. Part A 173 (2017) 510-514.

Figure Legends:

Fig 1. (A) First generation sequencing confirmed frameshift mutations in the proband, but not in the parents. (**B**) Genome copy number variants (CNVs) found 0.86Mb repeat: seq[hg19]dup(11(q24.3q25)chr11:g.130420000_131280000dup11 chromosome q24.3-q25