Open Access

Article Type: Case Report
Volume 2 Issue 1 - 2024

SCIBASE Journals

SciBase Cardiology

Homozygous Variant on CLASP2 Gene Associated to Intellectual Disability and Rhythm Disorder

Susana Lemos Ferreira[1]; João Parente Freixo[2]; Pedro Silva Cunha[3,4,5]; Diana Oliveira Antunes[1,6]

[1]Genetics Department, Dona Estefânia Hospital, Lisbon Central University Hospital Center, Lisbon, Portugal.

[2]CGPP – Center for Predictive and Preventive Genetics, IBMC – Institute of Molecular and Cellular Biology, i3S – Institute of Research and Innovation in Health, University of Porto, Oporto, Portugal.

[3]Arrhythmology, Pacing and Electrophysiology Unit, Cardiology Service, Santa Marta Hospital, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal.

[4]Faculty of Medicine, University of Lisbon, Lisbon, Portugal.

[5]Cardiovascular Department, Hospital Lusíadas Lisboa, Lisbon, Portugal.

[6]GenoMed Diagnostic Molecular Medicine, Institute of Molecular Medicine, Lisbon, Portugal.

Corresponding Author: Diana Oliveira Antunes

Genetics Department, Dona Estefânia Hospital, Center Hospitalar Universitário Lisboa Central, Lisbon, Portugal.
Email: diana.antunes@chlc.min-saude.pt

Article information

Received: Dec 06, 2023
Accepted: Jan 05, 2024
Published: Jan 12, 2024

SciBase Cardiology - scibasejournals.org

Citation: Ferreira SL, Freixo JP, Cunha PS, Antunes DO. Homozygous Variant on CLASP2 Gene Associated to Intellectual Disability and Rhythm Disorder. SciBase Cardiol. 2024; 2(1): 1006.

Abstract

Neurodevelopmental disorders are a group of clinical and genetic heterogeneous diseases characterized by impaired brain development, affecting personal, social, academic, or occupational functioning. Next-Generation Sequencing advent has allowed to unravel new diagnosis and improved knowledge of the molecular mechanism's underlying pathogenesis. Here we present the case of an adult male, born from a consanguineous couple, with intellectual disability and complete atrio-ventricular block. From family history it was noted an older sister also with heart rhythm disorder. It was performed an clinical exome sequencing which revealed an homozygous variant on CLASP2 gene. CLASP2 gene is a key regulator of synaptic activity and formation and also previously demonstrated to be associated with cardiac sodium channel function. This report intends to add further evidence of case of CLASP2 gene has a potential candidate gene for syndromic intellectual disability associated with heart rhythm disorder.

Keywords: Neurodevelopmental disorders; Intellectual disability; Heart rhythm disorder; Cardiogenetics; Complete atrio-ventricular block; CLASP2 gene.

Abbreviations: NDDs: Neurodevelopmental disorders; NGS: Next-Generation Sequencing; CES: Clinical exome sequencing; ID: Intellectual disability.

Introduction

Neurodevelopmental disorders (NDDs) are a heterogeneous group with onset in the developmental period characterized by impaired brain development, affecting personal, social, academic, or occupational functioning [1]. Not only NDDs are clinically complex, they are also genetically heterogeneous. Increasing molecular diagnosis of NDDs are due to application of Next-Generation Sequencing (NGS) techniques, namely clinical exome sequencing (CES) with a diagnostic yield of 30-43%, combined with chromosomal microarray of 15-20%. However up to 50% of patients remain without a definitive molecular diagnosis [2,3]. Although a limited number of NDDs have a targeted treatment, molecular diagnosis of NDDs can potentially improve clinical management, establishing long-term prognosis as well as provide the appropriated genetic counselling for the patient

and family [4,5]. As part of NDDs, intellectual disability (ID), results of impaired intellectual and adaptive functioning, and a diagnosis is established when deficits in two or more adaptive behaviours in daily life are present [1]. Affects between 1-3% of population, and both genetic and environmental factors can add to ID [5,6]. More than 1500 genes have been identified to be responsible for NDD, and an estimated 1000 to be] potentially associated with NDD. Many of these genes are expressed in early stages of fetal development of cerebellum and the cortex, particularly genes involved in synapse, cell division and chromosome organization [7,8].

Case presentation

Here we report a 43-years-old male with symptomatic bradycardia and a complete atrio-ventricular block. From personal history it states out a learning difficulties, in the spectrum of ID. He is the second child of consanguineous couple - first degree cousins. His older sister was reported to have similar phenotype and was implanted with a cardiac pacemaker at 14-years-old.

Pregnancy and birth were uneventful. No medical concerns were raised in the first years of life. At 12 years-old strabismus was diagnosed and he needed conservative treatment with glasses until 20 years-old. Learning difficulties with cognitive impairment was noted in the first years of schooling. He did not finish regular school, instead completed a professional program. No formal ID evaluation was performed, but he is fairly independent and maintain an working occupation as a farmer.

Symptomatic bradycardia was present in childhood, but unfortunately only at the age of 42 years-old after further investigation a complete atrio-ventricular block with an escape rhythm was identified. An echocardiographic showed left atrial dilatation (volume index of 54 mL/m^2) and mild left ventricular dilatation (volume index of 84 mL/m^2), with a normal left ventricular ejection fraction of 64% (biplane method). Due to the severe and symptomatic heart conduction disturbance, a dual chamber pacemaker was implanted without any complications.

At clinic evaluation, besides a rather long face not other specific facial dysmorphism were noted. A CES was requested which identified an homozygous variant in CLASP2 gene [NM_001207044.3]: c.1711+1G>A (r.(spl)). This variant is absent of populational databases and in silico prediction analyses suggest it can disrupt splice donor site. CES was performed through Twist Human Core Exome, Human RefSeq Panel and Twist Mitochondrial Panel were used as enrichment kits sequenced by massive sequencing (NGS) in a NovaSeq 6000 (Illumina).

Discussion

Although CLASP2 gene has been associated with ID and autism spectrum disorder, there yet is no definite correlation. CLASPs (cytoplasmic linker associated proteins) are an ubiquitous heterogeneous family of tracking proteins that stabilized microtubule dynamics, supressing microtubule catastrophes and localizing kinetochores during mitosis. Therefore, during mitosis they are responsible for ensuring chromosome segregation. So far, the underlying mechanisms remains poorly known [9-11].

Neurogenesis, neuron migration, and differentiation are fundamental processes for brain development. The Reelin signalling pathway regulates neocortical development, by controlling cytoskeleton during neuronal migration. It has been proposed that clasp2 is a key cytoskeletal effector in the Reelin signalling pathway. Consequently, regulating neuron production and controlling neuron migration, polarity, and morphogenesis. Downregulation of clasp2 affects neurons migration, mislocalized cells in deeper cortical layers, abnormal positioning of the centrosome-Golgi complex, and aberrant length/orientation during neurite/axon outgrowth [12,13].

Given the importance the impairment of neuronal migration as an underlying mechanism in NDDs [14], CLASP2 gene it is considerate as a strong candidate gene to NDDs/ID. A case report from 2014, identified a deletion encompassing CLASP2 gene segregating in a family with syndromic ID, and propose a potential pathogenic association of this gene with ID [15].

Clasp2 also modulates microtubule polymerization and stabilization, interacting with other end tracking proteins such as eb1 (end-binding protein 1) in axons, as well as in cardiomyocytes. Both proteins are enriched at the intercalated disc of cardiomyocytes, thus contributing to regulate cardiac sodium channel Na_v 1.5 trafficking. Loss-of-function eb1-clasp2 complex leads to reduced sodium current, conduction slowing, arrhythmias, and sudden cardiac death [16].

In summary, previous published literature demonstrated that CLASP2 gene controls microtubule network organization in other cellular contexts suggesting a potential role in syndromic NDDs. CLASP2 gene is an important regulator of axon and dendrite outgrowth, influencing synaptic activity and formation and it was also demonstrated to be associated with cardiac sodium channel function and leading heart rhythm disorder. This case report add further evidence of the role of CLASP2 gene as a likely candidate to syndromic ID associated with heart rhythm disorder. Future studies are needed to deepen our understanding of pathogenic role of CLASP2 disruption.

References

1. Association AP. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: The American Psychiatric Association. 2013.
2. Srivastava S, Love-Nichols JA, Dies KA, et al. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders [published correction appears in Genet Med. 2020; 22(10): 1731-1732]. Genet Med. 2019; 21(11): 2413-2421.
3. Bruno LP, Doddato G, Valentino F, et al. New Candidates for Autism/Intellectual Disability Identified by Whole-Exome Sequencing. Int J Mol Sci. 2021; 22(24): 13439.
4. Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021; 23(11): 2029-2037.
5. Maia N, Nabais Sá MJ, Melo-Pires M, de Brouwer APM, Jorge P. Intellectual disability genomics: current state, pitfalls and future challenges. BMC Genomics. 2021; 22(1): 909.
6. Maulik PK, Mascarenhas MN, Mathers CD, Dua T, Saxena S. Prevalence of intellectual disability: a meta-analysis of population-based studies [published correction appears in Res Dev Disabil. 2013; 34(2): 729]. Res Dev Disabil. 2011; 32(2): 419-436.
7. Leblond CS, Le TL, Malesys S, et al. Operative list of genes associated with autism and neurodevelopmental disorders based on database review. Mol Cell Neurosci. 2021; 113: 103623.

8. Kaplanis J, Samocha KE, Wiel L, et al. Evidence for 28 genetic disorders discovered by combining healthcare and research data. Nature. 2020; 586(7831): 757-762.

9. CLASP2 binding to curved microtubule tips promotes flux and stabilizes kinetochore attachments

10. Girão H, Okada N, Rodrigues TA, et al. CLASP2 binding to curved microtubule tips promotes flux and stabilizes kinetochore attachments. J Cell Biol. 2020; 219(2): e201905080.

11. Luo W, Demidov V, Shen Q, et al. CLASP2 recognizes tubulins exposed at the microtubule plus-end in a nucleotide state-sensitive manner. Sci Adv. 2023; 9(1): eabq5404.

12. Dillon GM, Tyler WA, Omuro KC, et al. CLASP2 Links Reelin to the Cytoskeleton during Neocortical Development. Neuron. 2017; 93(6): 1344-1358.e5.

13. Sayas CL, Basu S, van der Reijden M, et al. Distinct Functions for Mammalian CLASP1 and -2 During Neurite and Axon Elongation. Front Cell Neurosci. 2019; 13: 5.

14. Caracci MO, Fuentealba LM, Marzolo MP. Golgi Complex Dynamics and Its Implication in Prevalent Neurological Disorders. Front Cell Dev Biol. 2019; 7: 75.

15. Marangi G, Orteschi D, Milano V, Mancano G, Zollino M. Interstitial deletion of 3p22.3p22.2 encompassing ARPP21 and CLASP2 is a potential pathogenic factor for a syndromic form of intellectual disability: a co-morbidity model with additional copy number variations in a large family. Am J Med Genet A. 2013; 161(11): 2890-2893.

16. Marchal GA, Jouni M, Chiang DY, et al. Targeting the Microtubule EB1-CLASP2 Complex Modulates NaV1.5 at Intercalated Discs. Circ Res. 2021; 129(3): 349-365.