

CASE REPORTS

THE ROLE OF NACC1 C.892C>T (P.ARG298TRP) VARIANT IN A NEURODEVELOPMENTAL DISORDER: REPORT OF TWO NEW CASES

Carolina Folques^{1,2}, Liza Aguiar², Ana Luísa Carvalho^{3,4,5}, Catarina Paiva⁶, Patrícia Dias⁷, Mariana Soeiro Sá⁷, José Paulo Monteiro⁸, Filipe Palavra^{9,5,10}

¹Center for Child Development - Neuropediatrics Unit, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal,

²Department of Pediatrics, Centro Hospitalar de Leiria, Leiria, Portugal,

³Department of Medical Genetics, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal,

⁴University Clinic of Medical Genetics, Faculty of Medicine, University of Coimbra, Coimbra, Portugal,

⁵Clinical Academic Center of Coimbra, Coimbra, Portugal,

⁶Department of Ophthalmology, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal,

⁷Medical Genetics Unit, Department of Pediatrics, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte, Lisboa, Portugal,

⁸Center for Child Development Torrado da Silva, Hospital Garcia de Orta, Almada, Portugal,

⁹Center for Child Development – Neuropediatrics Unit, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal,

¹⁰Institute of Pharmacology and Experimental Therapeutics, Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal.

ABSTRACT

The NACC1 c.892C>T (p.Arg298Trp) gene variant is associated to a rare neurodevelopmental disorder characterized by epilepsy, cataracts, feeding difficulties and delayed brain myelination, with only eight cases published to date. We report two new cases and review the literature, summarizing the main clinical features, diagnostic and therapeutic interventions to perform.

Introduction

The NACC1 (nucleus accumbens associated 1) gene (19p13.13) encodes a protein that acts as a transcriptional repressor, playing a role in stem cell self-renewal and pluripotency maintenance. That protein also suppresses transcription of the tumor suppressor Gadd45GIP1, which makes it a potential player in the regulation of cancer progression.¹ A variant of this gene, c.892C>T (p.Arg298Trp), is associated with a neurodevelopmental disorder with epilepsy, cataracts, feeding difficulties and delayed brain myelination among the most paradigmatic manifestations (MIM #617393). There are eight cases of this NACC1 variant published to date, this being the first two case reports from Portugal.²

Advances in next generation sequencing such as whole-exome sequencing (WES) have increasingly enabled diagnostic rates for rare neurodevelopmental disorders, with new potentially pathogenic gene variants being identified. This report aims to expand the knowledge on phenotypic features affecting individuals who harbor the same missense variant in NACC1 (MIM *610672) gene.

Case Report

Case 1

A 5-month-old caucasian male was referred to Medical

Address for Correspondance: Carolina Folques, Department of Pediatrics, Leiria Hospital Centre, Rua das Olhalvas, Pousos, 2410-197 Leiria, Portugal.

Email: carolinafolques@gmail.com

©2025 Pediatric Oncall

ARTICLE HISTORY

Received 17 February 2023

Accepted 19 May 2023

KEYWORDS

NACC1, Neurodevelopmental disorder, Epilepsy, Congenital cataract.

Genetics and Pediatric Neurology consultations for bilateral congenital cataracts, global development delay, breath-holding spells and bilateral preauricular appendages. He was born at 40 weeks of gestation, through cesarean delivery with vacuum extraction, after an uneventful pregnancy to a 37-year-old G2P1 mother and a 40-year-old father, non-consanguineous. The newborn made a successful transition to extrauterine life, receiving an Apgar score of 9/10/10. At birth, he weighed 3360 g (33rd percentile), with a birth length of 50 cm (30th percentile) and an occipitofrontal circumference (OFC) of 34.5 cm (35th percentile), according to the Fenton 2013 growth charts. On clinical observation, bilateral preauricular appendages were identified. The neonatal course was complicated by hyperbilirubinemia treated with phototherapy, with good recovery. He failed the first universal newborn hearing screening (using otoacoustic emissions) but passed in the second evaluation.

He attended routine follow-up at primary care and some additional dysmorphic features were noted, such as broad nasal tip and overlapping fifth feet fingers. Growth assessment using the World Health Organization (WHO) Growth Charts showed weight, length and OFC following under the 3rd percentile. Complementary feeding was started at 5 months of age, with good acceptance and tolerance (no history of feeding difficulties).

Developmental concerns started at 4 months of age, with hypertonia and global developmental delay. When placed on abdomen, he did not lift his head, neither used forearms for support nor roll over. When lying

on back, he kept both arms flexed and hands closed, legs extended. Limb movements were symmetrical but restricted and stiff. At 6 months of age, he started bringing hands into midline and reaching the mouth, but did not try to grasp objects. He was described as a very silent baby, with few vocalizations. He presented poor eye tracking since the first months of age, being diagnosed with bilateral congenital cataracts at 5 months and undergoing surgical removal one month after.

He had a history of frequent breath-holding spells and the mother described paroxysmal events very suggestive of tonic seizures occurring during sleep, with symmetrical abduction of the upper limbs.

At 15 months, he started having periods of irritability, with bouts of inconsolability and screaming for days, occurring with regular periodicity of 2 weeks. In the first episode he was admitted to the hospital, but the clinical and analytical investigation ruled out infectious or other systemic causes. In between these episodes, he attended daycare, with no complaints regarding behavior and no sleep or feeding disturbances.

Regarding family history, he had a 7-year-old female sibling with PFAPA syndrome (Periodic Fever, Aphthous stomatitis, Pharyngitis, Adenitis) and no other relevant medical history. Both parents have myopia and astigmatism; a maternal great-aunt had severe intellectual disability, as well as a second-degree cousin of the father, in both cases of unknown etiology. The remaining family history was noncontributory.

An electroencephalogram (EEG) was obtained at 6 months of age, showing focal paroxysmal activity in left temporo-parietal area, increased during sleep. Brain Magnetic Resonance Imaging (MRI) at the same age showed cerebral atrophy, including atrophic corpus callosum, frontal polymicrogyria, hippocampal asymmetry and mega cisterna magna. A metabolic screening (serum aminoacids, acylcarnitine profile, ammonia, lactate/pyruvate, carbohydrate deficient transferrin, arylsulfatase) and Array-CGH were also performed, with no relevant findings. WES finally identified the NACC1 c.892C>T (p.Arg298Trp) variant, de novo, in heterozygosity.

Regarding medical therapeutics, topiramate was initiated at 6 months of age, but later switched to sodium valproate, at 10 months. In context of irritability, risperidone was initiated at a low-dose, but discontinued after a paradoxical adverse effect. These symptoms are being managed with clobazam and diazepam.

After a thorough evaluation, rehabilitation measures including physiotherapy, occupational therapy and hydrotherapy were developed by a multidisciplinary team, with mild benefit in gross motor skills and movement patterns.

On follow-up, at 17 months, neurological exam showed no visual tracking, inconsistent reaction to sudden loud sounds, stereotyped tongue protrusion movements, axial and appendicular hypertonia, poor spontaneous movements (essentially limb extension) but no identifiable asymmetries. Myotatic reflexes were present and symmetrical.

Case 2

A 4-month-old caucasian male with microcephaly and global psychomotor developmental delay was referred to Pediatrics and Developmental Medicine. He later associated multidisciplinary follow-up in Pediatric Neurology, Gastroenterology, Metabolic Medicine and

Pneumology for epilepsy, cyclic vomiting and sleep disturbance.

He was born via spontaneous vaginal delivery at 40 weeks to a 38-year-old G1P0 mother and a 32-year-old father, non-consanguineous, with a birthweight of 3200 g (21st percentile), length of 46,5 cm (2nd percentile) and OFC of 34,2 cm (28th percentile), according to the Fenton 2013 growth charts. The pregnancy was complicated by placental abruption in the first trimester, gestational diabetes diagnosed at 26 weeks of gestational age (diet-controlled) and increased nuchal translucency (NT) >P99 (7.6 mm). Biochemical screening for chromosomal abnormalities showed low risk and invasive prenatal diagnosis (amniocentesis) demonstrated normal fetal karyotype (46, XY). Fetal echocardiogram was performed, with no relevant findings. The routine newborn assessment was normal and the neonatal course was uncomplicated, except for bilateral congenital cataracts, which were surgically removed. Follow-up was sustained in Ophthalmology for intermittent convergent strabismus (alternating) and nystagmus.

Routine follow-up using the WHO Growth Charts identified impaired growth with postnatal microcephaly (weight and OFC following under the 3rd percentile, length on the 5th percentile). There was evidence of delayed psychomotor development within the first 4 months of life, with poor head and neck control and marked global hypotonia. At 12 months old, he was not able to roll over, sit unassisted, reach toys, crawl or interact socially. At 24 months, language and ambulation were absent. He manifested feeding difficulties (inability to swallow solid food), cyclical vomiting and gastro-oesophageal reflux associated to hiatal hernia. In addition, he had severe constipation with recurrent intestinal sub-occlusion. Epilepsy had onset in the first year of life. An EEG disclosed mild to moderate paroxysmal activity of spikes and spike-wave complexes projecting into centroparietal areas of the left hemisphere. He started treatment with levetiracetam and clonazepam, with good seizure control. Furthermore, he developed a sleep disorder characterized by insomnia with short sleeping periods (4 hours) resistant to several therapeutic attitudes.

Rehabilitation comprising occupational, physical and speech therapy was established, with mild improvement in visual-motor integration and oral-motor coordination and strength.

Brain MRI at 2 years of age presented accentuation of cortical sulci, decrease in the thickness of the corpus callosum and a decrease in thickness of the white matter of the cerebral hemispheres. Metabolic screening, Array-CGH and mitochondrial DNA sequencing showed no relevant findings. Echocardiogram was normal. Family history was noncontributory. Additional etiological investigation was performed at the age of 9 years by a trio exome sequencing (using peripheral blood samples from the child and his parents) and the pathogenic de novo variant c.892C>T, p.(Arg298Trp) was identified in heterozygosity in the NACC1 gene.

Discussion

The nucleus accumbens associated 1 (NACC1) gene codifies a transcription factor, member of the BTB/POZ family. A de novo heterozygous c.892C>T (p.Arg298Trp) variant may define a rare neurodevelopmental disorder characterized by microcephaly, profound developmental delay and/or intellectual disability, congenital cataracts, severe epilepsy including infantile spasms, stereotypic hand movements, irritability and feeding difficulties. Many

Table 1. Summary of phenotypic features of NACC1 c.892C>T (p.Arg298Trp) variant cases in this report and previously published.

	Case 1	Case 2	Schoch K's and Lyu B's (eight cases)
Sex	Male	Male	Five male; three female
Age	2 years	13 years	13 months - 18 years
Development delay/ intellectual disability	Yes	Yes	Yes
Postnatal microcephaly	Yes	Yes	Five yes; three no
Hypotonia	Yes	Yes	Six yes; one no
Infantile epilepsy	Yes	Yes	Yes
Congenital cataract	Bilateral	Bilateral	Five bilateral; one unilateral; two no
Feeding difficulties/ intolerance	No	Yes	Yes
Irritability	Yes	No	Yes
Stereotypic movements	Yes (tongue protrusion)	No	Seven yes; one no.
Brain MRI findings	Decreased brain volume; Atrophic corpus callosum; Frontal polymicrogyria; Hippocampal asymmetry and megacisterna magna	Atrophic corpus callosum; Accentuation of cortical sulci; Decrease in thickness of the white matter	Six decreased brain volume; four delayed myelination; one focal cortical dysplasia
Features not previously described	Absent feeding difficulties; Neuroimaging findings	Absent irritability; Neuroimaging findings	
Reference	This report	This report	[1,2]

studies have found that NACC1 is highly expressed in a variety of tumors, such as ovarian, cervical, endometrial, breast, renal and pancreatic cancer. However, it is unknown whether individuals with the p.Arg298Trp variant are at risk for cancer.^{2,3}

We conducted a literature review using "NACC1" and "intellectual disability" as keywords in PubMed database, searching for papers published up to October 19, 2022. A total of four articles were screened, two were excluded because they were not related to any neurodevelopmental disorder.^{4,5}

There are eight cases with the NACC1: c.892C>T (p.Arg298Trp) variant described to date.^{2,3,3} Postnatal microcephaly was noted in seven out of ten individuals. Hypotonia was absent in only one case. Infantile epilepsy was noted in all ten individuals, with variable overall seizure control but generally requiring multiple anti-epileptic drugs. Feeding difficulties or intolerance and irritability are transversal aspects in all previously published cases, but absent in case 1 and case 2, respectively. Sleep-disorders, breath-holding spells, repetitive or choreiform movements, hand-flapping or Rett-like hand automatisms were described in the majority of individuals. Brain MRI findings have shown decreased brain volume in seven cases (including case 1) and delayed myelination in four cases. Our two reported cases presented atrophic corpus callosum, not previously described in literature.^{2,3}

More cases will be needed to improve the phenotypic characterization associated with this rare variant in the NACC1 gene. Moreover, summarizing the main clinical features, different treatments and follow-up evaluations

may contribute to obtain a comprehensive timeline of the syndrome, stimulate new approaches to diagnosis and improve management strategies. Future research, including transcriptional studies, may further clarify the role of p.Arg298Trp variant and its negative impact on transcriptional regulation, hopefully leading to targeted therapies.

Compliance with Ethical Standards

Funding: None

Conflict of Interest: None

References:

1. Weizmann Institute of Science. GeneCards - The Human Gene Database. Available at: <https://www.genecards.org/cgi-bin/carddisp.pl?gene=NACC1>. Accessed at 15th January 2023.
2. Lyu B, Dong Y, Kang J. A New Case of de novo Variant c.892C>T (p.Arg298Trp) in NACC1: A First Case Report From China. *Front Pediatr.* 2021;9.
3. Schoch K, Meng L, Szeling S, Bearden D, Stray-Pedersen A, Busk O et al. A Recurrent De Novo Variant in NACC1 Causes a Syndrome Characterized by Infantile Epilepsy, Cataracts and Profound Developmental Delay. *Am. J. Hum. Genet.* 2017;100(2):343-351.
4. Pavinato L, Villamor-Payà M, Sanchiz-Calvo M, Andreoli C, Gay M, Vilaseca M et al. Functional analysis of TLK2 variants and their proximal interactomes implicates impaired kinase activity and chromatin maintenance defects in their pathogenesis. *J. Med. Genet.* 2020;59(2):170-179.
5. Bellucco F, Mello C, Meloni V, Melaragno M. Malan syndrome in a patient with 19p13.2p13.12 deletion encompassing NF1X and CACNA1A genes: Case report and review of the literature. *Mol Genet Genomic Med.* 2019;7(12).