Genotype-phenotype correlations of Nance-Horan syndrome in male and female carriers of a novel variant

OLIVIA A. ZIN(1,2), LUIZA M. NEVES(3,4), FABIANA L. MOTTA(5), DALTRO C. JUNIOR(3), DANIELA P. CUNHA(3), BRUNA N. AGONIGI(3), JOCIELI MALACARNE(3), ANA S. RODRIGUES(1), GABRIELA D. RODRIGUES(1), MARIA C. TINOCO(1), DAFNE D. HOROVITZ(3), ADRIANA B. CARVALHO(6), ANDREA A. ZIN(2,3,7), ZILTON F. VASCONCELOS(3), JULIANA M. SALLUM(1,5). 1 Ophthalmology Department, Federal University of São Paulo, SP. 2 Instituto Brasileiro de Oftalmologia, RJ. 3 Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira, RJ. 4 Ophthalmology Department,, Universidade do Estado do Rio de Janeiro, RJ. 5 Instituto de Genética Ocular, SP. 6 Instituto Nacional de Cardiologia, RJ. 7 Instituto Catarata Infantil, RJ.

Introduction

Nance–Horan syndrome (NHS) (OMIM: 302350) is a rare X-linked disease characterized by ocular features, dental anomalies, and facial dysmorphisms. Its diagnosis can present a challenge since cataracts, the earliest finding, have many causes in infants. NHS is rare, and the only other South American patients reported are of Mexican ancestry. The purpose of this report is to describe a novel nonsense frameshift variant causing NHS in a Brazilian family, examining genotype–phenotype correlations in males and females.

Case Report

Proband was 15 years old and had congenital cataracts with no corneal abnormalities. (Figure 1). His 18-year-old brother also had congenital cataracts. He had a clear right cornea with a punctiform pupil, while the left cornea was opaque, with calcium deposits, making the anterior chamber unidentifiable. Mother, aged 45 years, had congenital cataracts with opaque corneas and an unidentifiable anterior chamber. (Figure 2). There is limited information regarding the phenotypes of cataracts in these individuals, as they had already undergone surgery and previous medical records were unavailable. Father and daughter showed no ophthalmic abnormalities. All five evaluated family members denied systemic conditions.

Next generation sequencing (NGS) revealed in all five examined members, except in the unaffected father, the novel likely pathogenic variant c.3333del (p.Phe1111Leufs*9). Following this result, clinical review revealed typical dental features, as well as evidence of mild intellectual disability in the affected children.

Figure 1. Proband, examined at age of 15 years, diagnosis of congenital cataracts was made at 2 months, and facectomy was performed at age 1. He has strabismus and Slit-lamp biomicroscopy revealed clear corneas bilaterally, normal intraocular pressure (IOP) and fundoscopy showed no abnormalities. Also, his teeth showed screw-driver shaped incisors and diastema.

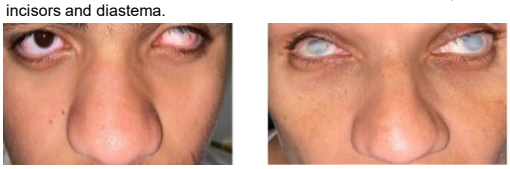

Figure 2. Bulbous nose, bilateral microcornea with clear right cornea and right opacity in male (left) Bulbous nose, bilateral microcornea with opaque corneas (right).

Discussion

The *NHS* gene is expressed in a variety of tissues, including lens and dental primordia. NHS protein acts as an actin regulatory protein, overseeing the activity of actin proteins to build cytoskeletal structures and facilitate cell adhesive interactions that are crucial for lens fiber elongation and differentiation. Disruption in these mechanisms can result in loss of lens transparency and the development of cataracts. The novel variant is in a region where most pathogenic mutations are found. It is classified as likely pathogenic because it is a null variant in a gene where the loss of function is a recognized mechanism for disease and is absent from population databases.

X-linked inheritance often results in more pronounced clinical manifestations in hemizygous males compared to heterozygous females. In women, traditional NHS phenotypes typically include posterior Y sutural cataracts. Symptom variability between our severely affected mother and her asymptomatic daughter could be due to skewed X inactivation.

Conclusion

Patients were initially diagnosed with isolated hereditary cataracts, underscoring the importance of genetic testing in familial pediatric cataract cases. They were investigated for congenital syphilis for their teeth appearance, the main dental differential diagnosis, whose true etiology was clarified by genetic testing.

Genetic testing not only identified extraocular features but also enabled accurate family genetic counseling, which can be particularly challenging in diseases with X-linked inheritance.

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