Clinical Genetics of Vitelliform Macular Dystrophy: An Asian Perspective

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Abstract

Vitelliform macular dystrophy (VMD) is a group of macular dystrophy characterized by the subretinal accumulation of yellow yolk-like materials which predominantly affect the macula. Best vitelliform macular dystrophy is among the most common autosomal dominant (AD) retinal dystrophy, caused by mutations in the *BEST1* gene. Since first identification of *BEST1* gene in 1998, molecular biology and pathophysiology of *BEST1* gene and vitelliform macular dystrophy were studied. Recent advances in genetic analysis have described over 200 different human *BEST1* mutations to date, associated with a broad spectrum of ocular diseases, called bestrophinopathy. However, the genotype-phenotype correlation in VMD is largely unexplored. Genetic test is clinically important in the diagnosis of VMD because the clinical features of VMD are similar to those of exudative age-related macular degeneration (AMD), choroidal neovascularization (CNV), or central serous chorioretinopathy (CSC). Here, in addition to describing the clinical characteristics of VMD, this chapter focuses on the clinical genetics of *BEST1* gene in VMD.

Keywords

Vitelliform macular dystrophy · Bestrophin-1 · Best vitelliform macular dystrophy · Adult-onset vitelliform macular dystrophy · *BEST1* gene mutation · Genome editing

21.1 Introduction

Macular dystrophy is a group of heritable disorders that cause ophthalmoscopically visible macular abnormalities. Vitelliform macular dystrophy (VMD) is a group of macular dystrophy characterized by the subretinal accumulation of yellow yolk-like materials which predominantly affects the macula. Best vitelliform macular dystrophy (BVMD) is named after Friedrich Best who described a family with a history of early-onset macular degeneration in 1905 [1]. BVMD is among the most common autosomal dominant (AD) retinal dystrophy, caused by mutations in the *BEST1* gene. Since the first identification of

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G. Prakash, T. Iwata (eds.), *Advances in Vision Research, Volume II*, Essentials in Ophthalmology,
https://doi.org/10.1007/978-981-13-0884-0_21

BEST1 gene in 1998 [2], molecular biology and pathophysiology of *BEST1* gene in VMD have been studied. Recent advances in genetic analysis have described over 200 different human *BEST1* mutations to date, associated with a broad spectrum of ocular diseases, called a bestrophinopathy [3, 4]. Bestrophinopathy includes five clinically distinct categories BVMD, adult-onset vitelliform macular dystrophy (AVMD), autosomal recessive bestrophinopathy (ARB), autosomal dominant vitreoretinochoroidopathy (ADVIRC), and retinitis pigmentosa. AVMD was first described by Gass in 1974 who initially termed it peculiar foveomacular dystrophy [5]. AVMD is one of the most common forms of macular dystrophy as well [6]. Many investigators suggested that AVMD is a mild form of BVMD within the same spectrum because the clinical features of AVMD were similar to those of early-stage BVMD and the age of onset were highly variable [7–9]. Clinically, BVMD is distinguished from AVMD by earlier age of onset, larger lesion size, and an abnormal electrooculogram (EOG). Clinical features of VMD are similar to those of exudative age-related macular degeneration (AMD), choroidal neovascularization (CNV), or central serous chorioretinopathy (CSC). Thus, genetic test is clinically important in the diagnosis of VMD. Here, in addition to describing the clinical characteristics of VMD, this chapter focuses on the clinical genetics of *BEST1* gene in VMD (BVMD and AVMD).

21.2 Epidemiology and Asian Perspective

VMD is an autosomal dominant macular dystrophy with an estimated prevalence of 1 in 10,000 in the USA [10], 2/10,000 in Sweden [11], 1.5/100,000 in Denmark [12], and 1 in 16,500 to 1 in 21,000 in Olmsted County, Minnesota, USA [13]. Males are more affected than females (3:1) [11, 12]. Despite the update of novel mutations of *BEST1* in Asian VMD patients, there was no report of the prevalence of VMD in Asian countries. Thus, a study of the prevalence of VMD with a genetic analysis in Asian countries is necessary.

21.3 Molecular Biology

The *BEST1* gene consists of 11 exons that encode the bestrophin-1 protein (585 amino acids). Bestrophin-1 is a retinal pigment epithelium (RPE) protein hypothesized to function as a Ca^{2+}-activated Cl^- channel (CaCC), or a regulator of ion transport [14]. Bestrophin-1 is predominantly expressed in the basolateral membrane of the RPE [15]. X-ray structure of chicken BEST1-Fab complexes indicates that Bestrophin-1 forms a homo-pentamer and functions as a CaCC [16]. Disease-causing mutations are prevalent within the gating apparatus. In addition, Bestrophin-1 functions as a regulator of intracellular calcium signaling and influences transepithelial electrical properties [17]. Recently, patient's stem cell-derived RPE is used for the function of bestrophin-1 and reveals that bestrophin-1 assembles into a key calcium-sensing chloride channel in human RPE [18]. Further study using RPE cells from patient-derived induced pluripotent stem cells (iPSc) harboring *BEST1* mutations is required to elucidate the exact functional role of bestrophin-1.

21.4 Clinical Features

21.4.1 BVMD

BVMD is an early-onset autosomal dominant disorder showing extremely variable penetrance and expressivity. The diagnosis of BVMD shows a bimodal age distribution; the first maximum peak was made during the childhood, but the second peak was made following puberty and extending into the sixth decade of life [19]. Before the era of genetic analysis, the diagnosis of BVMD was based on typical fundus findings, family history, and a decreased Arden ratio (light peak/dark trough) of EOG with a normal electroretinogram (ERG), which may contribute to variability of penetrance, expressivity, and onset age.

BVMD is caused by dysfunction of Bestrophin-1 protein, a CaCC protein located on the basolateral membrane of RPE, which causes abnormal fluid and ion exchange that decreases

pumping of fluid from the subretinal space, and results in swelling of RPE and subretinal lipofuscin accumulation [20]. Histopathologically, autofluorescent material was accumulated in the outer retina and the subretinal space in BVMD, which is considered as indigestible components of photoreceptor outer segments that accumulate due to the lack of direct apposition of the outer segments and the RPE [21]. Eventual phagocytosis of these older materials over time would load the RPE cells and may account for excessive accumulation of abnormal lipofuscin in RPE cells across the entire fundus [22]. These findings coincide with the decreased Arden ratio of EOG, less than 1.5, seen in BVMD, which suggest generalized dysfunction of the RPE. Even otherwise asymptomatic carriers of *BEST1* mutations will exhibit an altered EOG [23]. Full-field ERG is generally normal, but the multifocal ERG amplitudes of the central and pericentral responses were significantly reduced in the majority of patients [24]. However, the photoreceptor structure evaluated cellular imaging with adaptive optics scanning light ophthalmoscopy was retained within active BVMD lesions, even in apparently advanced disease [25, 26].

Five progressive stages can be defined based on fundus examination [20, 27]. However, these stages are not observed in all patients, nor do they occur consecutively. The first previtelliform stage is characterized by the absence of symptoms and subtle RPE changes such as RPE mottling and a small yellow spot. On optical coherence tomography (OCT), RPE and ellipsoid zone (EZ) disruption was detectable in a small fraction of eyes [28, 29]. A slight thickening of the interdigitation zone was also observed [30]. EOG is abnormal and fluorescein angiogram (FA) shows window defects. Visual acuity remains intact in most patients. The previtelliform lesions are characterized by absence or only slight autofluorescence on fundus autofluorescence (FAF) imaging.

The second vitelliform shows a well-circumscribed, circular, homogeneous, yellow-opaque, 0.5–3 disc diameter sized, yolk-like macular lesions. The remaining part of fundus usually has normal appearance, but multifocal lesions also can be seen. The accumulation of hyperreflective vitelliform material is clearly visible on OCT below the neurosensory retina, located between the EZ and the RPE. The disruption of outer retinal layers and neurosensory retinal detachment with subretinal fluid occur in many cases [28, 29]. The yellowish subretinal material is intensely hyperautofluorescent in FAF imaging. FA shows marked hypofluorescence in the zone covered by lesion by blockage of fluorescence. Metamorphopsia, blurred vision, and a decrease of central vision can occur.

In the third pseudohypopyon stage, the vitelliform material accumulates inferiorly and develops a fluid level. On OCT, the upper part of the lesion is observed as hyporeflective area located between RPE and EZ, with clumping of hyperreflective material on the posterior retinal surface. The lower part of the lesion, where the vitelliform material is still accumulated, shows a highly reflective area located in the subretinal space. FA shows hypofluorescence in the lower part resulted from the blockage by the vitelline material. The superior part shows hyperfluorescent due to transmission defects linked to RPE and chorioretinal atrophy in the early phase. FAF shows loss of autofluorescence, particularly in the upper part.

The fourth vitelliruptive stage is characterized by the partial reabsorption of the vitelliform material. This vitelliform material becomes less homogeneous to develop a "scrambled-egg" appearance. OCT shows an optically empty lesion between EZ and RPE, with clumping of hyperreflective material on the posterior retinal surface like the upper part of the pseudohypopyon. The areas of focal RPE hypertrophy can be observed as hyperreflective mottling on the RPE layer on some parts. FAF shows decreased of autofluorescence centrally but increased autofluorescence at the outer border of the lesion.

In the last atrophic/fibrotic stage, RPE atrophy and loss of central vision occur after rupture and reabsorption of the cystic lesion. FA shows hyperfluorescence without leakage. OCT reveals thinning of all the retinal layers and diffuse disappearance of outer retinal layers within the macular area, with highly hyperreflective thickening at the RPE level [29, 31]. Atrophic lesions are characterized by decreased autofluorescence on FAF.

Choroidal neovascularization (CNV) may develop and can lead to form a disciform scar. Patients usually underwent sudden visual disturbance with central scotoma and/or metamorphopsia, showing a macular hemorrhage on fundus examination. In that case, FA shows hyperfluorescence because of CNV and leakage. Intravitreal injection of anti-vascular endothelial growth factor (VEGF) agent was effective in treating CNV complicated with BVMD and safe even in children [32–34].

Patients with BVMD undergo a progressive decrease of vision over time. In a study that evaluated the course of visual decline of 53 patients in BVMD with *BEST1* mutation [35], the median age of onset of visual symptoms was 33 years. Twenty-five percent of patients retain visual acuity of 20/40 or better at the age of 66 years. Other study evaluated 47 patient with BVMD; 74% of patient older than 30 years had 20/100 or worse visual acuity at least one eye [36].

21.4.2 AVMD

Gass reported a three-generation family and six sporadic patients characterized by one-third disc diameter sized bilateral subfoveal vitelliform lesions with onset between the ages of 30 and 50 years accompanied by slowly progressive visual loss as "peculiar foveomacular dystrophy." They also showed occasional paracentral drusen, normal to slightly subnormal response on EOG but normal ERG and color vision [5]. AVMD shows a variable genetic inheritance, although most cases are sporadic [37]. Patients with AVMD may be asymptomatic but become symptomatic in the fourth or fifth decade of life with blurred vision, metamorphopsia, or scotoma and typically have slow progression of vision loss [38]. Patients with AVMD typically present a round, yellowish subretinal deposit in one-third to one disc diameter size within the macular area, similar fundus finding to the vitelliform stage of BVMD.

The initial yellow lesion may present in only one eye and appear as small yellow flecks in the paracentral area. EOG shows a normal or slightly reduced Arden ratio, which is obviously abnormal in BVMD. The macular lesion appears as hyperautofluorescent in FAF. The vitelliform deposit usually appears as initially hypofluorescent but gradually becomes hyperfluorescent on the edges by staining of the dye in FA [39] and hypofluorescent on indocyanine green angiography (ICGA). OCT reveals a dome-shaped hyperreflective lesion located between the retina and RPE [40]. The foveal thinning and EZ disruption are also observed and probably explain the progressive visual loss [41, 42].

AVMD progression is characterized by fragmentation and reabsorption of the vitelliform material [6]. Macular atrophy progressively replaces the vitelliform deposits at the advanced stages of the disease in most cases [42], but most patients retain reading vision throughout life [43, 44]. CNV may be complicated in few cases; 6 out of 51 patients developed CNV after a 6-year follow-up [45]. Anti-VEGF therapies have shown to be effective in the treatment of CNV associated with AVMD [46].

21.5 Genetic Aspects

21.5.1 BVMD

Currently, only genetic test for mutation analysis of the *BEST1* gene leads to confirmation of a clinical diagnosis of BVMD. Note that individuals with clinical findings of BVMD occasionally have a normal EOG, turning out to have a pathogenic variant of *BEST1* [47]. In case of atypical BVMD [3], genetic test for confirmation should be performed. Over 200 *BEST1* mutations with significant clinical heterogeneity require a thorough genetic analysis and clinical examinations to better understanding of genotype-phenotype correlations in BVMD. Most mutations of *BEST1* gene in BVMD and AVMD are missense mutations. Table 21.1 shows a list of missense mutations of *BEST1* gene in BVMD and AVMD.

Most genetic studies were performed in Western countries including the USA, England, Sweden, Denmark, Germany, the Netherlands, Italy, and France. *BEST1* mutations are extremely

Table 21.1 *BEST1* missense mutations in BVMD and AVMD

	Mutations a.a	Mutation nucleotide	Associated isease	Inheritance	Ethnicity	References
1	Thr2Ala	c.4A > G	BVMD	AD	Japanese	[48, 49]
			AVMD	AD	Iowa, USA	
2	Thr2Asn	c.5C > A	BVMD	AD	Chinese	[50]
3	Thr2Ile	c.5C > T	AVMD	AD	Iowa, USA	[49]
4	Ile3Asn	c.8 T > A	Atypical BVMD	AD	USA	[51]
5	Ile3Thr	c.8 T > C	BVMD	AD	Dutch	[52]
6	Thr4Ala	c.10A > G	BVMD	AD	French	[53]
7	Thr4Ile	c.11C > T	AVMD	AD	Chinese	[54, 49]
					Iowa, USA	
8	Tyr5His	c.13 T > C	AVMD	AD	Iowa, USA	[49]
9	Tyr5Term	c.15C > A	Multifocal	AD	French	[55]
			BVMD			
10	Thr6Ala	c.16A > G	BVMD	De novo	USA	[56]
11	Thr6Arg	c.17C > G	BVMD	AD	Iowa, USA	[57, 58]
				AD	USA or Swiss	
12	Thr6Lys	c.17C > A	AVMD	AD	Iowa, USA	49,
13	Thr6Pro	c.16A > C	BVMD	AD	Dutch	[59, 52, 60–62, 2]
			BVMD	AD	Dutch	
			Multifocal	AD	Dutch	
			BVMD			
			AVMD	AD	German	
			BVMD	AD	Dutch	
			BVMD	AD	Dutch	
14	Ser7Asn	c.20G > A	BVMD	AD	Japanese	[48]
15	Val9Ala	c.26 T > C	AVMD	AD	French	[53, 2]
					Swedish	
16	Val9Glu	c.26 T > A	BVMD	Unknown	Portuguese	[63]
17	Val9Leu	c.25G > C	BVMD	AD	USA	[64, 49]
			AVMD	AD	Iowa, USA	
18	Val9Met	c.25G > A	BVMD	AD	German	[65, 61, 66]
			BVMD	AD	German	
			BVMD	AD	German	
19	Ala10Thr	c.28G > A	BVMD	AD	German	[61, 66]
			BVMD	AD	German	
20	Ala10Val	c.29C > T	BVMD	AD	Dutch	[59, 62]
			BVMD	AD	Dutch	
21	Asn11Ile	c.32A > T	BVMD	AD	German	[67]
22	Arg13Cys	c.37C > T	AVMD	AD	Iowa, USA	[49]
23	Arg13His	c.38G > A	BVMD	AD	Chinese	[54, 68]
			BVMD	AD	USA	
24	Arg13Pro	c.38G > C	AVMD	AD	Iowa, USA	[49]
25	Gly15Arg	c.43G > C	BVMD	AD	Slovenian	[69]
26	Gly15Asp	c.44G > A	BVMD	AD	Italian	[53]
27	Ser16Phe	c.47C > T	BVMD	AD	Chinese	[70, 71]
			BVMD	AD	French	
28	Ser16Tyr	c.48C > A	BVMD	AD	Dutch	[59, 60]
			Multifocal	AD	Dutch	
			BVMD			

(continued)

Table 21.1 (continued)

	Mutations a.a	Mutation nucleotide	Associated isease	Inheritance	Ethnicity	References
29	Phe17Cys	c.50 T > G	BVMD	AD	French	[71, 58]
				AD	USA or Swiss	
30	Phe17Ser	c.50 T > C	AVMD	AD	Iowa, USA	[49]
31	Arg19Leu	c.56G > T	AVMD	AD	Iowa, USA	[49]
32	Leu20Val	c.58C > G	BVMD	AD	Danish	[12]
33	Leu21Val	c.61C > G	BVMD	AD	German	[61, 72]
			BVMD	AD	English, Canadian	
34	Trp24Cys	c.72G > T	BVMD	AD	USA or Swiss	[58, 66]
			BVMD	AD	German	
35	Arg25Gln	c.74G > A	BVMD	AD	German	[66]
36	Arg25Trp	c.73C > T	BVMD	AD	Japanese	[48, 53, 73, 58, 61]
			BVMD	AD	French	
			BVMD	AD	Italian	
			BVMD	AD	USA or Swiss	
			BVMD	AD	German	
37	Gly26Arg	c.76G > C	BVMD	AD	German	[67]
38	Ser27Arg	c.81C > G	BVMD	AD	German	[61]
39	Tyr29His	c.85 T > C	BVMD	AD	German	[67]
40	Lys30Arg	c.89A > G	BVMD	AD	USA or Swiss	[58]
41	Lys30Asn	c.90G > C	AVMD	AD	Iowa, USA	[49]
42	Glu35Lys	c.103G > A	BVMD	Unknown	Portuguese	[63]
43	Leu41Pro	c.122 T > C	BVMD	AD	German	[67]
44	Arg47Cys	c.139C > T	AVMD	AR	Iowa, USA	[49]
45	Arg47His	c.728C > T	BVMD	AD	Chinese	[70, 61]
			AVMD	AD	German	
46	Gln58Leu	c.173A > T	BVMD	AD	German	[65, 61]
			BVMD	AD	German	
47	Tyr72Asp	c.214 T > G	AVMD	AD	Iowa, USA	[49]
48	Ile73Asn	c.218 T > A	BVMD	AD	French	[71]
49	Ile73Phe	c.217A > T	BVMD	AD	USA	[64]
50	Leu75Phe	c.223C > T	BVMD	AD	Chinese	[50]
51	Ile76Asn	c.227 T > A	AVMD	AD	Iowa, USA	[49]
52	Ile76Val	c.226A > G	BVMD	AD	Iowa, USA	[49]
53	Phe80Leu	c.240C > A	BVMD	AD	Japanese	[48, 58]
			BVMD	AD	USA or Swiss	
54	Phe80Val	c.238 T > G	BVMD	AD	USA	[64]
55	Val81Met	c.241G > A	BVMD	AD	Japanese	[48, 49]
			BVMD	AD	Iowa, USA	
56	Leu82Val	c.244C > G	BVMD	AD	Danish	[12, 74, 52, 62]
			BVMD	AD	German	
			BVMD	AD	Dutch	
			BVMD	AD	Danish	
57	Phe84Val	c.250 T > G	AVMD	AD	Iowa, USA	[49]

(continued)

Table 21.1 (continued)

	Mutations a.a	Mutation nucleotide	Associated isease	Inheritance	Ethnicity	References
58	Tyr85His	c.253 T > C	BVMD	AD	Danish	[12, 74, 2]
			BVMD	AD	Danish	
			BVMD	AD	Swedish	
59	Val89Ala	c.266 T > C	BVMD	AD	Swedish	[75]
60	Thr91Ile	c.272C > T	BVMD	AD	French	[53, 58]
				AD	USA or Swiss	
61	Arg92Cys	c.274C > T	BVMD	AD	Italian,	[53, 62]
					French	
			BVMD	AD	Swedish	
62	Arg92Gly	c.274C > G	AVMD	AD	Italian	[53]
63	Arg92His	c.275G > A	BVMD	AD	Danish	[12, 74, 71]
			BVMD	AD	Danish	
			BVMD	AD	French	
64	Arg92Ser	c.274C > A	BVMD	AD	German	[65, 61]
			BVMD	AD	German	
65	Trp93Arg	c.277 T > C	AVMD	AD	Iowa, USA	[49]
66	Trp93Cys	c.279G > C	BVMD	AD	Swedish	[2]
67	Gln96Arg	c.287A > G	BVMD	AD	Danish	[12]
68	Gln96Glu	c.286C > G	AVMD	AD	Iowa, USA	[49]
69	Gln96His	c.288G > C	BVMD	AD	Dutch	[59, 62]
			BVMD	AD	Dutch	
70	Asn99Lys	c.297C > A	BVMD	AD	German	[61]
71	Asn99Tyr	c.295A > T	BVMD	AD	Iowa, USA	[49]
72	Leu100Arg	c.299 T > G	BVMD	AD	German	[67, 61]
			BVMD	AD	German	
73	Pro101Leu	c.302C > T	AVMD	AD	Iowa, USA	[49]
74	Pro101Thr	c.301C > A	BVMD	AD	USA or Swiss	[58]
75	Tryp102Arg	c.304 T > C	BVMD	AD	German	[67]
76	Asp104Glu	c.312C > A	BVMD	AD	Swedish	[2]
77	Asp104His	c.301G > C	BVMD	AD	German	[67]
78	Arg105Gly	c.313G > C	BVMD	AD	Slovenian	[69]
79	Phe113Leu	c.339C > G	BVMD	AD	Chinese	[76]
80	Arg130Ser	c.388C > A	BVMD	AD	USA	[64]
81	Asn133Lys	c.399C > G	BVMD	AD	USA or Swiss	[58]
82	Leu134Val	c.400C > G	BVMD	AD	Dutch	[59, 77, 60]
			BVMD	AD	French	
			Multifocal BVMD	AD	Dutch	
83	Gly135Ser	c.403G > A	BVMD	AD	USA or Swiss	[58, 62]
			BVMD	AD	Swedish	
84	Leu140Arg	c.419 T > G	BVMD	AD	USA or Swiss	[58]
85	Arg141His	c.422G > A	BVMD	AD	USA or Swiss	[58, 61]
				AD	German	
86	Arg141Ser	c.421C > A	BVMD	AR	Iowa, USA	[49]

(continued)

Table 21.1 (continued)

	Mutations a.a	Mutation nucleotide	Associated isease	Inheritance	Ethnicity	References
	Val143Phe	c.427G > T	AVMD	AD	Iowa, USA	[49]
87	Ser144Asn	c.431G > A	BVMD	AD	Chinese	[70, 50]
			BVMD	AD	Chinese	
88	Ser144Gly	c.430A > G	Multifocal	AD	French	[55]
			BVMD			
89	Ala195Val	c.584C > T	BVMD	AD	Japanese	[48, 59, 60, 67, 58]
			BVMD	AD	Dutch	
			Multifocal	AD	Dutch	
			BVMD	AD	German	
			BVMD	AD	USA or Swiss	
90	Ile201Thr	c.602 T > C	BVMD	AD	USA or Swiss	[58]
91	Ser209Asn	c.626G > A	BVMD	AD	English, Canadian	[61]
92	Leu211Thr	c.632 T > C	BVMD	AD	USA or Swiss	[58]
93	Arg218Cys	c.652C > T	BVMD	AD	Chinese	[54, 12, 67, 71, 50, 58, 62, 68]
			BVMD	AD	Danish	
			BVMD	AD	German	
			BVMD	AD	French	
			BVMD	AD	Chinese	
			BVMD	AD	USA or Swiss	
			BVMD	AD	Dutch	
			BVMD	AD	USA	
94	Arg218Gly	c.652C > G	BVMD	AD	Italian	[73]
95	Arg218His	c.653G > A	BVMD	AD	Japanese	[48, 59, 71, 58]
			BVMD	AD	Dutch	
			BVMD	AD	French	
			BVMD	AD	USA or Swiss	
96	Arg218Ser	c.652C > A	BVMD	AD	German	[67, 62]
			BVMD	AD	Swedish	
97	Arg218Gln	c.654 T > G	BVMD	AD	Dutch	[66]
98	Gln220Pro	c.659A > C	AVMD	AD	Iowa, USA	[49]
99	Cys221Phe	c.662G > T	BVMD	AD	Iowa, USA	[49]
100	Cys221Trp	c.663 T > G	BVMD	De novo	Italy	[78]
101	Gly222Glu	c.665G > A	BVMD	AD	Japanese	[48]
102	Gly222Val	c.665G > T	BVMD	AD	USA or Swiss	[58]
103	Leu224Met	c.670C > A	BVMD	AD	German	[61]
104	Leu224Pro	c.671 T > C	BVMD	AD	USA or Swiss	[58]
105	Tyr227Asn	c.679 T > A	BVMD	AD	Dutch	[59, 58, 66, 2]
			BVMD	AD	USA or Swiss	
			BVMD	AD	Dutch	
			BVMD	AD	Dutch	
106	Tyr227Cys	c.680A > G	BVMD	AD	USA or Swiss	[58, 66]
			BVMD	AD	Dutch	

(continued)

Table 21.1 (continued)

	Mutations a.a	Mutation nucleotide	Associated isease	Inheritance	Ethnicity	References
107	Tyr227Phe	c.680A > T	BVMD	AD	German	[79]
108	Trp229Gly	c.685 T > G	BVMD	AD	Chinese	[80]
109	Ile230Asn	c.689 T > A	AVMD	AD	Iowa, USA	[49]
110	Ile230Trh	c.689 T > C	BVMD	AD	French	[53]
111	Ser231Arg	c.693 T > G	BVMD	AD	German	[61]
112	Ser231Thr	c.692G > C	BVMD	AD	French	[77]
113	Ile232Asn	c.695 T > A	BVMD	AD	German	[79]
114	Pro233Ala	c.697C > G	BVMD	AD	Swedish	[81]
115	Pro233Gln	c.698C > A	BVMD	AD	French	[77]
116	Pro233Leu	c.698C > A	AVMD	AD	Iowa, USA	[49]
117	Leu234Pro	c.698C > T	BVMD	Unknown	USA	[18]
118	Val235Leu	c.703G > C	BVMD	AD	French	[71]
119	Val235Met	c.703G > A	BVMD	AD	Dutch	[66]
120	Thr237Arg	c.710C > G	BVMD	AD	German	[67, 61]
			BVMD	AD	German	
121	Thr237Ser	c.709A > T	BVMD	AD	German	[79]
122	Thr241Asn	c.722C > A	BVMD	AD	German	[67]
123	Val242Met	c.724G > A	BVMD	AD	Japanese	[48]
124	Ala243Thr	c.727G > A	BVMD	AD	Danish	[12, 61, 58]
			BVMD	AD	German	
			BVMD	AD	USA or Swiss	
125	Ala243Val	c.728C > T	BVMD	AD	Italian	[53, 67, 61]
			BVMD	AD	German	
			AVMD	AD	German	
126	Arg255Trp	c.763C > T	BVMD	AD	Chinese	[50]
127	Pro274Arg	c.821C > G	AVMD	AR	Iowa, USA	[49]
128	Phe276Leu	c.828C > G	BVMD	AD	USA or Swiss	[58]
129	Tyr284Cys	c.851A > G	BVMD	AD	Iowa, USA	[49]
130	Arg291Val	c.872C > T	BVMD	AD	Chinese	[54]
131	Glu292Lys	c.874G > A	BVMD	AD	Chinese	[70, 82]
			BVMD	AD	USA	
132	Gln293His	c.879G > C	BVMD	AD	Chinese	[54], 77]
			BVMD	AD	French	
133	Gln293Lys	c.877C > A	BVMD	AD	Dutch	[59, 62]
			BVMD	AD	Dutch	
134	Leu294Val	c.880C > G	BVMD	AD	German	[67]
135	Ile295Thr	c.884 T > C	BVMD	AD	German	[67, 83]
			BVMD	AD	Japanese	
136	Ile295Val	c.883A > G	BVMD	AD	Iowa, USA	[49]
137	Asn296His	c.886A > C	BVMD	AD	USA or Swiss	[58]
138	Asn296Lys	c.891C > A	Multifocal	AD	Dutch	[60]
			BVMD			
139	Asn296Ser	c.887A > G	BVMD	AD	Danish	[12, 71]
			BVMD	AD	French	
140	Pro297Ala	c.889C > G	BVMD	AD	USA or Swiss	[58, 66]
			BVMD	AD	Dutch	
141	Pro297Ser	c.889C > T	BVMD	AD	Iowa, USA	[49]

(continued)

Table 21.1 (continued)

	Mutations a.a	Mutation nucleotide	Associated isease	Inheritance	Ethnicity	References
142	Pro297Thr	c.889C > T	BVMD	AD	Chinese	[50]
143	Phe298Cys	c.893 T > G	BVMD	AD	USA	[64]
144	Phe298Ser	c.893 T > C	BVMD	AD	Dutch	[59, 60, 67]
			Multifocal	AD	Dutch	
			BVMD			
			BVMD	AD	German	
145	Phe298Val	c.892 T > G	BVMD	Unknown	English	[84]
146	Gly299Ala	c.896G > C	BVMD	AD	Dutch	[59, 52]
			BVMD	AD	Dutch	
147	Gly299Arg	c.895G > A	BVMD	AD	French	[77]
148	Gly299Glu	c.896G > A	BVMD	AD	Swedish	[2]
149	Glu300Asp	c.900G > C	BVMD	AD	Iowa, USA	[49, 58, 68]
			BVMD	AD	USA or Swiss	
			BVMD	AD	USA	
150	Glu300Lys	c.898G > A	BVMD	AD	Chinese	[70, 61, 58]
			BVMD	AD	German	
			BVMD	AD	USA or Swiss	
151	Asp301Asn	c.901G > A	BVMD	AD	German	[61]
152	Asp301Glu	c.903 T > G	BVMD	AD	German	[65, 67, 61, 68]
			BVMD	AD	German	
			BVMD	AD	German	
			BVMD	AD	USA	
153	Asp301Gly	c.902A > G	BVMD	AD	Chinese	[50, 54]
			BVMD	AD	Chinese	
154	Asp302Ala	c.905A > C	BVMD	AD	Danish	[12, 64, 59]
			BVMD	AD	USA	
			BVMD	AD	Dutch	
155	Asp302Asn	c.904G > A	BVMD	AD	Danish	[12]
156	Asp302Gly	c.905A > G	BVMD	AD	USA or Swiss	[58]
157	Asp302His	c.904G > C	BVMD	AD	French	[85]
158	Asp302Val	c.905A > T	BVMD	AD	USA or Swiss	[58]
159	Asp303Asn	c.907G > A	BVMD	AD	Italian	[86]
160	Asp303Glu	c.909 T > A	BVMD	AD	French	[85]
161	Asp303Gly	c.908A > G	AVMD	AD	Iowa, USA	[49]
162	Asp304Asn	c.910G > A	AVMD	AD	Iowa, USA	[49]
163	Asp304Gly	c.911A > G	BVMD	AD	Italian	[86]
164	Asp304Val	c.911A > T	BVMD	Unknown	Portuguese	[63]
165	Phe305Leu	c.915 T > A	BVMD	AD	Italian	[47]
166	Phe305Ser	c.914 T > C	BVMD	AD	Dutch	[66]
167	Phe305Tyr	c.914 T > A	AVMD	AD	Iowa, USA	[49]
168	Glu306Asp	c.918G > C	BVMD	AD	Japanese	[48, 58]
			BVMD	AD	USA or Swiss	
169	Glu306Gly	c.917A > G	BVMD	AD	USA or Swiss	[58]
170	Thr307Asp	c.920C > A	BVMD	AD	Chinese	[70]
171	Thr307Ala	c.919A > G	BVMD	AD	USA or Swiss	[58]

(continued)

Table 21.1 (continued)

	Mutations a.a	Mutation nucleotide	Associated isease	Inheritance	Ethnicity	References
172	Thr307Ile	c.902C > T	BVMD	AD	USA or Swiss	[58, 68]
				AD	USA	
173	Asn308Ser	c.923A > G	BVMD	AD	French	[85]
174	Trp309Arg	c.925 T > C	AVMD	AD	Iowa, USA	[49]
175	Ile310Thr	c.929 T > C	BVMD	AD	Germany	[61]
176	Val311Gly	c.932 T > G	BVMD	AD	Germany	[61]
177	Asp312Asn	c.934G > A	AVMD	AD	Germany	[61]
178	Asp312Glu	c.936C > A	BVMD	AD	Danish	[12, 74]
			BVMD	AD	Danish	
179	Gln316His	c.948G > T	AVMD	AR	Iowa, USA	[49]
180	Gln316Pro	c.947A > C	AVMD	AD	Iowa, USA	[49]
181	Pro346His	c.1037C > A	BVMD	AD	Japanese	[48]
182	Val492Ile	c.1474G > A	AVMD	AD	Iowa, USA	[49]
183	Glu557Lys	c.1669G > A	AVMD	AD	Iowa, USA	[49]

heterogenous, but several mutations have been frequently found (Thr6Pro, Arg25Trp, Arg218Cys, Tyr227Asn, Arg243Val, Ile295del, Gle300Asp, Asp301Glu, and Asp302Asn). Interestingly, these frequent mutations are ethnic specific (44.4% of Asp302Asn in Danish [12] and 36.8% of Arg25Trp in Italian [86]).

Currently, only limited reports are available in Asian genetic studies of BEST1 from Chinese [50, 54, 70, 76, 80, 87–89], Japanese [48, 83], and Korean [9]. The mutation spectrum of the *BEST1* gene in Asian patients of BVMD is differed from those in Western patients [88]. Six novel missense mutations (Thr2Asn, Leu75Phe, Ser144Asn, Arg255Trp, Pro297Thr, and Asp301Gly) and one previously reported mutation (Arg218Cys) were identified [50]. Three novel mutations Tyr4Ile [54], Ala291Val [54], and Phe113Leu [76] in BVMD were reported. Lin [80] reported two novel heterozygous mutations 304delAsp and Trp229Gly in Chinese BVMD patients. Liu [70] reported four previously reported mutations (Ser16Phe, Ser144Asn, Glu292Lys, and Glu300Lys) and two novel disease-causing mutations (Thr307Asp, Arg47His) in Chinese patients with BVMD.

In Japanese study [48], 22 patients including 16 probands from 16 families with BVMD were analyzed. All 16 probands exhibited characteristic BVMD fundus appearances, abnormal EOG, and normal ERG responses with the exception of one diabetic retinopathy proband. Genetic analysis identified 12 BEST1 variants in 13 probands (81%). Of these, ten variants (Tyr2Arg, Arg25Trp, Phe80Leu, Val81Met, Ala195Val, Arg218His, Gly222Glu, Val242Met, Asp304del, and Glu306Asp) have been previously reported in BVMD, while two variants (Ser7Asn and Pro346His) were novel disease-causing mutations.

In Korea, we report a BVMD patient (Fig. 21.1) carrying Asn296Lys mutation which is a causative mutation of multifocal BVMD in German patient [60]. Arg218Leu is a novel disease-causing mutation in BVMD (Fig. 21.2). These findings expand the spectrum of *BEST1* genetic variation in Asian and will be valuable for genetic counseling for patients with BVMD [88].

BVMD shows variable expressivity and incomplete penetrance at the clinical level. Disease-causing effect of *BEST1* mutations seems to be cumulative over time [79]. In genotype-phenotype relationship of Dutch study [59], median age of onset of visual symptoms was 33 years (range, 2–78). The cumulative risk of VA below 0.5 (20/40) was 50% at 55 years and 75% at 66 years. The cumulative risk of VA decline less than 0.3 (20/63) was 50% by age 66 years and 75% by age 74 years. Most patients (96%) had missense mutations; the Thr6Pro, Ala10Val, and Tyr227Asn mutations were most common. Visual decline was significantly faster in patients with an Ala10Val mutation than either the Thr6Pro or the Tyr227Asn mutation.

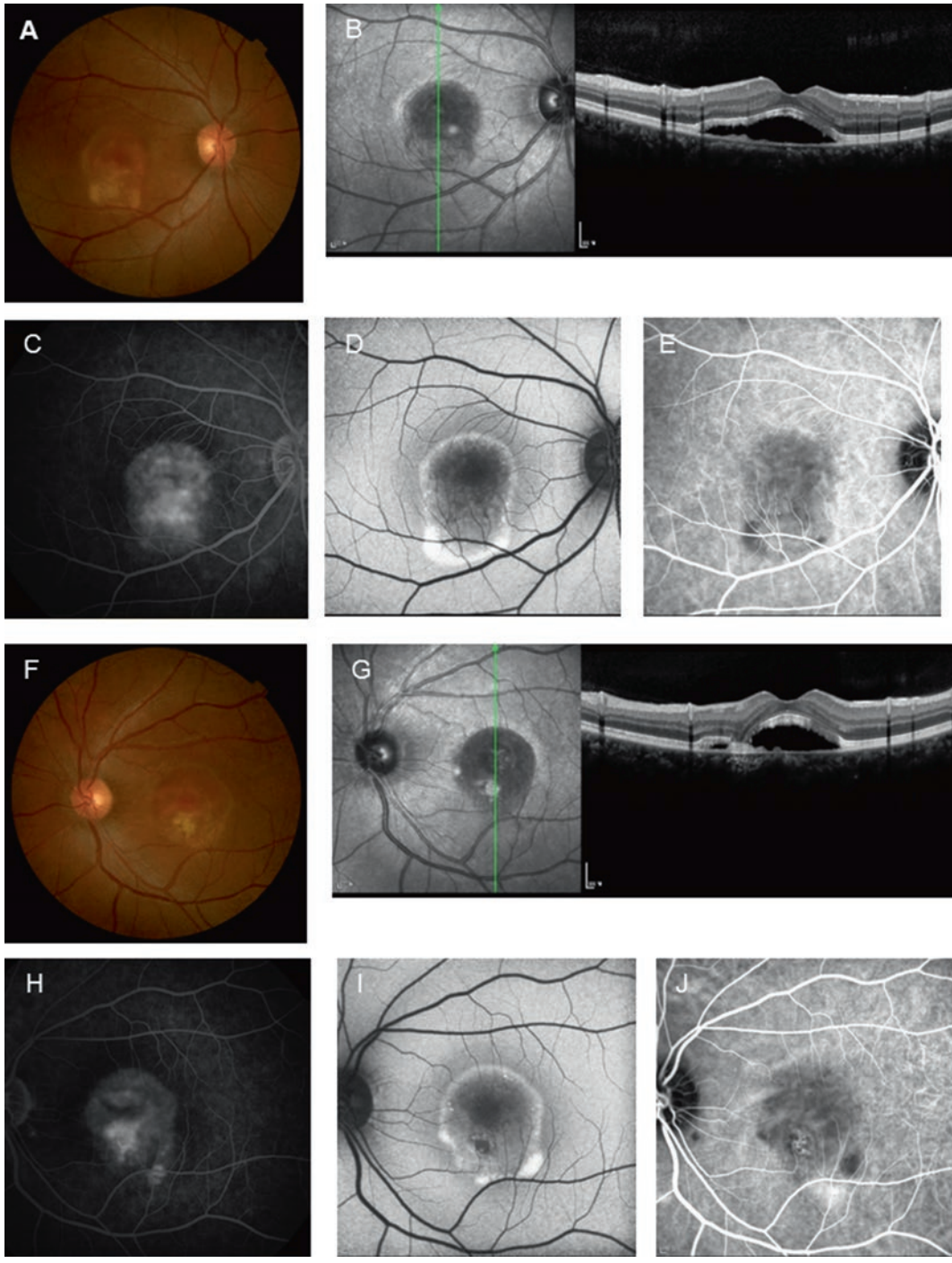

Fig. 21.1 Best vitelliform macular dystrophy (BVMD). A 32-year-old man carrying p.Asn296Lys mutation in the *BEST1* gene was incidentally found on routine fundus examination for a pilot license. The visual acuities (VA) were 20/20 in both eyes. (**a**, **f**) Bilateral BVMD of vitelliruptive stage shows scattered yellow-white vitelliform deposits. (**b**, **g**) Vertical optical coherent tomography (OCT) shows serous retinal detachment and hyperreflective vitelliform materials at RPE in both eyes. (**c**, **h**) Fluorescein angiography (FA) shows late pooling of fluorescein dye at the egg lesion. (**d**, **i**) Fundus autofluorescence (FAF) image of the vitelliruptive lesion shows increased autofluorescence at inferior part of ruptured vitelliform lesions and at the border of the serous retinal detachment. (**e**, **j**) Indocyanine green angiography (ICGA) shows active leakage spot in the left eye

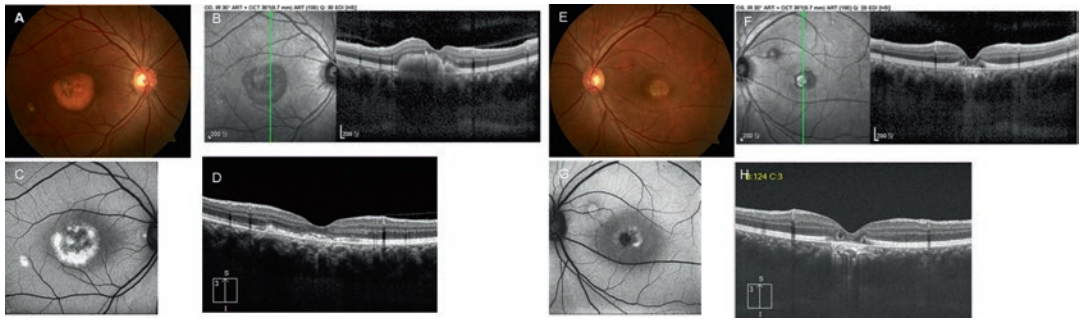

Fig. 21.2 Best vitelliform macular dystrophy (BVMD). A 39-year-old man carrying Arg218Leu mutation in the *BEST1* gene had multiple injections of anti-VEGF agents (ten for right eye and five for left eye) in both eyes. At initial visiting in our institute, vitelliform stage of right eye (**a**) reveals highly reflective subfoveal pillar without surrounding SRF (**b**). Small round vitelliform lesion with central cicatricial change was found in the left eye (**e**). OCT reveals marked RPE loss at the fovea (**f**). Six months later, FAF shows dispersed materials with hyperautofluorescent (**c**), and OCT reveals the disappearance of subfoveal pillar with a progression to vitelliruptive stage (**d**) in the right eye. FAF shows central hypoautofluorescent and surrounding hyperfluorescent lesions. OCT reveals that hypoautofluorescent lesion corresponds to the enlarged RPE loss (**h**)

In the recent Chinese study, despite typical macular appearance of BVMD, no clear genotype-phenotype correlation was observed [88]. In Asian BVMD cohort, genetic tests should be performed for the diagnosis with thorough clinical examinations to elucidate a genotype-phenotype correlation.

21.5.2 AVMD

In AVMD, several mutations in *BEST1* gene have been identified including p.Ala146Lys [90], p. Thr6Pro, p.Arg47His, P.Ala243Val, p.Asp312Asn [61], and p.Ile38Ser [9]. Table 21.1 includes the list of missense mutations in AVMD. In addition, AVMD is associated with mutations in *PRPH2* [91], *IMPG1* [92], *IMPG2* [93].

Age of onset is a major criterion to distinguish BVMD from AVMD [64]. Thus, systematic screening of *BEST1* and *PRPH2* has been suggested in BVMD and AVMD. *BEST1* screening should be recommended to patients with an age of onset less than 40 years, and *PRPH2* screening should be recommended to patients with an age of onset more than 40 years. For an onset between 30 and 40 years, *PRPH2* can be screened if no mutation has been detected in *BEST1*. In this screening approach, we found *PRPH2* mutation of p.Pro219_Pro221delinsPro in a 39-year-old female without *BEST1* mutation (Fig. 21.3).

21.6 Future Perspectives for Therapy

The development of gene and cell therapies is promising in various retinal diseases. Indeed, the results of clinical trials using iPSC-derived RPE cells in wet age-related macular degeneration [94] or AAV/RPE65 vectors in Leber's congenital amaurosis [95] were already reported. Therapeutic intervention of inherited retinal dystrophy should be primarily aimed at the restoration of normal gene (i.e., *BEST1* gene in BVMD and AVMD). However, until decade ago, this therapeutic goal was ideal but unachievable due to the lack of a proper biotechnology. Recent advances in genome editing technology using CRISPR system and gene delivery system are promising and harness the CRISPR-based genome editing for the therapeutic applications. Since its first therapeutic applications in retinal disease using wet AMD animal models [96, 97], in vivo genome editing using CRISPR-Cas9 enlarged its therapeutic applications both in genetic diseases harboring mutations [98, 99] and nongenetic degenerative diseases [96, 97, 100].

Conventional concept of gene therapy to deliver normal copy of *BEST1* gene into RPE would be effective in the treatment of VMD of haploinsufficiency phenotype, which is caused by *BEST1* mutations that exclusively result in a loss of sufficient wild-type protein. In addition,

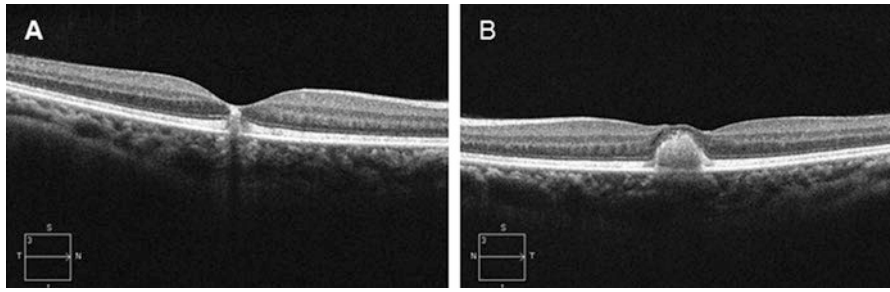

Fig. 21.3 Adult-onset vitelliform macular dystrophy (AVMD). A 39-year-old woman carrying Pro219_Pro221delinsPro in *PRPH2* gene suffered from dysmorphopsia of the right eye. OCT reveals subfoveal vitelliform lesion in the right eye (**a**) and left eye (**b**)

simple destruction of mutant proteins at the DNA level is achievable by genome editing of mutant *BEST1* allele using CRISPR-Cas9.

Currently, many BEST1 mutations cause VMD through dominant negative effect. In addition, over 200 mutations of *BEST1* gene, large amounts of *BEST1* mutations are missense mutations; thus, a precise base-editing using base-editors enables a literally complete recovery of normal gene [101, 102]. According to the recent advances in genome editing technology using CRISPR system, in vivo genome editing has emerged as a potential treatment strategy for inherited retinal dystrophies [103].

21.7 Summary

VMD is among the most common autosomal dominant macular dystrophy. Multimodal imaging with SD-OCT, FAF, FA, and ICGA is useful to the diagnosis of VMD. Genetic test is clinically important in the diagnosis of VMD because the clinical features of VMD can be similar to those of exudative AMD, CNV, or CSC. Future studies are needed to identify the prevalence with precise genetic mutations of *BEST1* in Asian VMD patients. This could provide a clear genotype-phenotype correlation in VMD. *In vitro* studies using RPE cells from patient-derived iPSC help to understand molecular biology of bestrophin-1 protein. Furthermore, in vivo genome editing using CRISPR-based base-editors might be a potential treatment strategy for the correction of missense mutations in VMD.

Compliance with Ethical Requirements Sung Wook Park, Chang ki Yoon, Dae Joong Ma, Un Chul Park, and Hyeong Gon Yu declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on institutional review board and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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