Cerebral palsy needs a review: a novel DDX3X mutation in a family

Liqin Hu (✉ HuLiQin6611@163.com)

Ganzhou Maternal and Child Health Hospital

Xiaoqin Xin

Ganzhou People's Hospital

Shaobin Lin

The First Affiliated Hospital of Sun Yat-Sen university

Min Luo

Ganzhou Maternal and Child Health Hospital

Junkun Chen

Ganzhou Maternal and Child Health Hospital

Hongsheng Qiu

Ganzhou Maternal and Child Health Hospital

Li Ma

Ganzhou Maternal and Child Health Hospital

Jungao Huang (✉ jungaohuang@sina.com)

Ganzhou Maternal and Child Health Hospital <https://orcid.org/0000-0002-3197-6044>

Short report

Keywords: Cerebral palsy, MRX102, whole exome sequencing, diagnostics

Posted Date: December 5th, 2019

DOI: <https://doi.org/10.21203/rs.2.18259/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Cerebral palsy (CP) is a non-progressive disorder of movement and posture due to a static insult to the brain. Some conditions of other disorders can mimic CP, and thus CP needs to be pursued for its underlying cause. In this paper, we reported a novel DDX3X mutation in a girl afflicted with MRX102 which had been confused with CP in her early life. The application of whole exome sequencing may be the best method to distinguish between actual CP and other disorders with similar characteristics. A thorough and conscientious review is suggested during the diagnostic progress.

Introduction

Cerebral Palsy (CP) is a non-progressive group of developmental disorders of movement and posture caused by a static insult occurring in the brain of the fetus or infant. CP is regarded as the most common cause of physical disability in childhood with a prevalence of approximately 2 per 1,000 live births (Jan, 2006). It has been classified into four categories: spastic, dyskinetic or dystonic, ataxic or hypotonic ("Cerebral palsy," 2016). CP has medical comorbidities, such as intellectual disability, epilepsy, and visual disturbances, and clinical heterogeneity may exist (Graham et al., 2016; McMichael et al., 2015).

The phenotype-gene relationship X-linked mental retardation-102 (MRX102, MIM: 300958) has been described in patients with mutations in DDX3X at Xp11.4, which encodes a DEAD-box RNA helicase (Brennan et al., 2018; Nicola et al., 2019). It plays an important role in transcription, splicing, transport of RNA, and translation, and works as a key regulator in the Wnt/ β -catenin signaling pathway (Abdelhaleem, 2005; Cruciat et al., 2013). DDX3X consists of 17 coding exons and is the most commonly pathogenic gene on the X chromosome. The inheritance of both X-linked dominant and recessive modes has been observed. De novo mutations of DDX3X have been identified in 1–3% of females with intellectual disability (Dikow et al., 2017). MRX102 occurs in infancy and may involve the head, face, ears, mouth, skin and muscle in affected individuals. Although MRX102 mainly manifests as intellectual disability and dyskinesia, symptoms of autism may accompany it (Kellaris et al., 2018). In some patients with DDX3X mutations, the disorder may even involve the endocrine glands as precocious puberty has been observed. Here, we report the case of a girl diagnosed with ataxic CP as an infant. Subsequently, genetic investigation via whole-exome sequencing of the family indicated that the patient had MRX102, with identification of a novel mutation in DDX3X. This case may highlight the need for genetic analysis to determine the underlying cause of a disorder before a diagnosis of CP is made.

Clinical Report

The Chinese girl was born at 39 weeks and 6 days gestation by natural labor following a normal pregnancy when her mother was 27 and her father was 24 years of age. Her birth weight was 3,300 g, birth length 52.3 cm, and birth head circumference 34.7 cm. There was no history of asphyxia and abnormalities found in the newborn screening at birth. The girl was unable to sit up by herself at 10 months of age. This developmental delay was documented by pediatricians, along with reduced activities

of the arms and legs, and thus a diagnosis of ataxic CP was considered. Brain magnetic resonance imaging (MRI) at that time showed abnormal signals from the posterior horn and trigonometry region of the lateral ventricle, and the lateral and third ventricles were slightly enlarged, which suggested cerebral dysplasia (Figure.1) At 2 years and 6 months of age, a neurologist noted that the girl had a special face with a prominent forehead, two hollow eye sockets, two low-set ears and a wide bridge of the nose, an unsteady gait and walked with help, fell frequently and was unable to eat with cutlery. In addition, she rarely communicated and had difficulty understanding, bad eye contact and no reaction upon the calling of her name. There were no history of infection, including hepatitis, tuberculosis, measles and chicken pox. The tests for the syndromes of Kernig, Brudzinski and Babinski were negative. Liver, kidney, and heart function were all normal, the level of lactic acid and ammonia in plasma was within limits and the results of the analysis of tandem mass spectrum for peripheral blood were also normal. With the consideration of her chronic non-progressive course with hypotonia and intellectual disability, the girl was diagnosed with ataxic CP. She underwent rehabilitation training between the ages of one and two, but her motor function was still abnormal compared with her peers, especially for intellectual level. Subsequently, genetic analysis was performed, and traditional chromosome analysis and chromosome microarray analysis were normal. The girl was then tested with whole-exome sequencing and analysis within her family. The test identified a novel heterozygous variant of DDX3X gene, confirmed by sanger sequencing. The c.1251 G>C mutation was located in exon 12 of the DDX3X gene, resulting in a p.Gln417His substitution (Figure. 2). This variant was within the functional domain, without benign variants in the ClinVar database. The variant was absent from the Exome Aggregation Consortium database and predicted to be pathogenic by at least two of the in-silico prediction tools. Parental testing showed the heterozygous variant to be *de novo*, confirmed to the inheritance of X-linked dominant. Eventually, a diagnosis of MRX102 was made.

Written informed consent was obtained from the family for this study.

Discussion

During the progress of the diagnosis of CP, a neurological syndrome, a thorough family history and examination was suggested to look for signs of a non-CP diagnosis (Andersen, Leventer, ReddiHough, Davis, & Ryan, 2016). The presence of non-motor symptoms such as vision or hearing deficits, cranial nerve dysfunction and epilepsy should be paid more attention to (Appleton & Gupta, 2019). For the diagnosis of CP, it is believed that MRI is the highest yield investigation method, with almost 89% abnormal MRI among children with CP (Ashwal et al., 2004). Meanwhile, considering that the symptoms and signs of CP change over time, some difficulty may be encountered when diagnosing CP, especially for some of the underlying insult. It is possible that there are some diseases that can be confused with CP, especially for ataxic CP (McMichael et al., 2013).

We report the case of a girl who was considered to have ataxic CP at early phase by her primary pediatrician. A primary diagnosis was made according to the presence of cerebral dysplasia, delayed motor development and a non-progressive course, ataxic in nature, combined with frequent falls.

However, the presence of her intellectual disability had only been treated as a comorbidity of CP. After a review by a geneticist, a novel mutation in the DDX3X gene was identified by the whole exome sequencing. The mutation locus was at the same amino acid residue but with a different pathogenic base pair in the DDX3X gene and had been reported before (Snijders Blok et al., 2015). The American female described previously to also be suffering from unexplained intellectual disability was carrying the DDX3X mutation: c.1250 A>C, p.Gln417Pro. However, further details were not described. Nearly all published DDX3X variants resulting in MRX102 so far are de novo and proved 'damaging in biology' (Nicola et al., 2019). There is no report that MRX102 is confused with ataxic CP until now. This illustrates that in this case, similar characteristics in both disorders should be paid due attention. Additionally, the abnormal MRI results of the patient made the diagnosis difficult in MRX102.

In summary, the girl reported in this paper exemplifies the problem that clinicians may face in distinguishing between CP and other similar disorders. When a diagnosis is carried out early in childhood, the clinical features may meet the characteristics of CP but a careful review before a final diagnosis is essential. Since there are few reports of this novel DDX3X mutation, further research into its biological significance and mechanism of action is warranted. Genetic investigation of individuals with CP will play a great role in its diagnosis compared with other methods.

Declarations

Acknowledgements

The Authors would like to thank the family members in the study.

Funding

This work has received funding from the Research Project of Health Department of Jiangxi Province (360040034, BEAF, project number: 20174057).

Availability of data and materials

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

Authors' contributions LQH, XQX drafted manuscript, reviewed the data analyses. JGH reviewed data analyses, involved in drafting the manuscript. SBL, HSQ, JKC, LM reviewed evaluated the patients, undertook patient care and management, collected clinical data, delineated the patients' phenotype. ML performed the experiments. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The patients were ascertained under the Ethics Committee of Ganzhou Maternal and Child Health Hospital. Before the sample collection, the patients signed the written informed consents.

Consent for publication

Written informed consents were obtained from the related parties.

Disclosure statement

The authors report no conflicts of interest.

References

- Abdelhaleem, M. (2005). RNA helicases: regulators of differentiation. *Clin Biochem*, 38(6), 499-503. doi:10.1016/j.clinbiochem.2005.01.010
- Andersen, E. W., Leventer, R. J., Reddihough, D. S., Davis, M. R., & Ryan, M. M. (2016). Cerebral palsy is not a diagnosis: A case report of a novel atlastin-1 mutation. *J Paediatr Child Health*, 52(6), 669-671. doi:10.1111/jpc.13200
- Appleton, R. E., & Gupta, R. (2019). Cerebral palsy: not always what it seems. *Arch Dis Child*, 104(8), 809-814. doi:10.1136/archdischild-2018-315633
- Ashwal, S., Russman, B. S., Blasco, P. A., Miller, G., Sandler, A., Shevell, M., . . . Practice Committee of the Child Neurology, S. (2004). Practice parameter: diagnostic assessment of the child with cerebral palsy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*, 62(6), 851-863. doi:10.1212/01.wnl.0000117981.35364.1b
- Brennan, R., Haap-Hoff, A., Gu, L., Gautier, V., Long, A., & Schroder, M. (2018). Investigating nucleocytoplasmic shuttling of the human DEAD-box helicase DDX3. *Eur J Cell Biol*, 97(7), 501-511. doi:10.1016/j.ejcb.2018.08.001
- Cerebral palsy. (2016). *Nat Rev Dis Primers*, 2, 15083. doi:10.1038/nrdp.2015.83
- Cruciat, C. M., Dolde, C., de Groot, R. E., Ohkawara, B., Reinhard, C., Korswagen, H. C., & Niehrs, C. (2013). RNA helicase DDX3 is a regulatory subunit of casein kinase 1 in Wnt-beta-catenin signaling. *Science*, 339(6126), 1436-1441. doi:10.1126/science.1231499
- Dikow, N., Granzow, M., Graul-Neumann, L. M., Karch, S., Hinderhofer, K., Paramasivam, N., . . . Moog, U. (2017). DDX3X mutations in two girls with a phenotype overlapping Toriello-Carey syndrome. *Am J Med Genet A*, 173(5), 1369-1373. doi:10.1002/ajmg.a.38164
- Graham, H. K., Rosenbaum, P., Paneth, N., Dan, B., Lin, J. P., Damiano, D. L., . . . Lieber, R. L. (2016). Cerebral palsy. *Nat Rev Dis Primers*, 2, 15082. doi:10.1038/nrdp.2015.82

Jan, M. M. (2006). Cerebral palsy: comprehensive review and update. *Ann Saudi Med*, 26(2), 123-132. doi:10.5144/0256-4947.2006.123

Kellaris, G., Khan, K., Baig, S. M., Tsai, I. C., Zamora, F. M., Ruggieri, P., . . . Katsanis, N. (2018). A hypomorphic inherited pathogenic variant in *DDX3X* causes male intellectual disability with additional neurodevelopmental and neurodegenerative features. *Hum Genomics*, 12(1), 11. doi:10.1186/s40246-018-0141-y

McMichael, G., Bainbridge, M. N., Haan, E., Corbett, M., Gardner, A., Thompson, S., . . . MacLennan, A. H. (2015). Whole-exome sequencing points to considerable genetic heterogeneity of cerebral palsy. *Mol Psychiatry*, 20(2), 176-182. doi:10.1038/mp.2014.189

McMichael, G., Haan, E., Gardner, A., Yap, T. Y., Thompson, S., Ouvrier, R., . . . MacLennan, A. H. (2013). *NKX2-1* mutation in a family diagnosed with ataxic dyskinetic cerebral palsy. *Eur J Med Genet*, 56(9), 506-509. doi:10.1016/j.ejmg.2013.07.003

Nicola, P., Blackburn, P. R., Rasmussen, K. J., Bertsch, N. L., Klee, E. W., Hasadsri, L., . . . Clayton-Smith, J. (2019). De novo *DDX3X* missense variants in males appear viable and contribute to syndromic intellectual disability. *Am J Med Genet A*, 179(4), 570-578. doi:10.1002/ajmg.a.61061

Snijders Blok, L., Madsen, E., Juusola, J., Gilissen, C., Baralle, D., Reijnders, M. R., . . . Kleefstra, T. (2015). Mutations in *DDX3X* Are a Common Cause of Unexplained Intellectual Disability with Gender-Specific Effects on Wnt Signaling. *Am J Hum Genet*, 97(2), 343-352. doi:10.1016/j.ajhg.2015.07.004

Figures

Figure 1

MRI performed when the girl was at 10 months, showing that the posterior horn and trigonometry region of the lateral ventricle existed abnormal signals, and the lateral ventricle and the third ventricle were slightly enlarged.

Figure 2

The sequence chromatogram for the mutation: c.1251 G>C located at exon12 of DDX3X gene in X chromosome. This mutation was existed only in the proband identified by using primers: F (5'-CAGATGCTGGCTCGTGATTT-3') and R (5'-ACCTGTGAATAACCCCTGCA-3').