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## **DICER1 Syndrome: Characterization of the ocular phenotype in a family-based cohort study**

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### **Abstract**

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**Purpose:** To characterize the ocular phenotype of *DICER1* syndrome

**Design:** Prospective, single-center, case-control study

**Subjects, Participants, and/or Controls:** One hundred and three patients with an identified germline, pathogenic *DICER1* variant (*DICER1*-carriers) and 69 family control subjects underwent clinical and ophthalmic examination at the National Institutes of Health between 2011 and 2016.

**Methods:** All participants were evaluated with a comprehensive ophthalmic exam including best corrected visual acuity, slit-lamp biomicroscopy and a dilated fundus examination. A subset of patients returned for a more detailed evaluation including spectral-domain optical coherence tomography, color fundus photography, fundus autofluorescence imaging, visual field testing, full field electroretinogram and genetic testing for inherited retinal degenerative diseases.

**Main Outcome Measures:** Visual acuity and examination findings

**Results:** Most *DICER1*-carriers (97%) maintained a visual acuity of 20/40 or better in both eyes. Twenty three *DICER1*-carriers (22%) had ocular abnormalities compared with four (6%) family controls ( $P=0.005$ ). These abnormalities included retinal pigment abnormalities ( $N=6$ , 5.8%), increased cup-to-disc ratio ( $N=5$ , 4.9%), optic nerve abnormalities ( $N=2$ , 1.9%), epiretinal membrane ( $N=2$ , 1.9%) and drusen ( $N=2$ , 1.9%). Overall, we observed a significant difference ( $p=0.03$ ) in the rate of retinal abnormalities in *DICER1*-carriers ( $N=11$ , 11%) vs. controls ( $N=1$ ; 1.5%). One patient had an unexpected diagnosis of retinitis pigmentosa with a novel variant of unknown significance in *PRPF31*, and one had optic nerve elevation in the setting of increased intracranial pressure of unclear etiology. Three patients (3%) had *DICER1*-related ciliary body medulloepithelioma (CBME), two of which were identified during routine examination, a significantly higher rate than that previously reported.

**Conclusions:** Ophthalmologists should be aware of the ophthalmic manifestations of the *DICER1* syndrome and individuals and families should be counseled on the potential signs and symptoms. We recommend that children with a germline pathogenic variant in *DICER1*, especially those under the age of 10 years, undergo annual dilated ophthalmic examination, looking for evidence of CBME, signs of increased intracranial pressure and perhaps changes in the retinal pigment epithelium.

## Précis

Ciliary body medulloepitheliomas have previously been described in patients with *DICER1* syndrome. In addition to these findings, *DICER1*-carriers should be monitored for changes in the optic nerve and retina.

## Introduction

The *DICER1* syndrome is a recently-recognized tumor predisposition disorder that arises from pathogenic germline variants in *DICER1*. *DICER1* is a widely expressed gene essential to the processing of mature microRNA (miRNA), single-stranded RNA molecules critical to regulating gene expression and protein synthesis.<sup>1,2</sup> The disorder is associated with a variety of rare malignancies including pleuropulmonary blastoma (PPB), Sertoli-Leydig cell tumor, embryonal rhabdomyosarcoma of the cervix, pineoblastoma, pituitary blastoma and thyroid

cancer. The non-malignant *DICER1* phenotype includes macrocephaly, multi-nodular goiter, nasal chondromesenchymal hamartoma and cystic nephroma.<sup>3–8</sup>

Ciliary body medulloepithelioma (CBME) is a primitive neuroepithelial neoplasm typically arising from the nonpigmented ciliary epithelium, with 75–90% of cases presenting in the first decade of life,<sup>9</sup> typically with visual symptoms or abnormalities on ophthalmologic examination. These tumors are divided into benign and malignant by their histopathology, however, the most important feature for prognosis is extraocular extension, although distant metastasis and mortality are rare. CBME presents as a fleshy mass with clear cysts, leading to secondary glaucoma in approximately 50% of patients, as well as cataract and retinal detachment<sup>10</sup>. Although it is associated with the *DICER1* syndrome, fewer than 1% of patients with PPB manifest CBME and conversely, 5% of patients with CBME have a history of ppb<sup>6,9,11,12</sup>. Current consensus guidelines for the surveillance of individuals with a *DICER1* pathogenic variant suggest visual acuity screening and routine eye examination from age 3 years to at least age 10 years<sup>13</sup>.

In recent years, the role of Dicer enzymes in the retinal pigment epithelium (RPE) has been an area of interest for ophthalmic researchers. Donor human eyes with geographic atrophy in the setting of age-related macular degeneration (ARMD) have been found to have reduced *DICER1* messenger RNA (mRNA) in macular RPE *versus* controls<sup>14</sup>. Multiple animal models have been created to further study the retinal effects of downregulating this miRNA processing enzyme.

The full spectrum of the human *DICER1* -associated ocular phenotype is currently unknown. To better define this, we investigated the prevalence of ocular anomalies detected on routine clinical evaluation in a cohort of prospectively-ascertained individuals who harbor a pathogenic variant in *DICER1* and in family controls. Select individuals were more thoroughly evaluated with additional ophthalmic examinations and testing at the National Eye Institute (NEI).

## Methods

### Study recruitment, phenotyping and *DICER1* genetic testing.

Individuals with a history of a *DICER1*-associated tumor or who harbored a known pathogenic *DICER1* variant were recruited to an on-going natural history study of the *DICER1* syndrome at the National Cancer Institute (NCI) (NCT-01247597). After genetic counseling, probands and their family members underwent germline *DICER1* genetic testing as previously reported.<sup>15</sup> All participants or their guardians completed detailed questionnaires about past medical and surgical history, including eye-associated problems. Pathogenic *DICER1*-mutation carriers (hereafter, “*DICER1* -carriers”) and family controls (no detected pathogenic germline *DICER1* mutations by sequencing, or inferred negative by pedigree analysis) were invited to undergo a three-day evaluation at the National Institutes of Health (NIH) Clinical Center (CC), including comprehensive ophthalmic evaluation, between 2011 and 2016.

Study participants were assessed with a review of any previous examination records, medical and ocular histories, slit-lamp biomicroscopy and a dilated funduscopy examination. Best-corrected visual acuity was measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart recorded as Snellen Acuity or age-appropriate pediatric vision testing methods, including Allen figures, HOTV charts, fix and follow (FF) or central, steady and maintained (CSM). Spectral domain optical coherence tomography (OCT) (SD-OCT: Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA) as well as color fundus photography (Topcon and Optos ultrawide-field retinal imaging device; Dunfermline, Scotland) were obtained per the examining physician's discretion. All participants provided written, informed consent, and the study was approved by the Institutional Review Boards of the National Cancer Institute and the National Eye Institute. All study protocols adhered to the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act.

### **Focused ophthalmic evaluation and genetic testing.**

After reviewing data from the comprehensive CC evaluation, *DCERI*-carriers with any significant ophthalmic abnormality (N=7) were invited back for a more detailed evaluation at the NEI. Seven patients were consented to the Genetics of Inherited Eye Disease Protocol (NCT-02471287) and underwent a comprehensive ocular examination, including best-corrected visual acuity testing, slit-lamp biomicroscopy, and dilated fundus examination. In addition, patients also completed visual field testing, electroretinography (ERG) and retinal imaging, including SD-OCT, fundus autofluorescence imaging, and color fundus photography. International Society for Clinical Electrophysiology of Vision (ISCEV) standard full-field flash ERGs were recorded from corneal bipolar Burian-Allen electrodes (Hansen Ophthalmic Laboratories, Iowa City, IA) using a commercial electrophysiology system (LKC, Gaithersburg, MD).<sup>16,17</sup> Following genetic counseling, four patients with findings suggesting retinal degeneration underwent Clinical Laboratory Improvement Amendments (CLIA) clinical molecular genetic testing with a 280- gene inherited retinal dystrophy panel (Molecular Vision Laboratory; Hillsboro, Oregon; CLIA Lab ID: 38D2059762). Variants were interpreted using (1) publicly available population and disease databases, including the Exome Aggregation Consortium (ExAC),<sup>18</sup> 1,000 Genomes (1,000G)<sup>19</sup> Exome Sequencing Project (ESP),<sup>20</sup> Human Gene Mutation Database (HGMD)<sup>21</sup> and ClinVar,<sup>22</sup> as well as (2) *in silico* prediction tools, including Polymorphism Phenotyping v2 (PolyPhen-2)<sup>23</sup> and Sorting Intolerant from Tolerant (SIFT).<sup>24</sup> The Fisher exact test, chi-square and t-tests were used for determining statistical significance.

## **Results**

### **Cohort Demographics**

One hundred and three *DICERI*-carriers and 69 family controls were evaluated at the outpatient eye clinic at the NIH CC between 2011 and 2016. There was a significant difference in gender distribution ( $p = 0.04$ ; chi-square). The mean age at exam was 27.0 years for *DICERI*-carriers and 37.9 years for controls (Table 1), a statistically significant difference ( $p = 0.001$ ; two-tailed t- test).

### Ocular characteristics of controls

Of the 69 family controls, only four (6%) had ophthalmic abnormalities greater than refractive error or age appropriate cataract formation (Table 1): increased cup-to-disc ratio (N=2), iris nevus (N=1) and drusen (N=1). Best corrected visual acuity for this group ranged from 20/12.5 to 20/25.

### Ocular characteristics of *DICER1*-carriers

Ninety-six of the 103 (93%) *DICER1*-carriers who could participate in ETDRS testing maintained acuity of 20/40 or better in both eyes; four pediatric patients were noted to have age-appropriate acuity of FF and CSM, without a Snellen equivalent. Only two patients had best-corrected visual acuity measured to be worse than 20/60 in one eye (excluding the one patient with a history of enucleation): an 18-year-old boy with anisometropia of five diopters leading to amblyopia with a visual acuity of 20/60, and a 57-year-old with long-standing history of amblyopia, leading to 20/100 acuity.

Twenty-three *DICER1*-carriers (22%) had an ocular abnormality that exceeded simple refractive error or age-related cataracts, compared with 6% of controls ( $p=0.005$ ; Table 1). Of these, eleven *DICER1*-carriers (11%) had retinal findings (drusen, RPE, retinal degeneration) compared with one control (1.5%), a significant difference ( $p = 0.03$ ). One participant with red-green color blindness had a strong family history of color blindness and an otherwise normal examination. One *DICER1*-carrier (with *DICER1* c.1507G>T: p.E503X) developed CBME and underwent enucleation at an outside institution at age four, 47 years prior to NIH evaluation; his presenting symptoms were unknown. He has not been diagnosed with other malignancies. Additionally, two NIH patients developed a CBME after their initial visit.

One 7-year-old boy (with *DICER1* c.3658C>T: p.Q1220X) with a history of type I PPB as an infant reported vision loss in one eye during his yearly pediatric well-child visit, five years after evaluation at NIH and one year after a normal well child check with the pediatrician. Ophthalmologic examination found hand motion vision, a sluggish right pupil, sensory exotropia, cataract and a right ciliary body mass. He underwent enucleation, and subsequent pathology identified total cataract with focal capsular rupture and phacoantigenic uveitis, focal temporal tractional retinal detachment attached to a cyclitic membrane covering a ciliary body tumor. This tumor was a medulloepithelioma, confined to the eye with no malignant features. (Figure 1) A second patient, a 7-year-old girl with *DICER1* c.1408G>T:p.E470X and no other history of malignancy, expressed no visual complaints, but was noted to have new-onset strabismus by her mother, and when directly queried, the child reported blurry vision. Ophthalmic examination revealed light perception vision, sensory exotropia, a shallow anterior chamber with anteriorly displaced lens and a large mass filling the posterior chamber, 4.5 years after her initial NIH examination. Ten months prior to this at her pediatrician well-child check, her mother reported a significant increase in blinking and the patient's acuity was slightly asymmetric at 20/20 and 20/25 at that time. She underwent enucleation, and pathology confirmed abnormal proliferation of primitive neuroepithelial cells surrounded by myxoid stroma centered at the ciliary body, consistent with medulloepithelioma.

Optic nerve abnormalities were noted in a total of seven *DICER1*-carriers. Five of these had an increased cup to disc ratio without any signs of glaucoma or retinal nerve fiber layer (RNFL) thinning on OCT. Two patients were found to have elevation of the optic nerve head and were asked to return for more comprehensive testing. One patient with optic nerve findings was a 7- year-old boy who complained of headaches, transient blurring of vision and occasional ringing in his ears. His acuity at the time of his assessment was 20/20 OD and 20/25 OS with no color vision deficits as measured by Ishihara color plates. His anterior segment exam was normal, however his dilated exam demonstrated retinal vascular tortuosity and disc elevation without evidence of optic nerve head drusen (Figure 2A). His symptoms and clinical exam suggested increased intracranial pressure. His subsequent magnetic resonance imaging/magnetic resonance venography (MRI/MRV) was normal and lumbar puncture opening pressure was elevated at 37 mm H<sub>2</sub>O; cerebral spinal fluid (CSF) laboratory testing was otherwise within normal limits. He had improvement of both his headache and disc elevation with acetazolamide treatment and continues to be monitored closely. The other participant with optic nerve abnormalities was a 65- year-old woman with optic nerve head drusen who maintained good visual acuity in the range of 20/25–20/30 but developed paracentral scotomas in the setting of RNFL thinning on OCT (Figure 2B).

Retinal changes in *DICER1*-carriers included epiretinal membranes (N=2), drusen (N=2), RPE abnormalities (N=6) and retinitis pigmentosa (N=1). Patients with RPE abnormalities ranged from small focal areas of RPE dropout to congenital hypertrophy of the RPE (CHRPE), without any diffuse changes suggestive of a retinal degeneration. The one patient with a small, flat choroidal nevus was 16 years old at the time of evaluation and had no characteristics worrisome for melanoma: no overlying orange pigment, surrounding halo or associated subretinal fluid. The patient with CHRPE was a 33-year-old woman with no personal or family history of familial adenomatous polyposis. One 37-year-old female *DICER1*-carrier reported a diagnosis of retinitis pigmentosa prior to her study enrollment (Figure 3). Her fundus exam demonstrated classic waxy pallor of the optic nerve, retinal atrophy with bony spicules and vascular attenuation. Her electroretinogram responses were severely reduced and delayed, confirming a diagnosis of retinitis pigmentosa. Genetic testing revealed a novel missense variant in *PRPF31* (NM\_015629.3:c.829A>C; NP\_056444:p.Ser277Arg), altering a deeply conserved Serine residue in the Nop domain. This variant was absent from population and disease databases (ExAC, gnomAD, ESP, 1000G, HGMD, ClinVar) and was predicted to be damaging by in silico prediction programs (SIFT and Polyphen-2). Her mother, who is also a *DICER1*-carrier, underwent comprehensive ophthalmic testing. She had no retinal degeneration, and did carry the *PRPF31* missense variant, therefore, the classification of this *PRPF31* allele is a variant of uncertain significance. However, retinal degenerations associated with small nuclear riboproteins such as *PRPF31* are known to exhibit incomplete penetrance.

## Discussion

*DICER1* is an endonuclease critical for the production of miRNA, which helps regulate gene expression in embryologic and early developmental stages.<sup>1</sup> The *DICER1* syndrome is an autosomal dominant tumor-predisposition disorder that features a mixture of rare and common tumors primarily affecting children and young adults, including pleuropulmonary

blastoma, cystic nephroma, Sertoli-Leydig cell tumors, thyroid cancer and multinodular goiter. Medulloepithelioma of the ciliary body is known to be associated with the *DICER1* syndrome, and was the primary reason for ophthalmic evaluation. A 2011 review of 299 patients in the International PPB Registry identified three patients who had both PPB and CBME, and one patient whose father had medulloepithelioma<sup>12</sup>. Presenting signs and symptoms include decreased visual acuity or leukocoria, leading to identification of a mass on the iris or ciliary body. In our two incident pediatric CBME patients, the presenting symptom was vision loss of unknown duration, noted upon direct questioning, and strabismus noted by a parent. Both patients had documented normal undilated ocular examinations by their pediatricians within the one year prior to ciliary body tumor diagnosis; one with only mildly asymmetric acuity. MRI imaging is important to identify extent of invasion, while ocular imaging with ultrasound biomicroscopy (UBM) may help identify the typical heterogeneous, cystic features of CBME. Definitive diagnosis, however, is based on pathology in most cases. We did not observe any genotype-phenotype or clinical correlates in the three patients in this study with CBME, who all harbored different germline truncating *DICER1* variants. Our ability to draw firm conclusions on CBME correlations is limited by the small number of affected individuals and their young age. It has been reported that fewer than 1% of patients with PPB manifest CBME, which is lower than our experience (3%) with this cohort.

There are other *DICER1*-associated tumors that may present with ocular signs and symptoms. *DICER1*-carriers are at increased risk of developing pituitary blastoma. de Kock *et al.* described twelve pituitary blastoma cases with germline and/or somatic *DICER1* mutations<sup>25</sup>. Patients most often presented with ophthalmoplegia and Cushing disease; only a minority (17%, N=2) demonstrated proptosis and visual disturbance. None of the participants in our study were found to have proptosis or ophthalmoplegia, and none harbored a known pituitary blastoma. Similarly, Sabbaghian *et al.* described a pathogenic *DICER1* germline variant in a patient with a pineoblastoma.<sup>26</sup> Although none of the patients in the current study had a known pineoblastoma, we did identify a 7-year-old boy *DICER1*-carrier who presented with disc elevation (Figure 2) in the setting of idiopathic increased intracranial pressure (ICP). It is unclear if this boy's ICP is associated with his *DICER1* status; data from additional patients is needed. Our findings show that the ocular phenotype of the *DICER1* syndrome is not fully established. This highlights the importance of a full dilated examination in *DICER1*-carriers, specifically to evaluate the optic nerve for disc edema or other signs of increased ICP.

The 65-year-old female *DICER1*-carrier with identified optic nerve head drusen and RNFL thinning (Figure 2B) likely falls into the 1% of the general population that may present with this finding. Optic nerve head drusen is bilateral in 75–85% of patients and presents most often in whites.<sup>27,28</sup> As optic nerve drusen enlarge, they can compress nerve fibers leading to visual field defects, as seen in our patient. We do not believe this finding is related to the *DICER1* syndrome, however further observations are necessary.

We report, for the first time, a significant difference in retinal abnormalities in *DICER1*-carriers *versus* controls. We identified 11 *DICER1*-carriers (11%; *versus* 1.5% in controls;  $p=0.03$ ) with retinal findings ranging from drusen, RPE abnormalities to retinal degeneration.

Although some of these retinal findings are certainly common in the general population (*e.g.* CHRPE, RPE drop-out), some may be *DICER1*-associated. Some authors speculate that the processing of miRNA is critical to the normal health and development of the retina.<sup>29</sup> If true, then some of the retinal changes we observe may be *DICER1*-associated. Our observations merit long-term follow-up to determine the natural history of these changes. In addition, replication of our observations in other cohorts is needed. Awareness of these retinal differences, especially in younger people, may aid in the identification of previously unrecognized, at-risk individuals.

The ocular phenotype of *DICER1* deficiency has been investigated in a variety of animal models. Heterozygous *Dicer1*-mutant zebrafish have normal RPE cells with no evidence of degeneration by age 20 months.<sup>30</sup> In mice, loss of *Dicer1* impairs the processing of long double-stranded *Alu* RNAs, which is hypothesized to contribute to the formation of geographic atrophy in age-related macular degeneration.<sup>14</sup> In our study, two *DICER1*-carriers over the age of 65 years had retinal findings consistent with a diagnosis of age-related macular degeneration (ARMD). Since the number of patients over the age of 50 years in this group was small (N=25), it is difficult to ascertain whether or not there is an increased incidence of ARMD in *DICER1*-carriers.

It is unclear whether the retinitis pigmentosa in one *DICER1*-carrier in our study is attributable to the novel missense variant in *PRPF31* or to her germline loss-of-function *DICER1* variant. While the identified *PRPF31* variant is rare and predicted to be pathogenic by *in silico* prediction tools, there currently is insufficient evidence for pathogenicity. Pathogenic germline variation in *PRPF31* accounts for 5–10% of autosomal-dominant retinitis pigmentosa. Family studies consistently show incomplete penetrance, with some mutation carriers having no vision problems.<sup>33</sup> The incomplete penetrance in families with *PRPF31*-associated retinitis pigmentosa further complicates the interpretation of the *PRPF31* variant of uncertain significance identified in the mother-daughter duo in this cohort. There is no additional family history of retinitis pigmentosa. If the retinal changes are not *PRPF31*-related, then perhaps they arise from discrete *DICER1* somatic “second hit” mutations in the retina. Careful documentation and genetic testing of additional cases of retinitis pigmentosa in *DICER1*-carriers are needed to establish an association.

Our study is the largest evaluation of the ocular phenotype in *DICER1*-carriers, with family controls, to date. A strength of this study is the detailed phenotyping examination that all patients underwent at the NIH CC. However, we recognize that this may lead to an over-estimation of the ocular phenotype findings. Replication of our findings is needed in other cohorts. Recommendations on surveillance in *DICER1*-carriers have recently been published and suggest individuals and families should be counseled regarding visual acuity changes, strabismus or leukocoria with annual routine dilated ophthalmologic exam with visual acuity screening from 3 years of age through at least 10 years of age.<sup>13</sup> Given that self-reported ocular symptoms are often limited in the pediatric population, we agree that all children under the age of ten years undergo an annual dilated eye examination. This can generally be done unседated and should focus on evidence of ciliary body tumors (*e.g.*, cataract, mass, secondary glaucoma, retinal detachment), retinal pigment abnormalities, as well as optic nerve changes that may give insight into intracranial pressure status. There are no routine



ophthalmic imaging studies recommended in asymptomatic individuals, though providers should be aware of the ophthalmic *DICER1*-associated phenotypes and the need for thorough examination by an ophthalmologist. Providers should have a low threshold to add ancillary testing if there is a suspicion of ciliary body mass or intracranial mass causing increased ICP. A limitation of this study is the lack of ultrasound biomicroscopy (UBM), specifically looking at the ciliary body in this cohort. Future work evaluating *DICER1* carriers with UBM may help us gain a better understanding of the incidence of CBME as well as identify occult lesions before developing ophthalmic symptoms and therefore UBM should be considered when available.

Limitations of our study include marginally significant differences in male/female ratios in cases and controls. This is likely to have limited relevance given the lack of known predilection for retinal problems based on sex. The case cohort is significantly younger than controls, a difference that strengthens our findings.

In summary, we found that 22% of *DICER1*-carriers harbored an ocular abnormality, a significant difference when compared with 6% of family controls. Although the retinal changes we observed are similar to those found in *Dicer1* animal models, additional validation is needed to show that these changes are truly attributable to *DICER1*. Children with a pathogenic germline *DICER1* variant warrant annual dilated eye exams, and patients and families must be educated about the ocular signs and symptoms that could prompt further ophthalmic evaluation.

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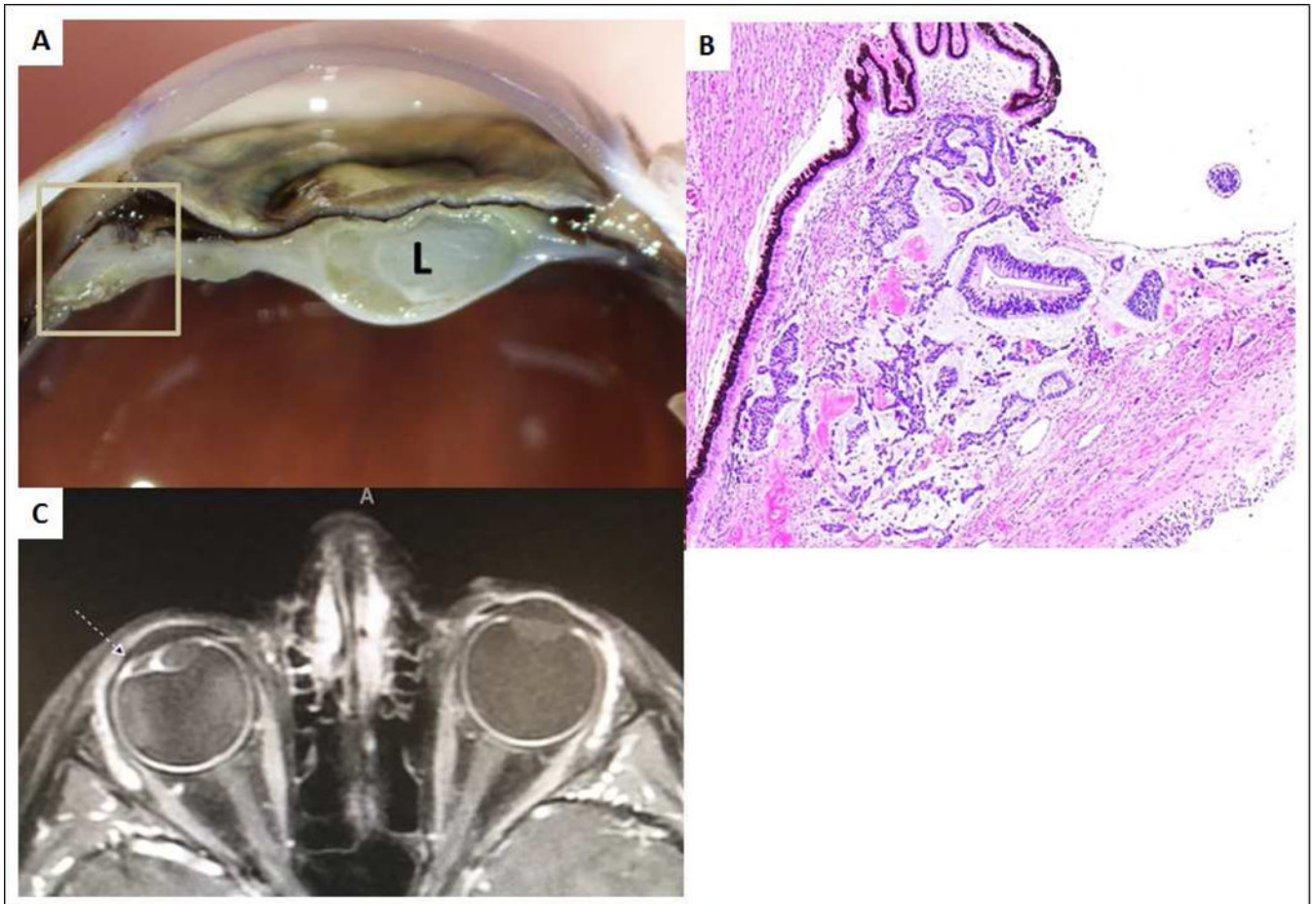
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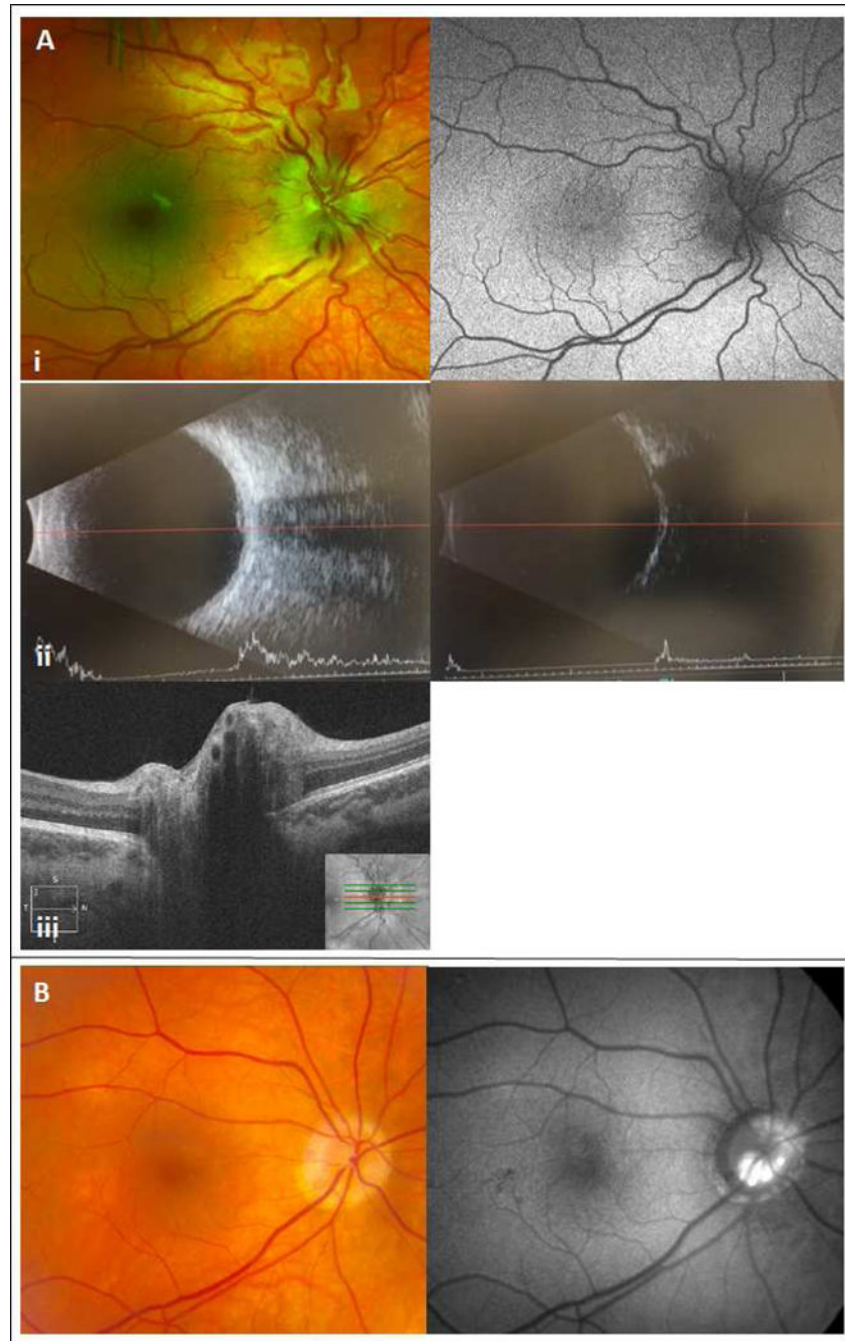
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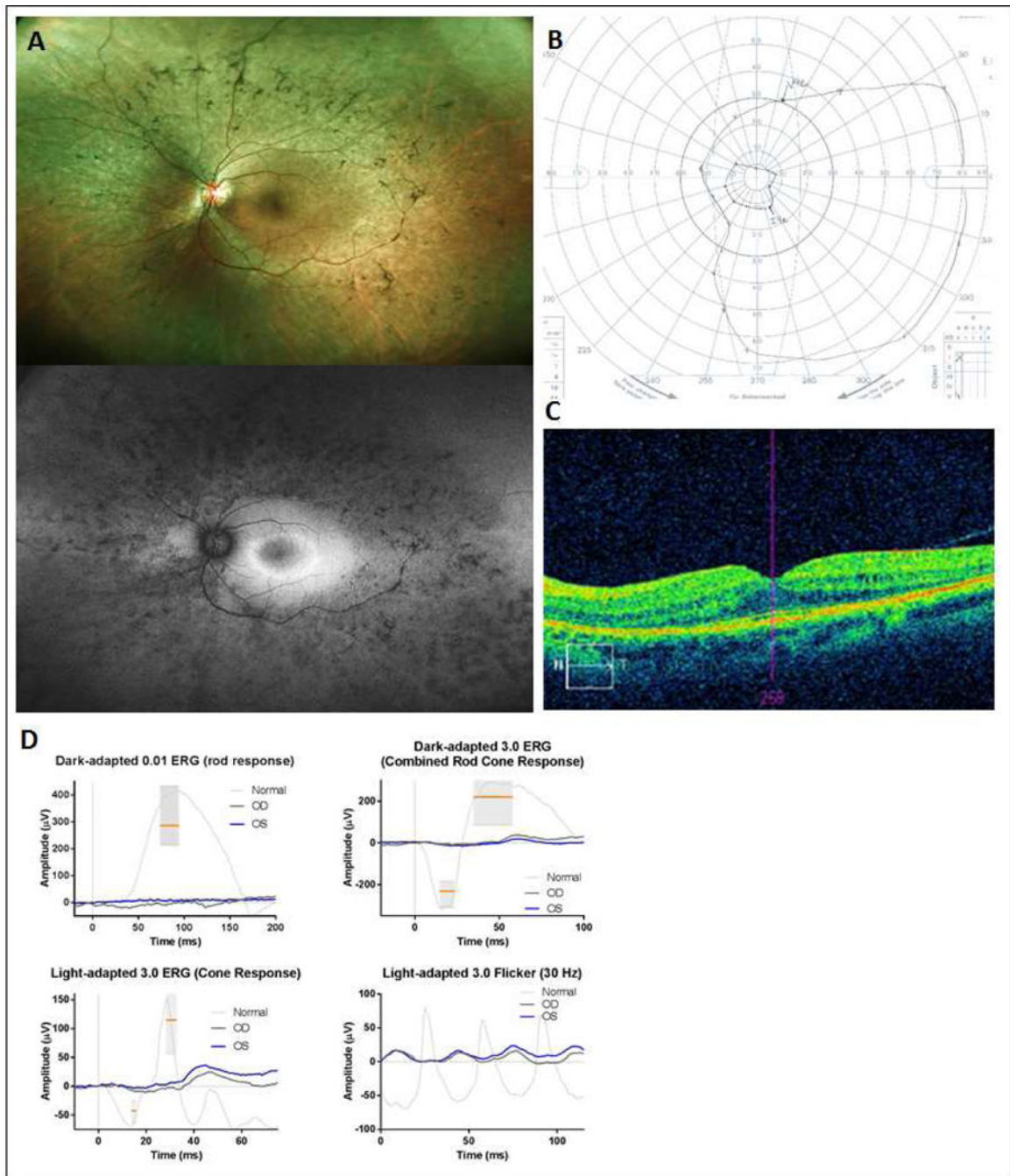
**Figure 1.**

7-year-old boy, *DICER1* carrier with medulloepithelioma of the ciliary body. A: Macroscopic photograph of the anterior portion of the eye after sectioning demonstrating a tan-white lesion (inside square) adjacent to the ciliary body with a membrane extending around the cataractous lens (L). B: Microscopic photograph of the tumor (same site as in the previous photo inside the square) adjacent to the pigmented epithelium of ciliary body. The tumor is composed by tubular structures of neoplastic neuroepithelium seen on a basophilic loose stroma. Hematoxylin and Eosin stain. Original magnification 4X. C: T1 weighted axial image with contrast demonstrating the ciliary body tumor (dashed arrow). Note the displacement of the lens laterally.



**Figure 2.**

Panel A: 7-year-old boy with headaches and transient blurred vision. Examination of the fundus revealed disc elevation with retinal vascular tortuosity and no hyperautofluorescence at the nerve head (i). There was no obvious hyper- or hypo-reflective lesion in the peripapillary area on b-scan imaging in high (ii left) or low gain (ii right). OCT does not demonstrate any classic optic nerve head drusen features (iii). Panel B: 65-year-old female with optic nerve head drusen noted on direct visualization and hyperautofluorescent lesions on imaging.



**Figure 3.** 37-year-old *DICER1*-carrier woman presenting with retinitis pigmentosa. Fundus examination revealed classic features of retinal atrophy, bony spicules and vessel attenuation (top panel A) with peripheral hypoautofluorescence with a central hyperautofluorescent ring (lower panel A). Visual acuity was preserved at 20/20 in each eye with a constricted visual field (B) and macular cystic changes and loss of photoreceptor IS/OS band demonstrated on

OCT (C). Full-field ERG showed nearly unrecordable scotopic responses with severely reduced photopic responses, consistent with a rod-cone dystrophy (D).

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**Table 1.**

Demographics and ocular characteristics of DICER1-carriers and family control

	<i>DICER1-carriers</i>	<i>Controls</i>
Total	103	69
Male	47 (46%)	43 (62%)
Female	56 (54%)	26 (38%)
Age (mean, years)	27.0	37.9
Age (range, years)	0.8 – 73.9	0.9 – 74.3
BCVA	20/12.5 – 20/80	20/12.5 – 20/25
<i>Ophthalmic Findings</i>		
Optic Nerve Abnormality	7	2
Retinal Pigmentary Abnormality	6	0
Cilliary Body Tumor	3	0
Macular Drusen	2	1
Epiretinal Membrane	2	0
Color Blindness	1	0
Choroidal Nevus	1	0
Retinal Degeneration	1	0
Iris Nevus	0	1

BCVA= best corrected visual acuity