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# Ophthalmological phenotype associated with homozygous null mutation in the NEUROD1 gene

**Orsolya Orosz,[1] Miklós Czeglédi,[2] Irén Kántor,[3] István Balogh,[4] Attila Vajas,[1] Lili Takács,[1] András Berta,[1] Gergely Losonczy[1]**

*[1]Department of Ophthalmology, University of Debrecen, Clinical Center, Debrecen, Hungary; [2]Department of Ophthalmology, Jósa András Hospital, Nyíregyháza, Hungary; [3]Department of Pediatrics, Jósa András Hospital, Nyíregyháza, Hungary; [4]Division of Clinical Genetics, Department of Laboratory Medicine, University of Debrecen, Clinical Center, Debrecen, Hungary*

**Purpose:** NEUROD1 is a tissue-specific basic helix loop helix (bHLH) protein involved in the development and maintenance of the endocrine pancreas and neuronal elements. Loss of NEUROD1 causes ataxia, cerebellar hypoplasia, sensorineural deafness, and severe retinal dystrophy in mice. Heterozygous loss-of-function mutations in NEUROD1 have previously been described as a cause of maturity-onset diabetes of the young (MODY) and late-onset diabetes. To date, homozygous loss-of-function NEUROD1 mutations have only been detected in two patients. Both mutations caused permanent neonatal diabetes and severe neurologic defects, including visual impairment. However, a detailed ophthalmological phenotype of this novel syndrome has not yet been reported. Our aim was to characterize the ophthalmological phenotype associated with the previously reported homozygous c.427_428CT mutation in the NEUROD1 gene.
**Methods:** The female patient was investigated on multiple occasions between 2009 (age 14) and 2014 (age 19), including visual acuity testing, automated perimetry, funduscopy, anterior-segment imaging, optical coherence tomography of the posterior pole, standard full-field electroretinography, and fundus-autofluorescence imaging.
**Results:** The patient had nyctalopia, blurry vision, and visual field constriction from early childhood. Her best corrected visual acuity ranged between 20/25 and 15/25 during the investigation period. Perimetry showed concentric constriction of the visual field, sparing only the central 30 degrees in both eyes. The anterior segment did not show any morphological changes. Optical coherence tomography revealed total absence of the photoreceptor layer of the retina outside the fovea, where a discoid remnant of cone photoreceptors could be detected. Neither setting of the standard full-field electroretinography could detect any electrical response from the retina. Color fundus photos presented peripheral chorioretinal atrophy and central RPE mottling. A hyperreflective parafoveal ring was detected on fundus autofluorescent photos, a characteristic sign of hereditary retinal dystrophies.
**Conclusions:** To the best of our knowledge, this is the first report on the ophthalmological phenotype associating with a homozygous NEUROD1 null mutation in humans. Our results indicate that the loss of NEUROD1 has similar functional and anatomic consequences in the human retina as those described in mice. The present description can help the diagnosis of future cases and provide clues on the rate of disease progression.

NEUROD1 is a tissue-specific basic helix loop helix (bHLH) transcription factor that plays an important role in the development and maintenance of neuronal elements [1] and the endocrine pancreas [2, 3]. It also plays a key role in maintaining normal glucose homeostasis [2, 3].

Most of our knowledge on the function of NEUROD1 comes from animal experiments. NEUROD1 is expressed in differentiated neurons of frogs and mice [4]. It has been shown that NEUROD1 can transform ectodermal cells into differentiated neurons in *Xenopus* [4]. In addition, NEUROD1 is expressed in the fully differentiated neurons of the adult *Xenopus* brain structures, including the hippocampus, cerebellum, and olfactory bulbs [4]. NEUROD1 null mutant mice kept alive by either a transgene encoding the mouse NEUROD1 gene under the insulin promoter [5] or by crossing the null mutation into a different genetic background [6] showed concordant neuronal phenotypes, including ataxic gate, impaired balance, circling, impaired cerebellar function [5-7], and epilepsy [6]. Abnormal hearing and vision are caused by sensory defects of the inner ear and neural retina [7-9].

Morrow et al. [9] investigated the expression of NEUROD1 in rat and mouse retinas. Despite the two different methods, NEUROD1 was found to be expressed mainly in undifferentiated retinal cells, developing amacrine interneurons, and photoreceptors. Moreover, its expression could be observed in terminally differentiated photoreceptors in the mature retina. The suppression of NEUROD1 gene expression leads to severe impairment of photoreceptor development

Correspondence to: Gergely Losonczy, Department of Ophthalmology, University of Debrecen, Clinical Center, Debrecen, Hungary; Phone: +3652255456; FAX: +3652255456; email: losigeri@gmail.com

in chick retinas, indicating its importance in the formation of photoreceptors [10].

To define the role of NEUROD1 in the retina, Ochocinska et al. [11] used NEUROD1 conditional knockout mice (cKO). They observed that two-month-old NEUROD1 cKO retinas underwent dramatic changes, including reductions in rod- and cone-driven electroretinograms and disorganized outer segments. Furthermore, photoreceptors totally disappeared in later ages. Microarray analysis identified two downregulated genes: Aipl1, which is necessary to prevent retinal degeneration, and Ankrd33, which is expressed in the outer segment of the retina. It is suggested that NEUROD1 is involved in receptor homeostasis through these genes [11]. Although NEUROD1 is expressed in all three layers of the mouse retina, degeneration only affects the photoreceptors [12]. In contrast, Acharya et al. [13] demonstrated that NEUROD1 transcripts and NEUROD1 immunoreactivity are predominantly localized to the outer nuclear layer in the adult human retina.

Heterozygous loss-of-function mutations in the NEUROD1 gene have been described in the background of maturity-onset diabetes of the young (MODY) and late-onset diabetes [14-17]. There are only two unrelated patients with two different homozygous loss-of-function NEUROD1 mutations described so far. Both single base pair duplication (c.364dupG) and two base pair CT deletion (c.427_428del) result in a frameshift and a premature truncation of the C-terminus of the expressed protein (p.Asp122Glyfs*12 and p.Leu143Alafs*55, respectively), leading to mutated proteins completely lacking the transactivation domain [18]. These two probands were diagnosed with permanent neonatal diabetes (PNDM) and had similar neurologic abnormalities, including cerebellar hypoplasia, developmental delay, and visual and hearing impairment [18]. Interestingly, the rescued NEUROD1-null mice [5-9] and the two NEUROD1-deficient patients showed similar disease manifestations except epilepsy, which was only seen in the mice [6]. However, no further information on the ophthalmic phenotype and its functional consequences was provided in that article.

In the present study, we provide detailed ophthalmological characterization of the patient with homozygous c.427_428delCT NEUROD1 mutation. To the best of our knowledge, this is the first description of the ophthalmological phenotype caused by a homozygous NEUROD1 null mutation.

## METHODS

Color fundus photographs were taken with a Zeiss FF450+IR fundus camera (Carl Zeiss AG, Jena, Germany) mounted with a ZK-5 color sensor (Allied Vision Technologies GmbH, Stadtroda, Germany) and operated with Zeiss Visupack 4.4 software. Optical coherence tomography and confocal-scanning laser fundus autofluorescence imaging were performed with SpectralisOCT (Heidelberg Engineering, Heidelberg, Germany). Electroretinography was executed with Ganzfeld Q400 equipment (Roland Consult GmbH, Brandenburg, Germany) using standard ISCEV parameters [19]. The visual field was investigated with an Octopus 900 automated static perimeter, using its standard white/white full-size visual field program (Haag Streit AG, Koenitz, Switzerland). All of the procedures applied in this study strictly adhered to the tenets of the Declaration of Helsinki.

## RESULTS

We annually examined a female patient having neonatal diabetes caused by a homozygous loss-of-function mutation in the NEUROD1 gene between 2009 (age 14) and 2014 (age 19). The patient had normal blood glucose control using insulin supplementation. The patient complained about slowly progressive blurry vision, constriction of the visual field, and difficulties seeing at night or in dim light, beginning in early childhood. Her best corrected visual acuity showed a slow decrease during the exam period, ranging from 20/25 to 15/25. Refractive error did not show any changes between the examinations: -7.5D spherical with +3.0D cylindrical correction in both eyes. Automated full-size visual field perimetry showed concentric constriction of the visual field, sparing the central 30 degrees in both eyes, in 2013. The patient showed normal color recognition on pseudoisochromatic charts.

Scheimpflug imaging of the anterior segment showed regular oblique corneal astigmatism. Corneal thickness was near normal, with a central corneal thickness of 600 µm. No signs of Keratoconus could be detected with Scheimpflug imaging using the Belin-Ambrosio analysis. Anterior chamber depth and anterior chamber angle were within the normal range. Dilated funduscopy revealed optically clear media throughout the cornea, lens, and vitreous. The retinal pigmented epithelial layer showed mottling at the posterior pole and diffuse atrophy in the periphery (Figure 1). However, neither bone spicule formation nor pigment clumping could be observed. Unlike the pale and waxy optic disc associated with retinitis pigmentosa (RP), the optic disc in her case was slightly pale but had a near normal appearance. The diameter of retinal vessels was apparently normal, and vascular attenuation could not be observed. The central foveal spot was

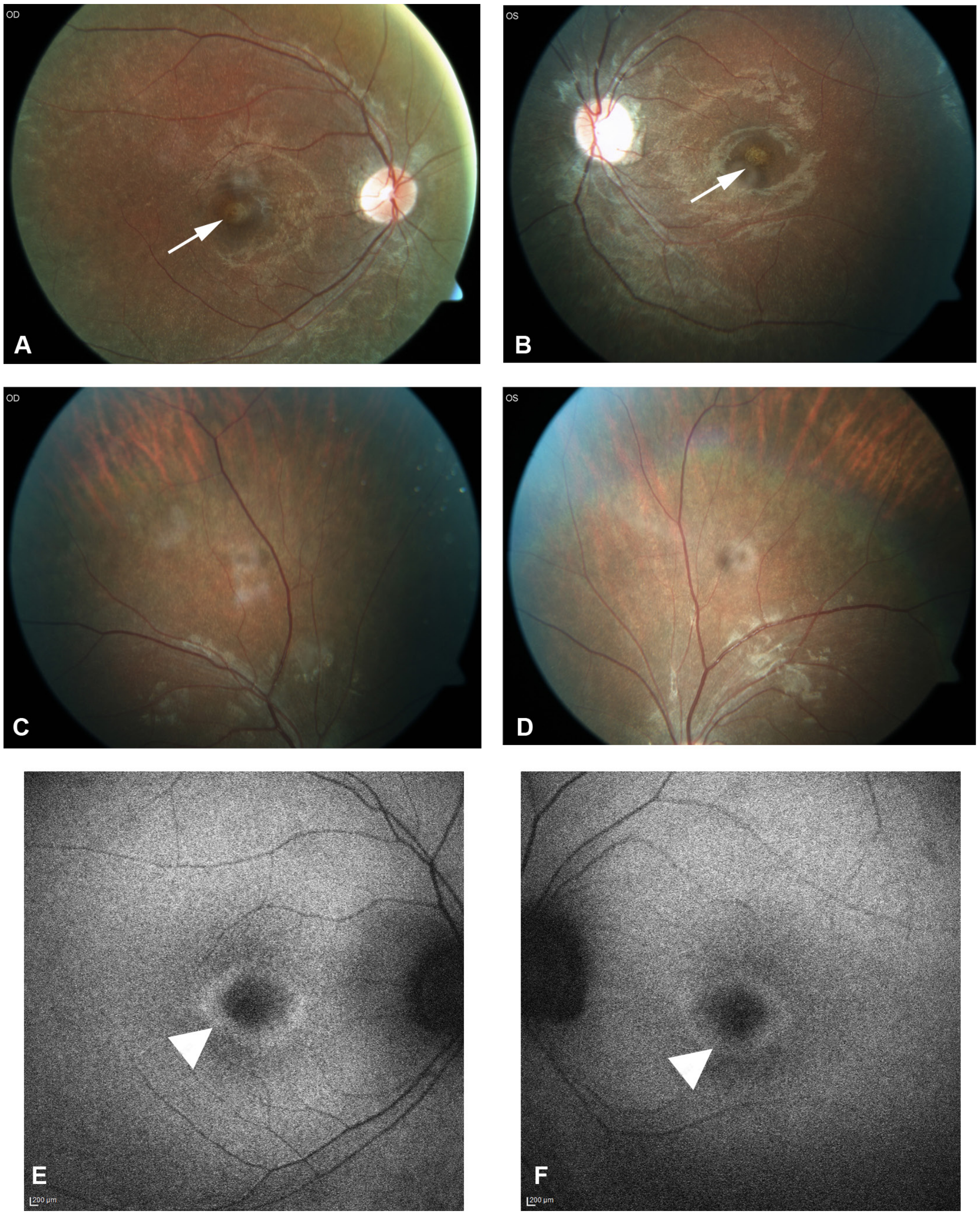


Figure 1. Fundus photography. Color fundus photos of the posterior pole (right eye: **A**; left eye: **B**) and periphery (right eye: **C**; left eye: **D**). Pictures represent fine mottling of the RPE in the macular area and RPE atrophy in the periphery. Arrows point to the enlarged fovea corresponding to the disc-shaped remnant of photoreceptors. Autofluorescent fundus photos (right eye: **E**; left eye: **F**) show increased overall autofluorescence, originating most likely from the choroid. Arrowheads point to the parafoveal hyperreflective ring, a characteristic sign of retinal dystrophies.

enlarged (Figure 1). Diabetic retinopathy was not observed during the investigation period.

Fundus autofluorescence imaging presented a dark fovea surrounded by a hyperreflective ring, as seen in other hereditary retinal dystrophies [20]. Increased autofluorescence of the choroid was detected, most likely due to the atrophy and mottling of the RPE in the posterior pole. No typical spot or patchy reflectance of lipofuscin could be seen. Optical coherence tomography showed reduced retinal thickness. Outside the fovea, the neurosensory retina was composed of only six layers, lacking the external limiting membrane, photoreceptor outer segment, and photoreceptor inner segment. An optically dense discoid remnant of photoreceptors was detected in the central fovea. The extent of the disc representing photoreceptors in the fovea showed constriction during the investigation period, indicating the progressive loss of cone photoreceptors (Figure 2).

Electric signals of retinal origin could not be differentiated from background noise with any of the standard ERG settings, including the dark-adapted 0.01 ERG (rod response), dark-adapted 3.0 ERG (maximal combined rod-cone response), dark-adapted 3.0 oscillatory potentials, light-adapted 3.0 ERG (single-flash photopic ERG), and light-adapted 3.0 flicker ERG (30 Hz flicker) settings (Figure

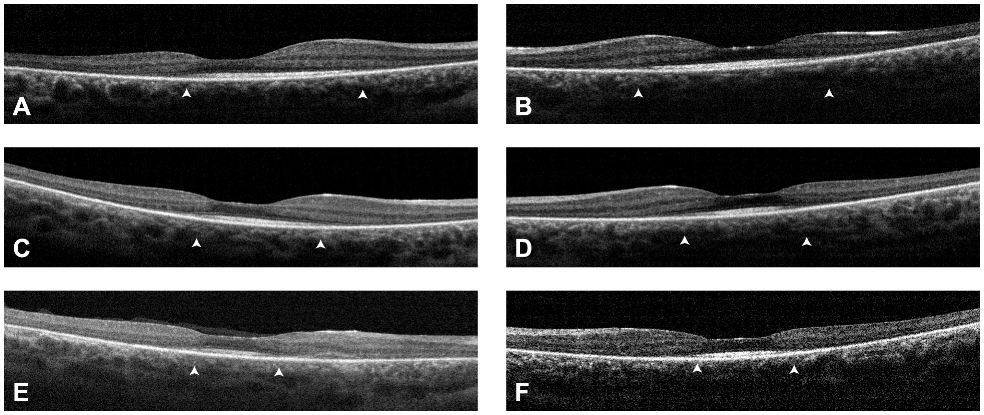


Figure 2. OCT imaging of the macula. Results of the OCT examinations in 2009, 2011, and 2014, right eye (**A**, **C**, **E**, respectively) and left eye (**B**, **D**, **F**, respectively). The arrowheads indicate the borders of the discoid remnant of cone photoreceptors in the central fovea. Note the progressive constriction of the photoreceptor layer. The retina outside this area lacks photoreceptors and is composed of only seven layers.

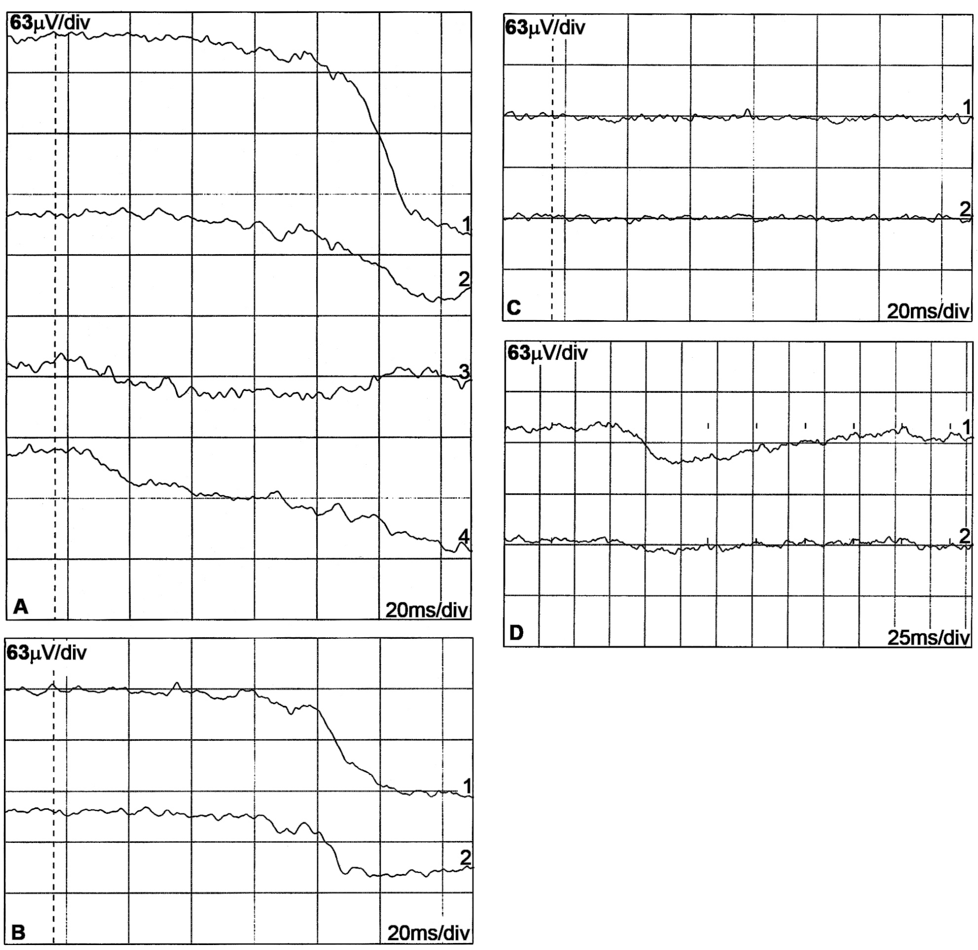


Figure 3. Standard full-field electroretinography. **A**: 1: dark-adapted 0.01 ERG (rod response) right eye; 2: dark-adapted 0.01 ERG (rod response) left eye; 3: dark-adapted 3.0 ERG (maximal combined rod–cone response), right eye; 4: dark-adapted 3.0 ERG (maximal combined rod-cone response), left eye. **B**: 1: light-adapted 3.0 ERG (single-flash photopic ERG), right eye; 2: light-adapted 3.0 ERG (single-flash photopic ERG), left eye. **C**: 1: dark-adapted 3.0 oscillatory potentials, right eye; 2: dark-adapted 3.0 oscillatory potentials, left eye. **D**: 1: light-adapted 3.0 flicker ERG (30 Hz flicker), right eye; 2: light-adapted 3.0 flicker ERG (30 Hz flicker), left eye.

3). Peripapillary nerve–fiber layer thickness showed normal values in both eyes.

## DISCUSSION

NEUROD1 takes part in the development of the endocrine pancreas and neuronal elements, including the retina. Most of our knowledge about the function of the protein comes from animal experiments. NEUROD1 knockout animals die shortly after birth due to severe diabetes. Long-term effects of gene knockout on the retina could only be investigated either by prolonging survival [6, 8] or restricting the gene knockout to the retina [11]. Pennesi et al. [8] investigated the role of NEUROD1 in the retina using knockout mice that survived until adulthood. The two- to three-month-old homozygous null mice showed a reduction in rod- and cone-driven electroretinograms and shortened outer photoreceptor segments. The thicknesses of the outer nuclear and the outer plexiform layers were reduced, but there were no changes in the inner nuclear, inner plexiform, and ganglion cell layers. In addition, the 18-month-old NEUROD1 KO retina was totally devoid of photoreceptors. Ochocinska et al. [11] used conditional KO mice to investigate the role of NEUROD1 in the adult retina. The retinal morphology represented a shortened and disorganized outer segment and dramatic reduction in rod- and cone-driven electroretinograms at two months of age. At older ages, photoreceptors were completely absent. Photoreceptor damage equally affected rods and cones. However, for the inner nuclear, inner plexiform, and ganglion cell layers, no obvious morphological changes were seen. These findings suggest that NEUROD1 plays an important role in maintaining functional and structural integrity of the photoreceptors, and that homozygous null mice progress rapidly to the complete loss of photoreceptors.

Homozygous null mutations in the NEUROD1 gene were suspected to be lethal in humans [8] until Cabezas et al. [18] reported two patients with homozygous loss-of-function mutations in the NEUROD1 gene in 2010. Both patients had permanent neonatal diabetes and severe neurologic abnormalities, including cerebellar hypoplasia, developmental delay, and visual and hearing impairment. However, detailed ophthalmological phenotypes of patients with homozygous NEUROD1 null mutations have not yet been documented. Our purpose with the present study was therefore to provide a detailed description of the functional and anatomic characteristics attributed to a homozygous NEUROD1 null mutation in humans and to compare our findings with those described in animal models.

The young female patient reported by Cabezas [18] with the homozygous c.427_428delCT NEUROD1 mutation was investigated on multiple occasions in a five-year period. The patient had diminished night vision from early childhood and showed severe visual field constriction with mostly preserved central visual acuity. These symptoms are similar to those caused by typical retinitis pigmentosa and indicate a rod–cone dystrophy pattern. In line with these symptoms, optical coherence tomography showed a discoid remnant of cone photoreceptors in the fovea and a total lack of photoreceptors outside the fovea. In this region, the retina was totally devoid of photoreceptors. Electroretinography showed absent dark- and light-adapted responses. The lack of dark-adapted ERG responses can be explained by the total lack of rod photoreceptors. Undetectable cone responses in the light-adapted ERG settings can be explained by the reduction in the number of cone photoreceptors and a damaged photoreceptor function. Despite the severely diminished retinal function, the ocular fundus was less compromised than with typical retinitis pigmentosa. Although RPE showed mottling in the posterior pole, no bone spicules or pigment clumps were present. Optic-disc pallor and retinal-vessel attenuation were also less prominent than in RP cases. Fundus autofluorescence imaging showed increased fundus autofluorescence and a hyperreflective parafoveal ring. This phenomenon has been described in cases of retinitis pigmentosa [20-23], rod–cone dystrophies [24], and other inherited retinal diseases [24-26]. Our result is in accordance with the presumption that the ring can be a prognostic factor of macular dysfunction [20, 22, 27, 28] and corresponds to a transition zone between a functional and dysfunctional retina [20, 27-29].

Most of our knowledge on the function of NEUROD1 comes from animal models. NEUROD1 seems to be necessary for the maintenance of normal photoreceptor structure and function. The absence of NEUROD1 leads to severe retinal dystrophy [8, 13]. Our study demonstrates the first detailed description of an ophthalmological phenotype caused by a homozygous NEUROD1 null mutation in humans and indicates that it causes severe rod–cone dystrophy. Although it resembles retinitis pigmentosa in many aspects, it can be clearly distinguished from it. The relatively spared pigmented epithelial layer, the normal appearance of the optic disc and retinal vessel, and the disc-shaped remnant of cone photoreceptors in the fovea are characteristic hallmarks of the disease, distinguishing it from any other hereditary retinal dystrophies. The total lack of rod photoreceptors, sharply demarcated from relatively spared foveal photoreceptors, is also an unusual phenotype.

Therefore, we believe that this case not only represents a novel genotype–phenotype correlation but also delineates a novel form of syndromatous hereditary retinal dystrophy, and provides insight into the role of NEUROD1 in retinal homeostasis. Moreover, we cannot exclude the possible role of the NEUROD1 gene in non-syndromatous retinal dystrophies of so-far undetermined genetic origin. The findings of our report confirm the observations of knockout animal models. To the best of our knowledge, this is the first detailed description of the ophthalmological consequences of a homozygous NEUROD1 mutation in humans. Our results are the first to show that the loss of NEUROD1 has similar effects on the human retina as have been previously shown in animal experiments. Our report can help in diagnosing NEUROD1-related retinal dystrophies in the future and provides information on disease progression.

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