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Ocular Pathology of Fukuyama Congenital Muscular Dystrophy

Tomoko Yamamoto, Yoichiro Kato and Noriyuki Shibata

Abstract

Fukuyama congenital muscular dystrophy (FCMD) is one of the congenital muscular dystrophies, showing central nervous system (CNS) and ocular lesions, in addition to muscular dystrophy. It is included in α-dystroglycanopathy, an entity of muscular dystrophies caused by reduced glycosylation of α-dystroglycan (α-DG). Studies of ocular lesions are not so many, compared with those of the muscle and CNS. Clinical ocular manifestations are myopia, strabismus, retinal detachment, and so on. Since the retina has a structure partly resembling the cerebral cortex, pathological findings similar to those found in the brain have been reported. The major observation considered to be involved in the pathogenesis of retinal lesions is abnormalities in the internal limiting membrane formed by Müller cells, which is corresponding to the glia limitans formed by astrocytes in the brain. Fukutin, responsible for FCMD, and α-DG are expressed in Müller cells. Moreover, fukutin may be involved in synaptic functions of retinal neurons through the glycosylation of α-DG. In this chapter, ocular lesions of fetal and child FCMD patients are presented, especially focusing on pathological findings of the retina, and functions of fukutin are discussed.

Keywords: eye, pathology, Fukuyama, muscular dystrophy, fukutin

1. Introduction

Fukuyama congenital muscular dystrophy (FCMD), described by Fukuyama et al., is an autosomal recessive disease, exclusively found in Japan [1, 2]. In addition to the muscular dystrophy, central nervous system (CNS) and eye anomalies are accompanied. Although there are mild to severe cases, patients are generally noticed as floppy infant, exhibit progressive muscular dystrophy and mental retardation, and die before 30 years [2]. The responsible gene is *fukutin* on chromosome 9q31 [3]. Among congenital muscular dystrophies, Walker Warburg syndrome (WWS) and muscle-eye-brain disease (MEB) show characteristics similar to FCMD [4, 5], although patients of FCMD show milder symptoms compared to those of WWS and MEB, in general [6]. Since responsible genes for WWS, MEB, and FCMD are implicated in the glycosylation of α-dystroglycan (α-DG), they are included in the entity of α-dystroglycanopathy [6].

At the sarcolemma of skeletal muscle, there is a complex composed of several proteins, including dystroglycans, sarcoglycans, and dystrophin. It is called the dystrophin-glycoprotein complex (DGC) that links extracellular matrix and intracellular proteins. The DGC is also observed in the CNS and in the eye.

The glycosylated area of α-DG existed outside the cell membrane works as a receptor for extracellular matrix proteins like laminin [6–8]. Thus, the glycosylation of α-DG is indispensable for formation of the basement membrane. To accomplish a fully glycosylated α-DG, several proteins, such as protein-O-mannosyltransferase 1/2 (POMT1/2) [9–11], O-linked mannose 1,2-N-acetylglucosaminyltransferase (POMGnT1) [12], fukutin [13], fukutin-related protein (FKRP) [14], and LARGE [15], are required. The recent study proves that fukutin transfers ribitol 5-phosphate to sugar chains of α-DG, which is necessary to make a functional α-DG [13].

Muscular dystrophies showing reduced glycosylation of α-DG due to malfunction of above proteins that add sugars on the glycosylation domain of α-DG are categorized to α-dystroglycanopathy, which include severe diseases like WWS, MEB, and FCMD to rather milder diseases like congenital muscular dystrophy 1C (MDC1C) [16], MDC1D [17], limb-girdle muscular dystrophy 2I (LGMD 2I) [16] LGMD2K, and LGMD2M [18]. In severe ones, CNS and eye anomalies are obvious. The CNS anomaly is represented by cortical dysplasia, generally called cobblestone lissencephaly [6, 7]. In FCMD, the cerebrum and cerebellum generally show an appearance of polymicrogyri [19–21]. In the surface of CNS, astrocytic endfeet form the glia limitans covered with the basement membrane, and both fukutin and α-DG are expressed in astrocytes [7, 22]. In the fetal FCMD brain, irregular disruptions of the glia limitans are observed. Neuronal tissues overmigrate from defects of glia limitans (**Figure 1**), which is considered to be the main cause of cobblestone lissencephaly [7, 8]. Hypoglycosylation of α-DG by malfunction of fukutin makes
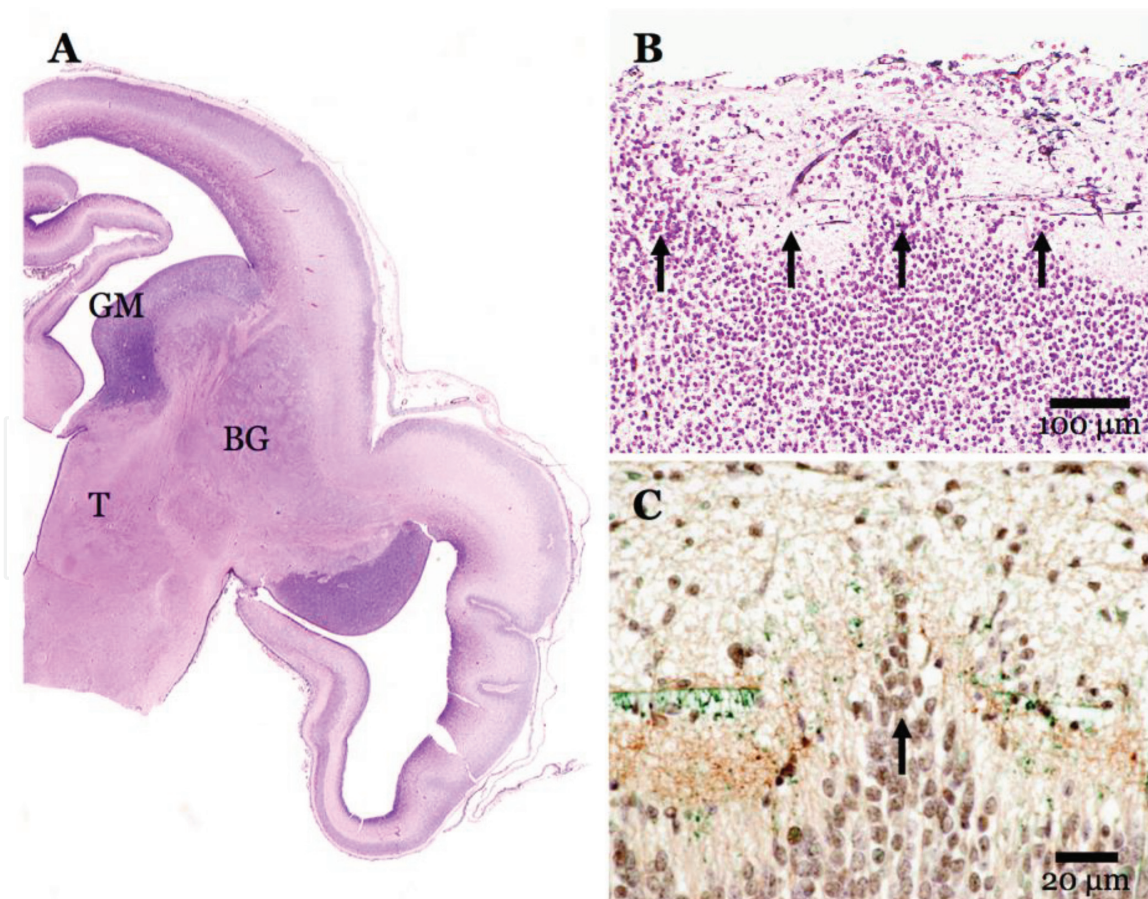

Figure 1.
Cerebral lesions of a FCMD fetus. The cerebral hemisphere almost retains fundamental structure (A). The glia limitans of the cerebral surface is irregularly disrupted, and neuronal tissues overmigrate through the disruptions (B, C; arrows). (B) Periodic acid-methenamine-silver (PAM) staining. (C) Photoshop-aided double immunostaining [25] of nestin (green) and synaptophysin (brown). BG: basal ganglia, GM: germinal matrix, T: thalamus.

the basement membrane fragile and this gives rise to partial defects in the glia limitans. Amounts of overmigrated neuronal tissues are various, depending on the size of defects [20, 23, 24].

Compared with the muscular and CNS lesions, studies about the ocular anomaly are rather scarce, but intriguing observations have been reported. Among the components of the eye, the retina has some characteristics common to the cerebral cortex. In this chapter, ocular lesions of FCMD are described, mainly focusing on retinal dysplasia and introducing resent studies on pathogenesis.

2. Normal development and structure of the eye

2.1 Normal development of the eye

Many genes are involved in the formation of ocular structure [26]. Morphologically, the initial eye structure becomes observable after 3 weeks of the gestation, as a pair of optic sulci at the rostral neural plate. By 4 weeks, the optic sulcus grows to form the optic vesicle, the proximal part of which develops to be the optic stalk, the future optic nerve, and the rest of which to be the optic cap. The distal part of the optic vesicle is closely adjacent to the surface ectoderm that develops to the lens after forming the lens vesicle by invagination. The lens vesicle is separated from the surface ectoderm at 6 and half weeks. The corneal epithelium begins to be formed from the surface ectoderm by 7 weeks. The choroid and the sclera develop from the periocular mesenchyme by 15 weeks.

The retina is differentiated from the optic cap. The inner layer of the optic cap becomes the neural retina, and the outer layer becomes the retinal pigmented epithelium. After retinal neurons are born, they move to their proper place, mimicking the development of CNS. However, the retina has its own mode for lamination [27]. In the retina, retinal ganglion cells and cone photoreceptors differentiate earlier, and then rod photoreceptors, bipolar cells, and Müller cells [26–28].

2.2 Normal structure of the eye

The eyeball can be divided into the anterior and posterior segments. The anterior segment includes the cornea, anterior and posterior chambers, iris, and lens. The posterior segment contains the vitreous, retina, choroid, sclera, and optic nerve (**Figure 2**). Histologically, the normal retina consists of the inner and outer segments of photoreceptors, outer nuclear layer, outer plexiform layer, inner nuclear layer, inner plexiform layer, ganglion cell layer, and nerve fiber layer (**Figure 2**). Outer segments of the photoreceptor are loosely connected to retinal pigmented epithelia. Microvilli of the pigmented epithelium surround the outer segments of photoreceptors [29]. The outer nuclear layer contains nuclei of the photoreceptors, the rod and cone. Rods are extremely sensitive to light, while cones are involved in the color vision. In the outer plexiform layer, photoreceptors form synapses between bipolar cells: roughly, rods to rod bipolar cells and cones to cone bipolar cells. Rod bipolar cells depolarize (ON) to the increase of light intensity. On the other hand, cone bipolar cells either ON or hyperpolarize (OFF) [28]. The inner nuclear layer is mainly formed by bipolar cells. Cell bodies of amacrine cells, horizontal cells, and Müller cells are also contained. In the inner plexiform layer, synapses are formed between retinal ganglion cells and bipolar cells or amacrine cells. Synapses with ON-bipolar cells are seen in the inner lamina of the inner plexiform layer and those with OFF-bipolar cells in the outer lamina [28]. In the ganglion cell layer, single to several layers of retinal ganglion cells are observed. The nerve fiber layer consisted
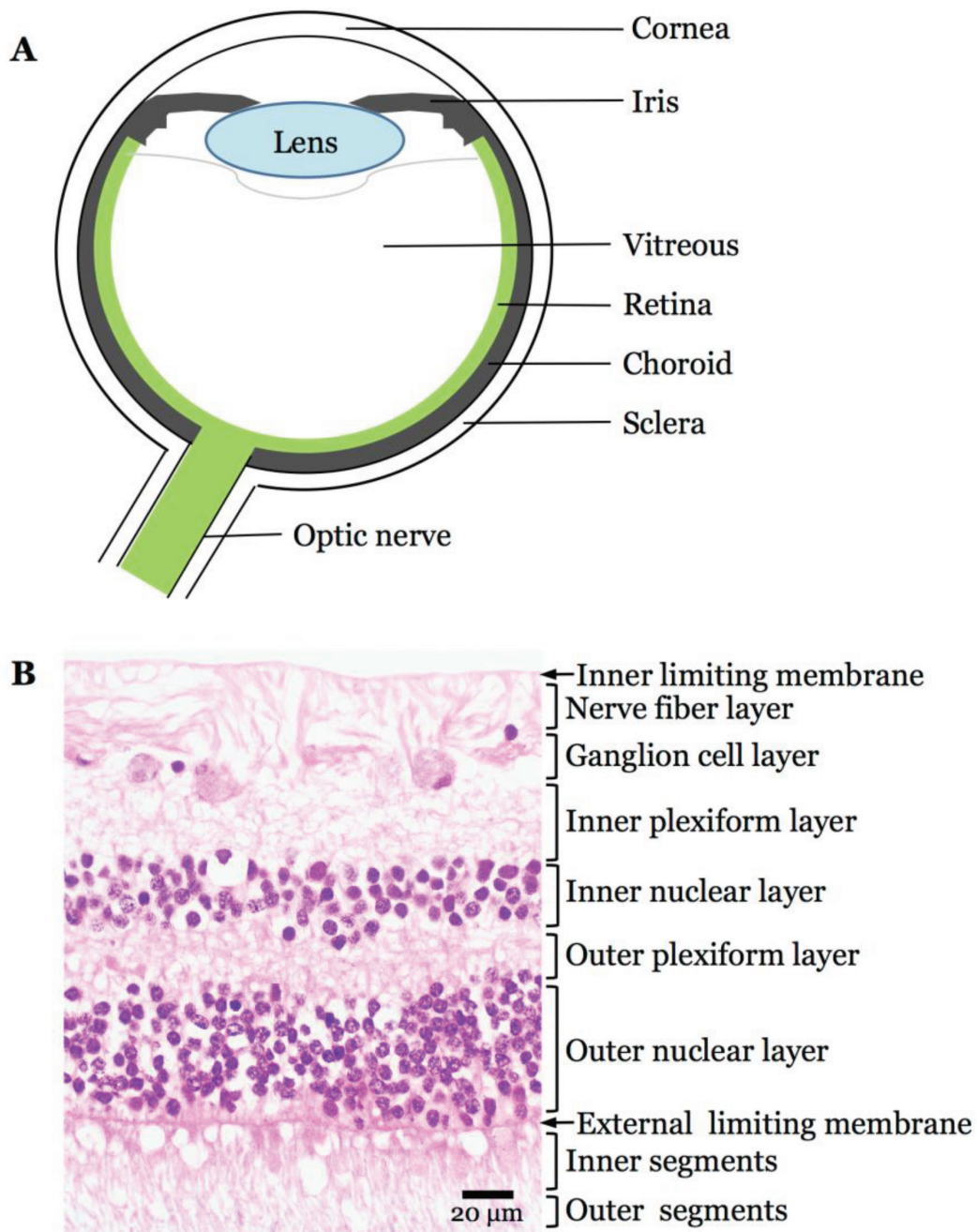
Figure 2.
(A) Schema of normal eye structure and (B) structure of normal retina.

of nerve fibers of retinal ganglion cells is situated beneath the inner limiting membrane that is formed at the inner surface of the retina by Müller cells. The external limiting membrane is formed by zonula adherens between Müller cells and inner segments of photoreceptor [29]. The basement membrane is abutted above the inner limiting membrane and beneath the basal surface of pigmented epithelium, attaching to the Bruch's membrane [29]. The basement membrane is also formed around capillaries.

3. Ocular lesions of FCMD

3.1 Clinical observations

In FCMD, both anterior and posterior components of the eye can be affected. Clinical symptoms include myopia, strabismus, and nystagmus [30–32]. Cataract,

atrophy of the optic nerve, and retinal detachment are also known. Severe cases may show microphthalmia [31]. Electroretinogram (ERG) of FCMD patients may be normal, but abnormal findings may be seen in both dark-adapted and light-adapted ERGs [32]. Patients of WWS and MEB, severe forms of α-dystroglycanopathy, also exhibit abnormalities in anterior and posterior components. In WWS, varieties of lesions are described, such as cataract, microcornea, microphthalmia, retinal detachment, retinal dysplasia, and optic atrophy [4]. Glaucoma and buphthalmos also may be observed. Clinical ocular findings of MEB reported are myopia, nystagmus, optic atrophy, and retinal degeneration [33]. ERG is abnormal as well. Like the CNS, ocular anomalies of FCMD are less severe than those of WWS and MEB [30, 31].

3.2 Histological findings

Although histological examinations of the eye of fetal FCMD cases are not so many, findings similar to those of the cerebrum can be found [31]. The inner limiting membrane is irregularly disrupted and ganglion cells exist beyond the inner limiting membrane, while there are areas exhibiting no apparent light microscopical abnormalities (**Figure 3**). Like child cases, some fetal cases may show local folding and fusion of the retina [31].

In child FCMD cases, detachment, local folding, and fusion of the retina are observed (**Figure 4**). The inner limiting membrane is discontinuous. A persistent
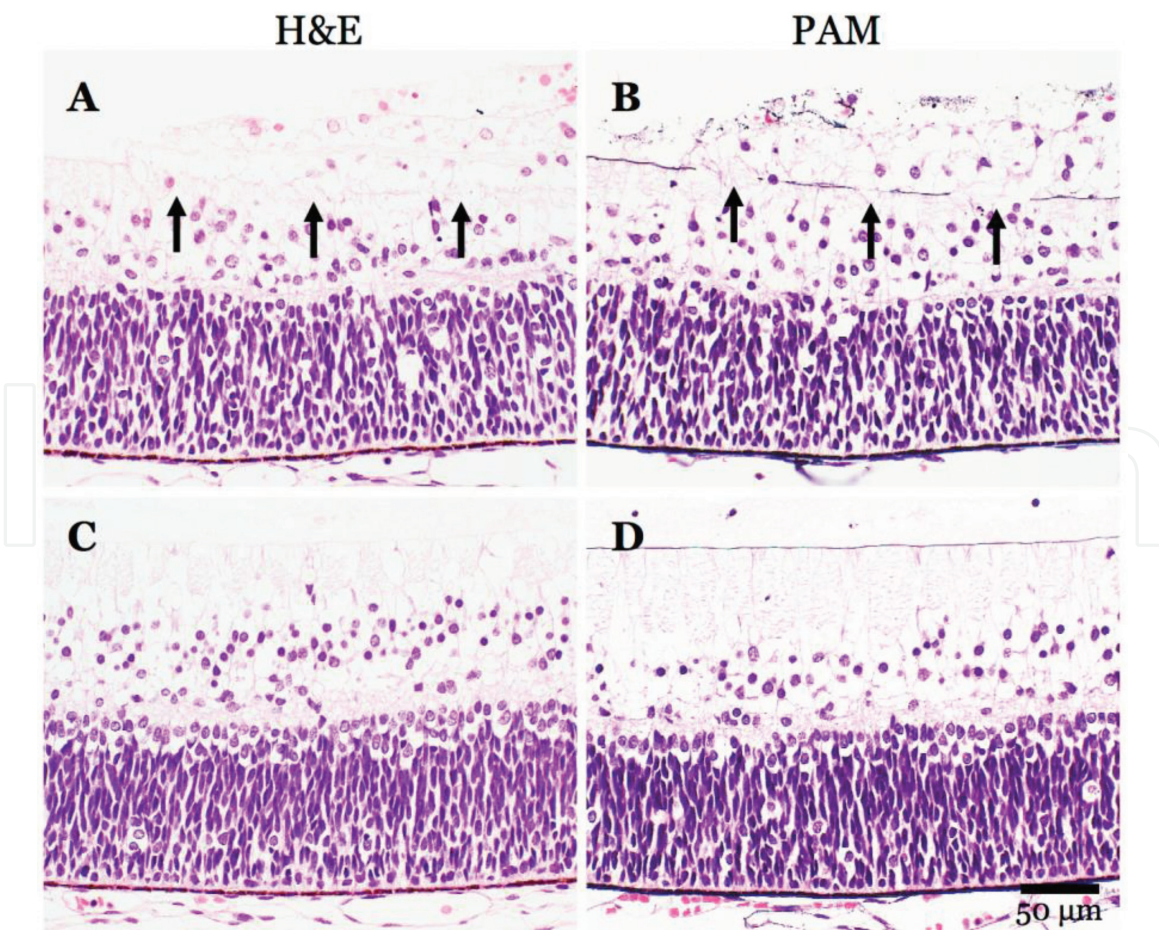

Figure 3.
Retinal findings in FCMD fetus. The internal limiting membrane, clearly depicted by PAM staining, is discontinuous in some part (A, B; arrows), while there are areas showing normal retinal appearance with continuous internal limiting membrane (C, D). Ectopic ganglion cells are observed beyond the inner limiting membrane.

hyperplastic primary vitreous body and a persistent hyaloid artery are also reported [31]. In severe cases, the layer of retina is markedly distorted with or without rosette formation. The outer and inner nuclear layers became thin in part. The layer of photoreceptor is also deranged with abnormal appearances of periodic acid-methenamine-silver (PAM)-positive structure (**Figure 4**). Reactive gliosis can be seen [31]. Severity of retinal dysplasia appears to be parallel to that of the CNS lesion [31].

3.3 Pathological consideration on retinal lesions of FCMD

In the CNS, fukutin and other related proteins are expressed in both glial cells and neurons [7, 34, 35]. Similarly, in the eye, fukutin is expressed in retinal neurons in addition to Müller cells [31, 36] (**Figure 5**).

Just above the inner limiting membrane formed by Müller cells abutted the basement membrane containing components of the DGC [37–39]. Like the CNS, abnormal basement membrane in the retinal surface may be involved in the pathogenesis of retinal dysplasia [31]. Focal fusion of the retina also may be caused by abnormal basement membrane. The glycosylation of α-DG is decreased in the inner limiting membrane of FCMD cases. Abnormalities of the basement membrane [40], decreased glycosylation of α-DG at the inner limiting membrane, and reactive gliosis [41] also have been reported in model mice of MEB. The study using α-dystroglycanopathy model mice and dystroglycan mutant mice suggest that DG is required for the maturation and maintenance of the inner limiting membrane, rather than its initial formation [42]. Retinal neurons can migrate properly under well-formed inner limiting membrane [42]. Although fukutin-null mice are lethal during pregnancy [43], the basic structure of retina and brain is relatively well kept in the early stage of the gestation of FCMD patients. Fukutin is considered to be essential for the embryogenesis. Severity of anomalies depends on a degree of functional loss of fukutin. On the brain of FCMD, lesions appear to be obvious after the second trimester. Strength of the surface structure may not catch up with the rapid increase of the volume of eye and brain. One of the interesting things is that the glycosylation of α-DG around the capillary is maintained. In POMGnT1 knock-out mice, the basement membrane of pigmented epithelium looks intact [40].

Müller cells have various roles to maintain retinal functions. One of the roles is to eliminate an excess of glutamate, a major transmitter in the retina, from the synaptic space. Glutamate is transported into Müller cells by glutamate transporter-1 (GLT-1) and metabolized to ornithine by ornithine aminotransferase (OAT) or to glutamine by glutamine synthase (GS). In FCMD patients, function of Müller cells seems to be decreased, because the expression of GLT-1, OAT, and GS is decreased [31].

In addition to the inner limiting membrane, the dystrophin-glycoprotein complex exists at presynaptic terminals of photoreceptor cells [41, 44]. As a ligand of α-DG, pikachurin is important for synaptic function between photoreceptor cells and bipolar cells [44]. In DG-knockout mice, pikachurin is markedly lost in both rod and cone photoreceptors with the loss of DG in these cells [44]. With the absence of DG, the retina becomes thin showing a decrease of photoreceptor cells, horizontal cells, and retinal ganglion cells in mice [42]. Decrease of ERG b-waves is observed in pikachurin-deficient mice and in dystroglycan-deficient mice [39]. Similar retinal lesions and abnormal ERGs are found in *fukutin-* [45], *POMGnT1-* [41], and *Pomt1-* [46] deficient mice, and *Large*[myd] and *Large*[vls] mice [47]. Hypoglycosylation of α-DG by hypofunction of fukutin and other proteins is considered to affect the function of retinal neurons as well as that of Müller cells.
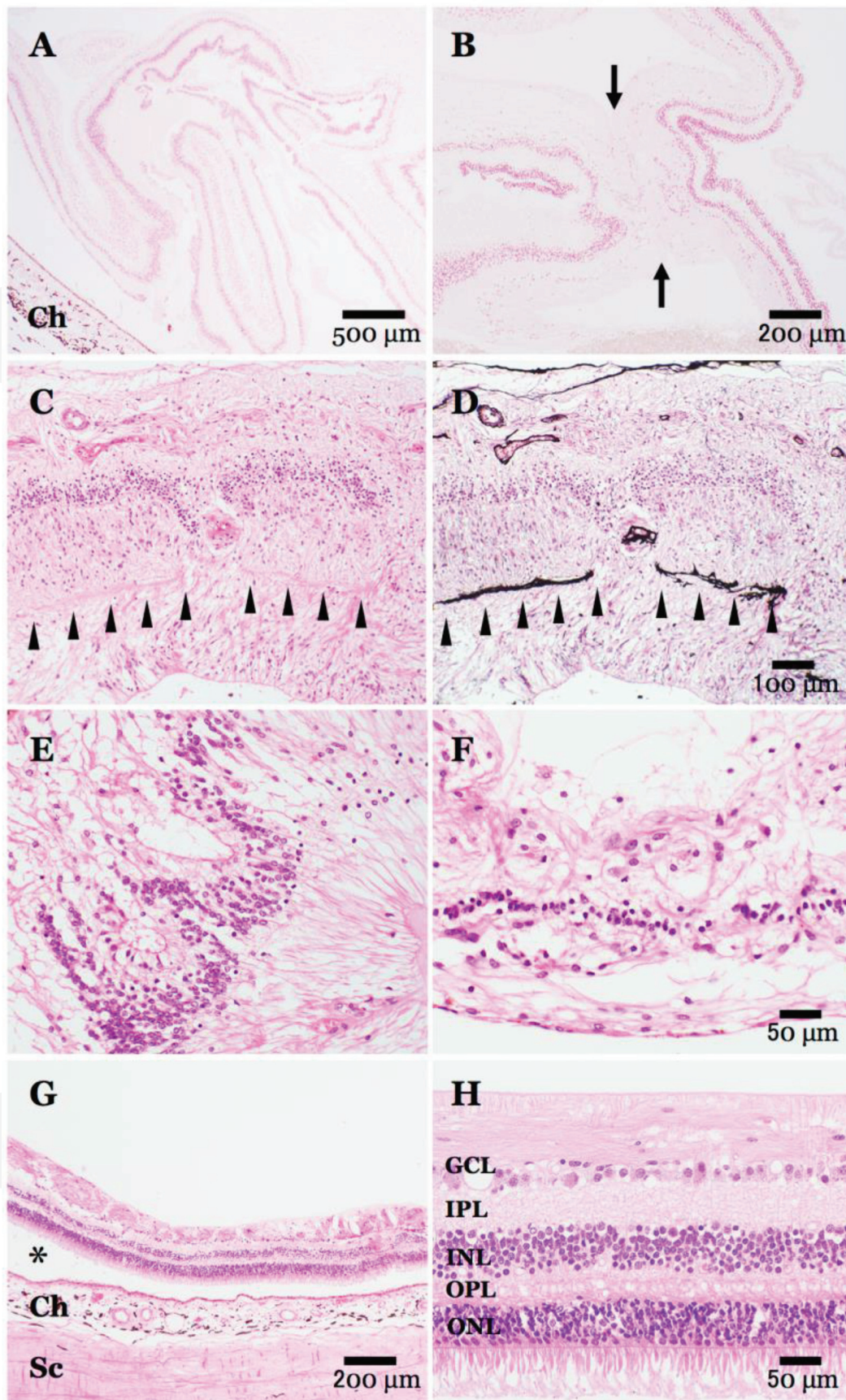
Figure 4.
Retinal findings in FCMD children. The retina is detached from the pigmented layer and abnormally folded (A, B), with focal surface fusion (arrows). In a severe case, retinal structure is abnormal with discontinuous PAM-positive structures, probably in the layer of photoreceptor cells. Normally, there is no such structure in this layer (C, D). Rosette structures are focally seen (E). The retina becomes thin with scarce retinal neurons (F). G and H show normal retina. The space indicated by the asterisk is an artifact during tissue preparation. Ch: choroid, Sc: sclera, GCL: ganglion cell layer, IPL: inner plexiform layer, INL: inner nuclear layer, OPL: outer plexiform layer, ONL: outer nuclear layer.
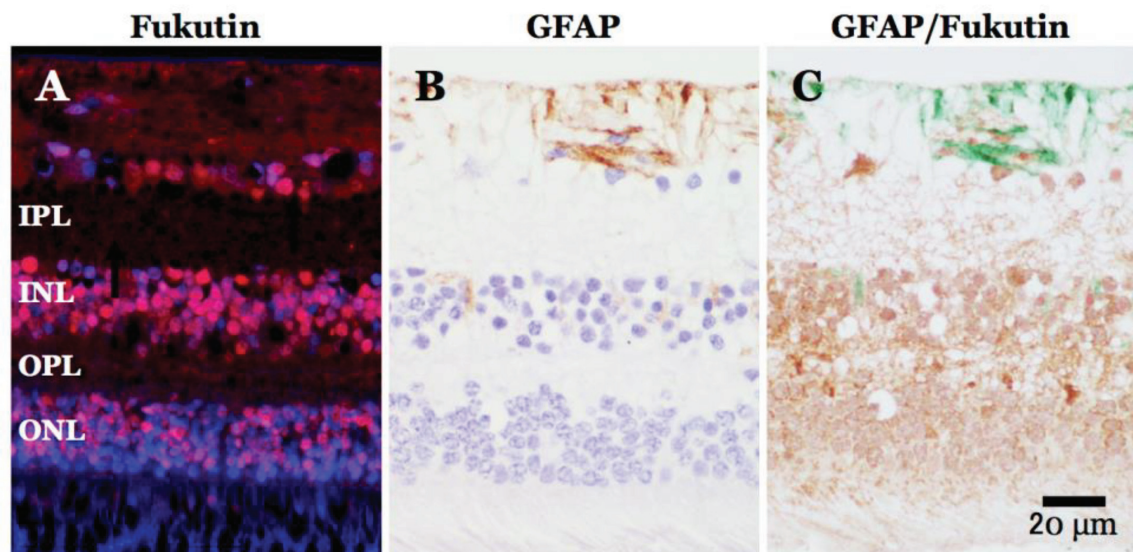
Figure 5.
Expression of fukutin in normal human retina. Fukutin is expressed in both retinal neurons and Müller cells (A–C). On fluorescent immunohistochemistry (A), fukutin is visualized in red (DAPI: blue). On Photoshop-aided double immunohistochemistry, green color indicates the elements positive for both fukutin and GFAP. IPL: inner plexiform layer, INL: inner nuclear layer, OPL: outer plexiform layer, ONL: outer nuclear layer.

Immunoreaction against antifukutin antibody is found in all the retinal layers, with stronger intensity in the inner segments of photoreceptors and in the outer plexiform layer [36]. In our immunostaining on formalin-fixed, paraffin-embedded human retina, all the layers are stained, but more intense in the outer and inner nuclear layer (**Figure 5**). This may due to the difference of tissue preparation like fixation. As for subcellular localization of fukutin, in retinal cells, it is mainly localized in the endoplasmic reticulum rather than the Golgi apparatus and in the nucleus *in vivo* [36]. Similar localization is observed in carcinoma cell lines [48]. These observations are contradict to the general consideration that fukutin is localized in the Golgi apparatus on cultured cells transfected with fukutin [3]. Further examinations are needed to explain the difference and clarify the localization of fukutin *in vivo*. If fukutin is truly localized in the endoplasmic reticulum and nucleus, this might suggest further unknown functions of fukutin, regardless of the relation to the glycosylation of α-DG.

4. Conclusions

Among severe forms of α-dystroglycanopathy like WWS, MEB, and FCMD, apparent CNS and ocular lesions are accompanied. Pathology of ocular lesions shares some characteristics common with that of CNS lesions. In this chapter, representative pathological findings of the eye of FCMD are presented, mainly focusing on the retinal dysplasia, and its pathogenesis is discussed with the review of literatures.

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Conflict of interest

The authors declared that they have no conflict of interest.

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