

Stargardt's Disease and Best's Vitelliform Macular Dystrophy : The Major Common Forms of Juvenile Macular Dystrophies



Günther Rudolph

Eye Hospital,
Ludwig-Maximilians-University
D-80336 München, Mathildenstrasse 8,
Germany

Abstract : Stargardt's disease (OMIM #248200/STGD1, chromosome 1p21-p13) and Best's vitelliform macular dystrophy (OMIM #607854/VMD2, chromosome 11q13) are the most common forms of macular dystrophies. The onset of the disease is variable, but often symptoms become apparent in the first or second decade of life with reduced visual acuity. Stargardt's disease is a recessive genetic disorder, while Best's disease is inherited as a dominant trait. The underlying mechanisms of these two diseases are only partly understood until now. In Stargardt's disease intraepithelial accumulation of a lipofuscin-like substance is a characteristic feature, creating retinal flecks and an so called "fundus flavimaculatus". Mutations in the ABCA4 gene seem to be the origin of the disease. Even more striking is the fact, that mutations in the ABCA4 transporter gene not only cause Stargardt's disease or fundus flavimaculatus, but also atypical retinitis pigmentosa or cone-rod dystrophy. Best's disease is characterized by subretinal accumulation of lipofuscin-like material resulting in an atrophic lesion at the posterior pole of the eye. The clinical expression is highly variable. The disease is the result of mutations in the VMD2-gene. VMD2 encodes bestrophin, a transmembrane protein with putative Ca²⁺-dependent chloride channel activity at the basolateral portion of the retinal pigment epithelium.

Key Words : Stargardt disease, STGD1, Best vitelliform macular dystroph, VMD2

Introduction :

In 1909, the German ophthalmologist Karl Stargardt described for the first time the features of a specific juvenile macular dystrophy (Stargardt, 1909). Franceschetti proposed, due to the presence of white spots around the lesion at the posterior pole of the eye, the name "fundus flavimaculatus" (Franceschetti and Francois, 1965). Today it is clear, that based on clinical, electrophysiological and moleculargenetic findings, Stargardt macular dystrophy without "fundus flavimaculatus" and "fundus flavimaculatus" are

* **Corresponding author :** Phone : +49 89 5160 3800; FAX : +49 89 5160 4569
Email : Guenther.Rudolph@med.uni-muenchen.de

different clinical manifestations of the same disease (OMIM #248200/STGD1) [Lois *et al.*, 2001; Rudolph *et al.*, 2002]. Histopathologic studies in Stargardt's disease could demonstrate an enrichment of lipofuscin-like material in the retinal pigment epithelium (RPE) (Birnbach *et al.*, 1994). ABCA4 mutations, located on chromosome 1, seem to be responsible for the development of Stargardt's disease. A combination of ABCA4 alleles with various functional consequences to protein activity can lead to different clinical phenotypes in different or in one and the same family, resulting either in typical Stargardt's disease, or in autosomal recessive retinitis pigmentosa. Mutations in the ABCA4 gene are also discussed to be causative for the development of autosomal recessive cone-rod dystrophy or age-related macular dystrophy (Rivera *et al.*, 2000).

Vitelliform macular dystrophy (OMIM #607854/VMD2), or Best's disease is named after the German ophthalmologist Friedrich Best, who published this disease in 1905 (Best, 1905). This juvenile macular dystrophy is characterized by subretinal accumulation of lipofuscin-like material in the macular area, leading to atrophic alterations of the RPE and retina. This macular dystrophy may be present at birth or develop decades later. Funduscopy may reveal various stages of the disease, from unremarkable up to the cicatricial stage (Gass, 1997; Rudolph and Kalpadakis, 2003). Best's vitelliform macular dystrophy is an autosomal dominant disease caused by mutations in the VMD2-gene located on the long arm of chromosome 11.

Patients and methods

We demonstrate two patients, a mother and a son, with mutations in the ABCA4 gene. The parents of the son were consanguineous. Clinical examination included measurement of visual acuity, perimetry, scanning-laser ophthalmoscope microperimetry, funduscopy, color vision testing, autofluorescence and electro-retinography (Ganzfeld-ERG, mfERG).

The patients with Best's disease showed autosomal dominant inheritance with eight affected persons over four generations. Clinical examination were the same as in patients with Stargardt's disease, completed by an electroculogram (EOG).

Results

Stargardt's Disease

Funduscopy in Fig. 1 the mother (I) revealed a "bronze-beaten"

appearance at the posterior pole of the eye. The periphery showed a normal retina. Visual acuity for distance was 0.08/0.08. Fluorescence angiography demonstrated pigment epithelium defects in the macula with consecutive hyperfluorescence. Scotopic ERG values were normal, while photopic 30Hz flicker stimulation showed reduced amplitudes (50%). Scanning-laser ophthalmoscope microperimetry showed a central scotoma (Fig. 1). Molecular genetic analysis demonstrated a heterozygote missense-mutation in exon 42 (5882G>A / codon G1961E) and a deletion at nucleotide position 5917 (5917delG / V 1973 stop mutation) in exon 43 of the ABCA4 gene, resulting in an In-frame-stop-codon, which interrupts protein-translation.

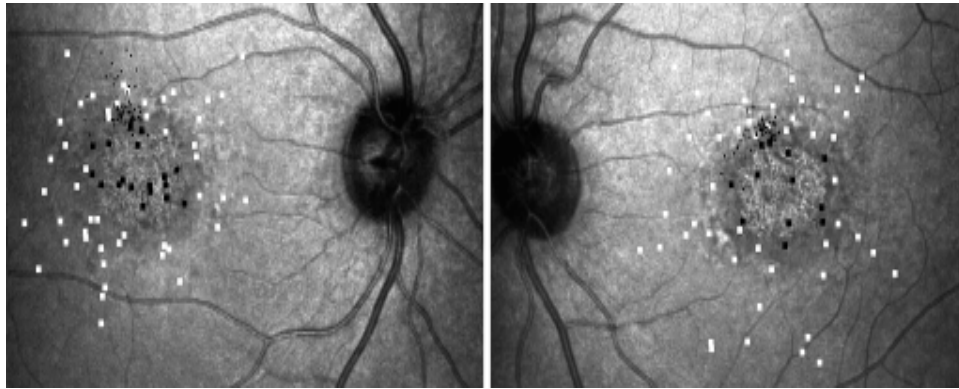


Fig. 1 : Patient I (mother) with Stargardt disease showing a “bronze beaten” appearance at the posterior pole. Scanning-laser ophthalmoscope microperimetry demonstrates a central scotoma covering the visible lesion on the retina. (White points – seen, dark spots – not seen)

Funduscopy in Fig. 1 the son (II) showed pigment epithelium mottling and a tapetoid reflex at the posterior pole, while in the periphery marked pigment epithelium dispersion and so called “bone spicules” were present, a typical finding in patients with retinitis pigmentosa (Fig. 2). Visual acuity was 0.06/0.06. Scotopic and photopic ERG values were markedly reduced, consistent with tapetoretinal degeneration. Visual acuity was poor and night-blindness was present since early childhood.

Molecular genetic analysis revealed no mutation in exon 42, but a homozygous deletion at nucleotide position 5917 / V 1973 stop mutation in exon 43 (Fig. 3). This means, that there exists no functional protein at all. Best disease

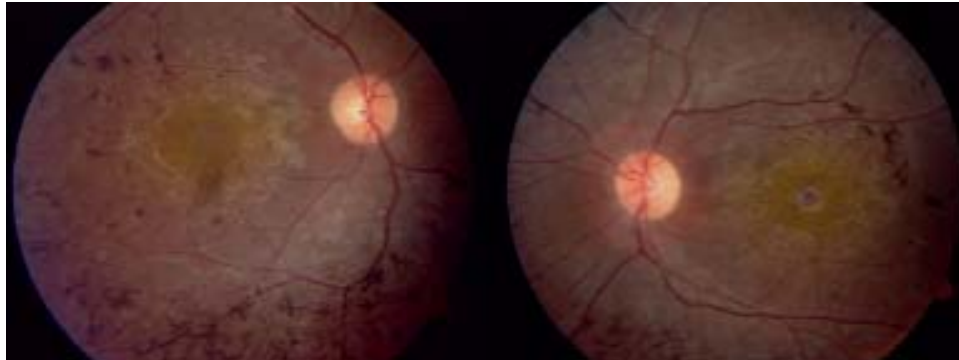


Fig. 2 : Patient II (son) with Stargardt disease showing retinal changes typical for retinitis pigmentosa with retinal pigment epithelium mottling and atrophy at the posterior pole as well as pigment epithelium atrophy in the peripheral retina with so called “bone spicules”, representing pigment accumulation.

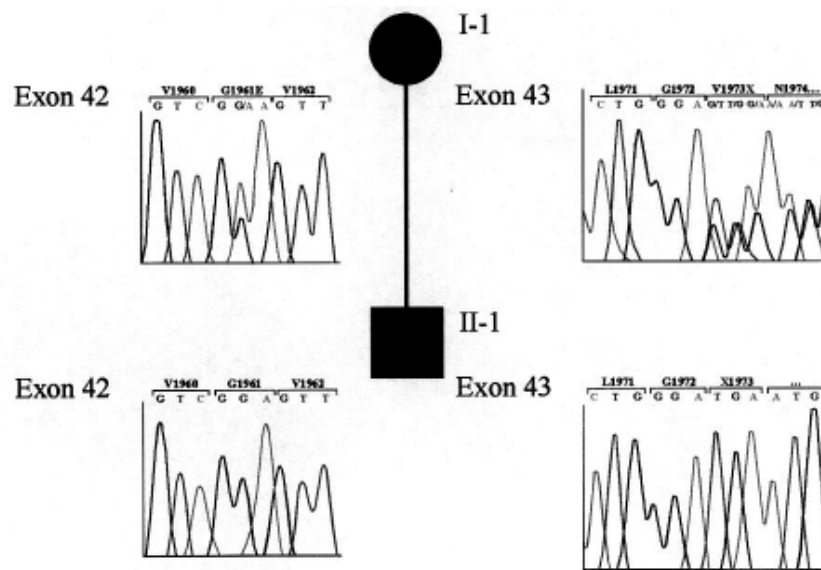


Fig. 3 : Analysis of exon 42 and exon 43 in the Stargardt patients I and II. Patient I (mother), being a compound heterozygote, shows the G1961E and the V1973 stop mutation. Patient II (son) has a V1973 stop mutation on both alleles, leading to truncation of the ABCA4 gene product.

Best's vitelliform macular dystrophy

In a four generation family with 7 affected individuals clinical and molecular genetic analysis was performed. The younger patients with an egg-yolk stage showed normal visual acuity, while in the patients with the

“scrambled egg” stage or the atrophic stage visual acuity was markedly reduced (Fig. 4). Analysing the 10 coding exons of the bestrophin-gene with exon-flanking oligonucleotide primers revealed a heterozygous mutation in nucleotide position 728 from cytosine to thymine (C728), resulting in an amino-acid change in codon 243 from alanine to valine (Ala243Val).

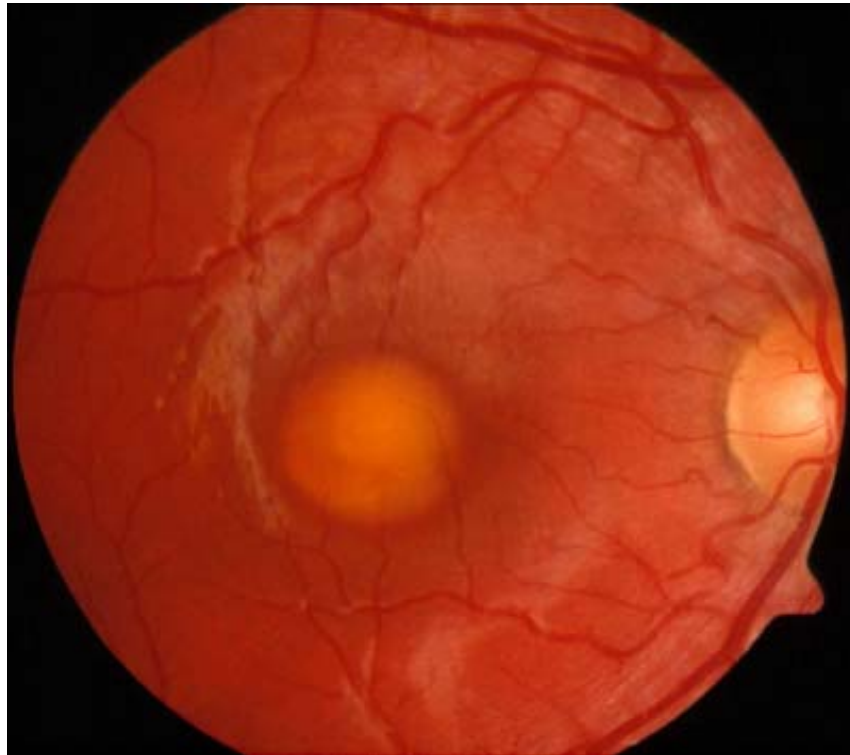


Fig. 4 : Fundusphotography in a young girl with Best disease, showing a typical “egg yolk” lesion in the foveal region at the posterior pole of the eye.

Further mutations in other families are summarized in <http://www.uni-wuerzburg.de/humangenetics/vmd2.html>.

Discussion :

Mutations in ABCA4, which encodes a photoreceptor specific ATP-binding cassette transporter, seem to be responsible for the development of Stargardt's disease (Allikmets *et al.*, 1997). The ABC-transporter family belongs to a group of membrane proteins involved in energy dependent transport of a variety of substances across membranes. ABCA4 is coding for

Rudolph G. (2006) *Asian J. Exp. Sci.*, 20 (Supplement), 45-52

a protein located at the rim of outer segments of rod and cones regulating the transport of all-trans-retinal aldehyde (atRAL) from the cytoplasmic to the cytosolic part of the photoreceptor membrane (Wenig *et al.*, 1999; Molday *et al.*, 2000). Slowed kinetics of the retinoid cycle and accelerated deposition of lipofuscin-like material in the retinal pigment epithelium (RPE) is assumed leading to morphological changes and reduced visual function (Cideciyan *et al.*, 2004). Different extents of RPE and photoreceptor loss and lipofuscin accumulation in different areas of the retina are not definitely understood.

A large number of mutations in the ABCA4 gene are known, summarized in <http://www.uwcm.ac.uk/uwcm/mg/search/370748.html> (Klevering *et al.*, 2005). But there also many allelic variants. Many patients show compound heterozygosity for missense mutations. In the patients described here, the mother presented with Stargardt's disease, caused by a missense mutation in exon 42, probably followed by a incomplete protein, while in exon 43 a null mutation was present. The son revealed on both alleles of exon 43 a null mutation, resulting in a frameshift and stop codon, leading to retinitis pigmentosa (RP19) (Rudolph *et al.*, 2002). We could demonstrate that the combination of ABCA4 alleles with various functional consequences to protein activity can produce different clinical phenotypes in one and the same family, resulting either in typical Stargardt's disease or in autosomal recessive retinitis pigmentosa (RP19).

Best's vitelliform macular dystrophy is an autosomal dominant macular dystrophy with lipofuscin-like deposits at the posterior pole of the eye. The phenotype varies considerably and is characterized either by the previtelliform stage with RPE defects, the egg-yolk stage with yellow material in a cyst, the scrambled egg stage, the pseudohypopyon appearance or finally the atrophic or cicatricial stage, sometimes complicated by subretinal neovascularisation (Gass, 1997; Mohler and Fine, 1981). Histopathological studies disclosed deposits of lipofuscin on Bruch's membrane, the innermost layer of which is the basal membrane of the retinal pigment epithelium (Weingeist *et al.*, 1982). Multifocal vitelliform lesions are rare. In contrast to Stargardt's disease fundusoscopic changes proceed visual impairment. Best's vitelliform macular dystrophy is caused by mutations in the VMD2 gene (Kramer *et al.*, 2000). VMD2 encodes bestrophin, a transmembrane protein with putative Ca²⁺-dependent chloride channel activity at the retinal pigment epithelium. The pathogenetic effect is most likely based on a dominant negative influence by oligomerization of normal and mutated bestrophin molecules to form a

defective ion channel (Stöhr *et al.*, 2005). Different mechanisms may produce distinct phenotypes with VMD2 mutations.

Insights in the genetic basis and the pathomechanism of these diseases will hopefully provide specific therapeutic possibilities. With regard to future therapeutic approaches, early recognition and classification of patients with ABCA4 or VMD2 associated retinal disorders is becoming increasingly important.

References :

Allikmets R. *et al.* (1997) : A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. *Nat Genet* **15**, 236-246

Best F. (1905) : Über eine hereditäre Maculaaffektion. *Z Augenheilkunde* **13**, 199-212

Birnbach C. D. *et al.* (1994) : Histopathology and immunocytochemistry of the neurosensory retina in fundus flavimaculatus. *Ophthalmology* **101**, 1211-1219

Cideciyan A. V. *et al.* (2004) : Mutations in ABCA4 result in accumulation of lipofuscin before slowing of the retinoid cycle: a reappraisal of the human disease sequence. *Hum Mol Genet* **13**, 525-534

Franceschetti A. and Francois J. (1965) : Fundus flavimaculatus. *Arch Ophthalmol* **25**, 505-530

Gass J. D. M. (1997) : Heredodystrophic disorders affecting the pigment epithelium and retina. In: Gass JDM (ed) *Stereoscopic Atlas of Macular Disease – Diagnosis and Treatment, Vol. 1, 4th edn. Mosby, St. Louis*, pp 303-436

Klevering B. J. *et al.* (2005) : The spectrum of retinal phenotypes caused by mutations in the ABCA4 gene. *Graefe's Arch Clin Exp Ophthalmol* **243**, 90-100

Kramer F. *et al.* (2000) : Mutations in the VMD2 gene are associated with juvenile-onset vitelliform macular dystrophy (Best disease) and adult vitelliform macular dystrophy but not age-related macular degeneration. *Eur J Hum Genet* **8**, 286-292

Lois H. *et al.* (2001) : Phenotypic subtypes of Stargardt's macular dystrophy-fundus flavimaculatus. *Arch Ophthalmol* **119**, 359-369

Molday L. L. *et al.* (2000) : ABCR expression in foveal cone photoreceptors and its role in Stargardt macular dystrophy. *Nat Genet* **25**, 257-258

Mohler C. W. and Fine S. L. (1981) : Long-term evaluation of patients with Best's vitelliform dystrophy. *Ophthalmology* **88**, 688-692

Rivera *et al.* (2000) : A comprehensive survey of sequence variation in the ABCA4 (ABCR) gene in Stargardt disease and age-related macular degeneration. *Am J Hum Genet* **67**, 800-813

Rudolph G. (2006) *Asian J. Exp. Sci.*, 20 (Supplement), 45-52

Rudolph G. *et al.* (2002) : Mutations in the ABCA4 gene in a family with Stargardt's disease and retinitis pigmentosa (STGD1/RP19). *Klin Mbl Augenheilk* **219**, 590-596

Rudolph G. and Kalpadakis P. (2003) : Topographic mapping of retinal function with the SLO-mfERG under simultaneous control of fixation in Best's disease. *Ophthalmologica* **217**, 154-159

Stargardt K. (1909) : Über familiäre, progressive Degeneration in der Makulagegend des Auges. *Graefe's Arch Clin Exp Ophthalmol* **71**, 534-550

Stöhr H. *et al.* (2005) : VMD2 and its role in Best's disease and other retinopathies. *Ophthalmologie* **102**, 116-121

Weingeist T. A. *et al.* (1982) : Histopathology of Best's macular dystrophy. *Arch Ophthalmol* **100**, 1108-1114

Wenig *et al.* (1999) : Insights into the function of Rim protein in photoreceptors and etiology of Stargardt's disease from the phenotype in *abr* knockout mice. *Cell* **98**, 13-23

