Progress in Retinal and Eye Research 45 (2015) 58–110

Contents lists available at ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

Congenital stationary night blindness: An analysis and update of genotype–phenotype correlations and pathogenic mechanisms

Christina Zeitz [a, b, c, *, 1], Anthony G. Robson [d, e, 1], Isabelle Audo [a, b, c, e, f, 1]

[a] INSERM, US968, Paris, F-75012, France
[b] CNRS, UMR_7210, Paris, F-75012, France
[c] Sorbonne Universités, UPMC Univ Paris 06, UMR_S 968, Institut de la Vision, Paris, F-75012, France
[d] Moorfields Eye Hospital, 162 City Road, London, EC1V 2PD, UK
[e] Institute of Ophthalmology, University College London, London, EC1V 9EL, UK
[f] Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts, DHU ViewMaintain, INSERM-DHOS CIC 1423, Paris, F-75012, France

ARTICLE INFO

Article history:
Received 3 July 2014
Received in revised form
25 September 2014
Accepted 30 September 2014
Available online 13 October 2014

Keywords:
Congenital stationary night blindness (CSNB)
Schubert-Bornschein
Fundus albipunctatus
Oguchi disease
Molecular genetics
Prevalence
Diagnostics
Protein function
Pathophysiology
Animal models

ABSTRACT

Congenital stationary night blindness (CSNB) refers to a group of genetically and clinically heterogeneous retinal disorders. Seventeen different genes with more than 360 different mutations and more than 670 affected alleles have been associated with CSNB, including genes coding for proteins of the phototransduction cascade, those important for signal transmission from the photoreceptors to the bipolar cells or genes involved in retinoid recycling in the retinal pigment epithelium. This article describes the phenotypic characteristics of different forms of CSNB that are necessary for accurate diagnosis and to direct and improve genetic testing. An overview of classical and recent methods used to identify specific CSNB genotypes is provided and a meta-analysis of all previously published and novel data is performed to determine the prevalence of disease-causing mutations. Studies of the underlying molecular pathogenic mechanisms based on cell culture techniques and animal studies are outlined. The article highlights how the study of CSNB has increased understanding of the mechanisms of visual signalling in the retina, likely to prove important in developing future treatments for CSNB and other retinal disorders.

Contents

* Corresponding author. Institut de la Vision Department of Genetics, 17, Rue Moreau, 75012 Paris, France. Tel.: +33 1 53 46 25 40; fax: +33 1 53 46 26 02.
E-mail address: christina.zeitz@inserm.fr (C. Zeitz).
[1] Percentage of work contributed by each author in the production of the manuscript is as follows: Christina Zeitz: 70%; Anthony G. Robson: 10%; Isabelle Audo: 20%.

http://dx.doi.org/10.1016/j.preteyeres.2014.09.001
1350-9462/

1. Introduction

Congenital stationary night blindness (CSNB) refers to a genetically determined largely non-progressive group of retinal disorders that predominantly affect signal processing within photoreceptors, retinoid recycling in the retinal pigment epithelium (RPE) or signal transmission via retinal bipolar cells (Zeitz, 2007). CSNB is clinically and genetically heterogeneous. Patients often complain of night or dim light vision disturbance or delayed dark adaptation, but photophobia is also reported in a subgroup of patients. Some forms may be associated with other ocular signs such as poor visual acuity, myopia, nystagmus, strabismus and fundus abnormalities (Zeitz, 2007). The night vision disturbance may be overlooked since it is highly subjective especially for individuals living in an urban or well-lit environment. Vision problems may also be denied (Dryja, 2000). Scotopic vision is rarely tested routinely and CSNB is likely under-diagnosed by clinicians, confounding estimates of prevalence.

To our knowledge, the first individuals diagnosed with CSNB were the descendants of Jean Nougaret, who was born 1637 in southern France. Since then many clinicians and researchers have contributed to the understanding of different CSNB phenotypes, genetic causes and pathogenic mechanisms. The purpose of this article is to summarise these findings and to extend current knowledge by inclusion of novel data and interpretation.

2. Phenotypic characteristics of CSNB

2.1. Clinical classification

CSNB can be subdivided according to the pattern of inheritance which may be X-linked, autosomal recessive or autosomal dominant (see also: 3. CSNB genes and mutations). Fundus appearance may be normal or abnormal but in all cases the full field electroretinogram (FF-ERG) is critical for functional phenotyping and precise diagnosis.

2.1.1. Electroretinography

FF-ERG is a non-invasive technique which detects, using corneal electrodes, the electrical responses generated within the retina upon flash stimulation. It allows the distinction between generalised rod and cone system activity and between photoreceptor and inner retinal function. Standard recording procedures and recommendations are regularly updated by the International Society for Clinical Electrophysiology of Vision (ISCEV, http://www.iscev.org/, (Marmor et al., 2009)). Current recommendations include a minimum recording of five basic responses to flashes of light delivered by a Ganzfeld stimulator, required to evenly illuminate the maximal area of retina after mydriasis. Three basic responses are recorded after a minimum of 20 min of dark adaptation (DA; scotopic conditions) and two are recorded after at least 10 min of light adaptation (LA; photopic conditions) to a background luminance of 30 cd.m^{-2}. The dark-adapted dim flash ERG is recorded to a flash strength of 0.01 cd.s.m^{-2} which is below cone system threshold (named the DA 0.01 ERG). This ERG is dominated by a positive polarity b-wave generated mainly at the level of rod depolarizing bipolar cells (DBCs or rod ON-bipolar cells) (Hood and Birch, 1996; Robson and Frishman, 1995; Shiells and Falk, 1999). A brighter flash (3 cd.s.m^{-2}) is used to elicit the standard ERG (formerly called the combined or mixed rod-cone response; now named DA 3.0 ERG). The DA 3.0 ERG shows a negative a-wave, some of which is generated in the photoreceptors, followed by a larger positive b-wave, originating in the inner nuclear layer. There is a contribution from the dark-adapted cone system to the scotopic ERG a- and b-waves, which is proportionately reduced to brighter flashes. An additional dark-adapted ERG is therefore recommended by ISCEV in response to a 10 or 30 cd.s.m^{-2} flash (DA10.0 ERG or DA30.0 ERG respectively) to better demonstrate the a-wave and to give a better measure of generalised rod photoreceptor function (see for review