

Functional study of SCCD pathogenic gene *UBIAD1* (Review)

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Abstract. Schnyder's crystalline corneal dystrophy (SCCD) is a rare autosomal dominant genetic disorder that is characterized by progressive corneal opacity, owing to aberrant accumulation of cholesterol and phospholipids in the cornea. A number of SCCD affected families have been reported in the world since 1924, when it was first described. In 2007, the molecular basis of SCCD was demonstrated to be associated with a tumor suppressor, UbiA prenyltransferase domain-containing 1 (*UBIAD1*), which was isolated from the bladder mucosa and demonstrated to be involved in vitamin K₂ and CoQ10 biosynthesis. This sterol triggers the binding of *UBIAD1* to 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGCR) at endoplasmic reticulum (ER) membranes, which is regulated by an intracellular geranylgeranyl diphosphate (GGpp) molecule. The inability of SCCD-associated *UBIAD1* to bind GGpp results in the consistent binding of *UBIAD1* to HMGCR at ER membranes. This binding leads to HMGCRs being redundant. Therefore, they cannot be degraded through ER-associated degradation to synthesize abundant cholesterol in tissue cells. Excess corneal cholesterol

accumulation thus leads to SCCD disease. After decades, the efforts of numerous ophthalmologists and scientists have helped clarify the molecular basis and pathogenesis of SCCD, which has guided the effective diagnosis and treatment of this genetic disorder. However, more studies need to be conducted to understand the pathogenesis of SCCD disease from a genetic basis by studying the defective gene, *UBIAD1*. Results would guide effective diagnosis and treatment of the inherited eye disease.

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1. Introduction

Schnyder's crystalline corneal dystrophy (SCCD; MIM 121800) is a rare autosomal dominant genetic disorder that is characterized by progressive bilateral corneal opacity, owing to abnormal accumulation of cholesterol and phospholipids in the cornea (1). The occurrence is equal in both sexes and progressive opacity in the cornea leads to visual loss and eventually blindness (2). In 1924, French ophthalmologists Van Went and Wibaut first reported eight patients from a family within this pedigree who recorded symptoms of corneal opacity in both eyes (3). The Swiss ophthalmologist Schnyder described the clinical manifestations and genetic characteristics of this eye disease in 1927, 1929 and 1939 (4,5). On the basis of his detailed elucidation, this special corneal disease was named Schnyder's crystalline corneal dystrophy (SCCD) (6). In 2007, Orr *et al* (7), Weiss *et al* (8) and Yellore *et al* (9), for the first time, demonstrated that a potential prenyltransferase, UbiA prenyltransferase domain-containing 1 (*UBIAD1*), was the causal gene responsible for SCCD, independently. Weiss *et al* and Yellore *et al* also confirmed that the loci of *UBIAD1* associated with SCCD were located on chromosome short arm 1, region 36 (8,9). After decades, the pathogenesis of SCCD was finally elucidated and linked to the *UBIAD1* gene.

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Abbreviations: SCCD, Schnyder's crystalline corneal dystrophy; *UBIAD1*, UbiA prenyltransferase domain-containing 1; *TERE1*, transitional epithelial response gene 1; HMGCR, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase; GGpp, geranylgeranyl diphosphate; ROS, reactive oxygen species; ERAD, endoplasmic reticulum-associated degradation

Key words: Schnyder's crystalline corneal dystrophy, UbiA Prenyltransferase Domain Containing 1, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, cholesterol biosynthesis, ER-associated degradation

UBIAD1, also known as transitional epithelial response gene 1 (TERE1), was obtained through reverse transcription from the human bladder mucosal extracted RNA. This cDNA fragment was novel and different from the existing full-length gene. Therefore, it was named TERE1. TERE1 is located at the band 6 short arm of region 3 of human chromosome 1 (1p36) and expresses two transcripts (1.5 and 3.5 kb), which are widely present in various human tissues but absent or down-regulated in bladder muscle-invasive cell carcinoma (10). These two transcripts were deposited in NCBI with accession numbers AF117064 and NM_013319. The two transcripts also harbor the same open reading frame and encode the UBIAD1 protein. Additionally, formation of these two transcripts is due to alternative splicing (10). This newly identified TERE1 gene was mapped to chromosome 1 p36.11-p36.33 between the microsatellite markers D1S2667 and D1S434, through loss of heterozygosity studies, by McGarvey *et al* (11), who also demonstrated a 61% reduced expression of the TERE1 transcriptome in prostate cancer cells. After expressing TERE1 in prostate cancer cell lines LNCAP and PC-3, the cell proliferation rate was reduced by 80%, indicating that TERE1 was a potential tumor suppression factor (11).

To further understand the function of TERE1, McGarvey *et al* (12) then isolated TERE1-interacted protein apolipoprotein E through bacterial two-hybrid assays. Results demonstrated that this gene reduced the p42/44 MAPK phosphorylation level in human 293 cells. In 2007, different teams confirmed the molecular basis of SCCD (7-9). However, the present data are still elusive in the pathogenesis of this rare hereditary eye disease.

Therefore, in this review studies the history and clinical symptoms of SCCD, UBIAD1 mutations causing SCCD and the pathogenesis of SCCD through diligent literature research. The present study also elucidates the critical correlations between SCCD and UBIAD1, to guide treatment and drug development for SCCD.

2. History and clinical symptoms of SCCD

History of SCCD. Swiss ophthalmologist Schnyder described the clinical symptoms and inheritance of the rare autosomal dominant corneal opacity disease and named it Schnyder's crystalline corneal dystrophy (SCCD) (4,5). Besides, some scientists also reported similar cases, for instance, Glees *et al* (1957) (6) and Garner *et al* (1972) (13). In 1972, Bron *et al* (14) reported a family with SCCD whose proband was a 47-year-old Caucasian male with two siblings having this eye disease. Bron *et al* spent 3 years tracking the causes of SCCD in this family. The patients with SCCD in this pedigree had hyperlipidemia disease and the level of their blood cholesterol, triglycerides and phospholipids from tests were higher compared with that in ordinary individuals. Their blood test results were also consistent within 3 years to this period. Bron *et al* recorded SCCD clinical features in this pedigree, such as the position of crystalline deposits in the cornea, size and shape of crystalline deposits and visual acuity level. Meanwhile, their study summarized reports of SCCD cases from 1924 to 1972 and was supplemented with patients' personal information and blood lipid-testing results. Finally, they concluded that SCCD occurrence correlated with dyslipidemia (14).

Similarly, Michaels (15) reported a disparate SCCD patient in 1974 with normal blood lipid whose crystalline deposits developed from speckles to circular needle-like crystal precipitates within 20 years. Thiel *et al* (16) also reported a 19-year-old male SCCD patient with inherited type IIA autosomal dominant hyperlipoproteinaemia that developed progressive deteriorated corneal opacity from 1964 to 1976. However Burns *et al* (17) used ^{14}C -cholesterol labeling of blood cholesterol before giving a penetrating keratoplasty surgery to the SCCD patient. At the time of surgery, 11 days later, cholesterol levels in the cornea were much higher compared with those in serum, suggesting that the cornea was an active site for cholesterol absorption and storage in this eye disorder. Ingraham *et al* (18) corrected the misunderstanding that once SCCD developed, it would never worsen in the cornea. Meanwhile, Ingraham *et al* reviewed previous studies of SCCD and concluded that only few patients with SCCD accompanied with hyperlipidemia and hypercholesterolemia were at risk of this disease and that these two indicators alone cannot be used as a biomarker for SCCD diagnosis.

Similarly, McCarthy *et al* (19) performed quantitative biochemical analysis on a corneal button obtained from an SCCD patient and found that accumulated corneal lipids are predominantly composed of phospholipids, free cholesterols and cholesterol esters. Those constituents were markedly elevated in the SCCD cornea than in the cadaveric control cornea. Results were: Phospholipid, 23.6 vs. 4.05 mg/g; free cholesterol, 6.99 vs. 0.52 mg/g and cholesterol ester, 3.16 vs. 0.26 mg/g. The authors concluded that the pathogenesis of SCCD was due to a primary disorder of lipid metabolism in the cornea. Weiss (20) collected 33 SCCD cases in 1987. Only 17 (51.5%) out of these demonstrated crystalline deposits in the cornea. As the name SCCD can mislead ophthalmologists in diagnosis and treatment, Weiss suggested renaming the disease Schnyder corneal dystrophy (SCD).

Clinical symptoms of SCCD. Schnyder crystalline corneal dystrophy (SCCD, MIM 121800) is a rare autosomal dominant inherited eye disease characterized by progressive opacification in the bilateral corneas, caused by the abnormal accumulation of cholesterols and phospholipids (1,21-23). To understand better the visual morbidity and surgical intervention of SCCD, Weiss *et al* (8) examined 115 cases from 34 affected families in 2007. Patients were divided into three categories on the basis of age for statistical analysis; i) <26 years, ii) 26-39 years and iii) ≥ 40 years (24). To date, the youngest SCCD patient found has been a 17-month-old and the occurrence age ranged from 2-81 years, with a mean age of 38.8 ± 20.4 years.

The clinical characteristics include i) early stage (≤ 26 years), crystalline deposits in the center stromal epithelium (Fig. 1A); ii) middle stage (26-39 years), crystalline deposits continue to accumulate and appear to join together, forming a haze (Fig. 1B); and iii) late stage (≥ 40 years), which is accompanied by aging. Here, the degree of crystallization is increasing, which leads to whole corneal opacity and blindness (Fig. 1C). In addition, $\sim 4\%$ patients with SCCD developed *Genu valgum* (24,25). Patients with SCCD gradually lose their vision as they age, but their visual acuity was restored to normal through surgery before they turned 40 years old. When patients with SCCD passed the age of 40, the corneal

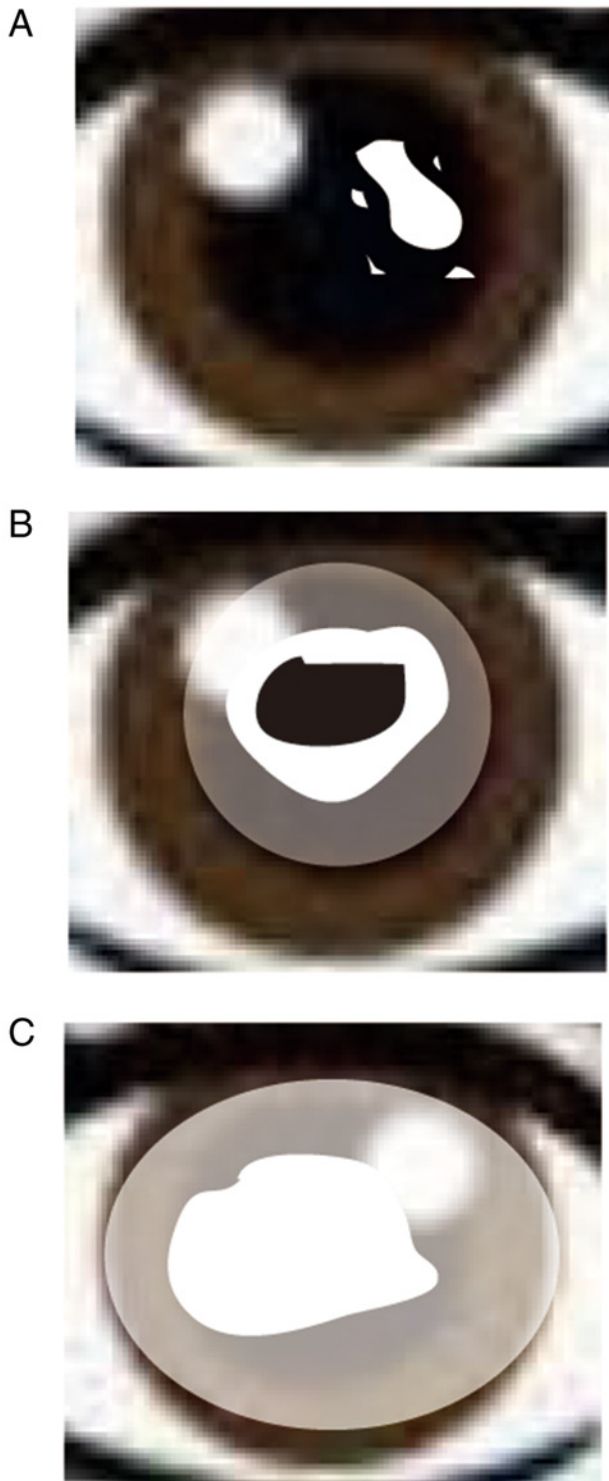


Figure 1. Cartoon illustration of different stages of SCCD. (A) Early stage (≤ 26 years old), crystalline deposits in the center stromal epithelium. (B) Middle stage (26-39 years old), crystalline deposits continue to accumulate and appear to join together, forming a haze. (C) Late stage (≥ 40 years old), the degree of crystallization is increasing, which leads to whole corneal opacity and blindness. Crystalline deposits were labeled with white and the haze is demonstrated in semitransparent circle.

opacity aggravated to final blindness. To date, patients with SCCD have had their vision restored mainly through penetrating keratoplasty and phototherapeutic keratectomy operation (1,24).

3. UBIAD1 mutations causing SCCD

UBIAD1 as the molecular basis of SCCD. The pathogenesis of SCCD remains to be elucidated and requires urgent attention. Innovative methods in molecular genetics have been used in uncovering the pathogenesis of corneal dystrophies (25). The traditional classification in clinics through histopathological and electron-microscopical examinations, which reflects an early disease and immunohistochemical analysis of the deposits, has already aroused a suspicion that is no longer fulfilled in dystrophy types (26,27). The BIGH 3 gene point mutation causes granular dystrophy types I and II, as well as lattice dystrophy types I and IIIA (28). Point mutations on the gelsoline gene on chromosome 9 (9q34) result in the lattice dystrophy type II, which is a manifestation of the Meretoja syndrome (28). As well as this mutation, other genes, gene-products and mutations are known as 16q22 for macular dystrophy, 1p36 for SCCD and 20p11.2-q11.2 for congenital hereditary endothelial and Schlichting's posterior polymorphous dystrophies (28). In another study, Riebeling *et al* (29) reported the case of a 66-year-old woman and her son with SCCD. The woman had type IV hyperlipoproteinemia and hypercholesterolemia, whereas her son had hypercholesterolemia with elevated LDL-cholesterol levels. Microsatellite marker analysis demonstrated that D1S228 within the candidate interval of 1p34.1-p36 led to the observed SCCD. In 1996, Shearman *et al* (30) narrowed the SCCD locus to the 16cM interval between D1S2663 and D1S228 microsatellite markers localized on 1p34.1-p36 through haplotype analysis in two large Swede-Finn kindreds in central Massachusetts.

Similarly, Theendakara *et al* (31) collected 13 families from Finland, Germany, Turkey and the USA to refine candidate intervals correlated with SCCD and they narrowed the putative region to 1.58 Mbp through identity-by-state analysis. To further identify the genetic basis of SCCD, mutation screening was used to analyze the 15 candidate genes (*CORT*, *CLSTN1*, *CTNNBIP1*, *DFFA*, *ENO1*, *GPR157*, *H6PD*, *KIF1B*, *LOC440559*, *LZIC*, *MGC4399*, *PEX14*, *PGD*, *PIK3CD* and *SSBI*), which were localized at putative regions in members of the two pedigrees affected with SCCD (32). Though none of these 15 genes were linked to SCCD, Aldave *et al* (32) reduced the remaining positional candidate genes by half and led to the identification of the genetic basis of SCCD.

Orr *et al* (7) also confirmed the genetic basis of SCCD, through intensive fine mapping in a large multigenerational family in Nova Scotia, to UBIAD1, which encodes a potential prenyltransferase and is involved in intracellular cholesterol metabolism. Furthermore, Weiss *et al* (8) analyzed DNA samples in six SCCD-affected families and uncovered that, of these six families, five possessed N102S mutations in UBIAD1 and one family had a G177R mutation in the UBIAD1 gene. Thus, the molecular basis of SCCD was clarified and linked to UBIAD1, which participates in cholesterol synthesis and storage intracellular. After years of efforts by generations of scientists and ophthalmologists, the genetic basis of SCCD was elucidated. Their work, therefore, provided molecular targets and references for SCCD treatment and drug development for this disease.

UBIAD1 mutations causing SCCD. It is 80 years since the initial description of SCCD by French ophthalmologists Van Went and

Table I. Point mutations of UBIAD1 causing SCCD (*marks hot spot).

Author(s) (year)	Number	Site	Type	(Refs.)
Orr <i>et al</i> (2007)	1	75	Ser-Phe	(7)
Nickerson <i>et al</i> (2010), Evans <i>et al</i> (2018)	2	97	Ala-Thr	(36,87)
Jing <i>et al</i> (2009)	3	98	Gly-Ser	(39)
Orr <i>et al</i> (2007), Weiss <i>et al</i> (2007), Yellore <i>et al</i> (2007), Riebeling <i>et al</i> (2003), Nickerson <i>et al</i> (2013), Al-Ghadeer <i>et al</i> (2011), Du <i>et al</i> (2011), Nickerson <i>et al</i> (2010), Weiss <i>et al</i> (2010), Meha <i>et al</i> (2009), Evans <i>et al</i> (2018)	4	102*	Asn-Ser	(7,8,9,29,33, 34,35-38,87)
Handa <i>et al</i> (2020), Evans <i>et al</i> (2018)	5	103	Thr-Ile	(83,87)
Orr <i>et al</i> (2007)	6	112	Asp-Gly	(7)
Nickerson <i>et al</i> (2013), Nickerson <i>et al</i> (2010), Sarosiak <i>et al</i> (2018)	7	112	Asp-Asn	(33,36,84)
Riebeling <i>et al</i> (2003)	8	118	Asp-Gly	(29)
Orr <i>et al</i> (2007), Yellore <i>et al</i> (2007)	9	119	Arg-Gly	(7,9)
Kitazawa <i>et al</i> (2018)	10	120	Thr-Arg	(85)
Yellore <i>et al</i> (2007), Riebeling <i>et al</i> (2003), Al-Ghadeer <i>et al</i> (2011), Evans <i>et al</i> (2018)	11	121	Leu-Phe	(9,29,34,87)
Nickerson <i>et al</i> (2010)	12	121	Leu-Val	(36)
Nickerson <i>et al</i> (2010)	13	122	Val-Glu	(36)
Nickerson <i>et al</i> (2010)	14	122	Val-Gly	(36)
Riebeling <i>et al</i> (2003), Nickerson <i>et al</i> (2010), Meha <i>et al</i> (2009)	15	171	Ser-Pro	(29,36,38)
Riebeling <i>et al</i> (2003), Nickerson <i>et al</i> (2010)	16	174	Tyr-Cys	(29,36)
Orr <i>et al</i> (2007), Weiss <i>et al</i> (2007), Riebeling <i>et al</i> (2003), Nickerson <i>et al</i> (2010)	17	175	Thr-Ile	(7,8,29,36)
Evans <i>et al</i> (2018)	18	176	Gly-Glu	(87)
Weiss <i>et al</i> (2007), Nickerson <i>et al</i> (2010)	19	177	Gly-Arg	(8,36)
Nickerson <i>et al</i> (2013), Kitazawa <i>et al</i> (2018)	20	177	Gly-Glu	(33,85)
Riebeling <i>et al</i> (2003)	21	181	Lys-Arg	(29)
Riebeling <i>et al</i> (2003)	22	186	Gly-Arg	(29)
Nickerson <i>et al</i> (2010)	23	188	Leu-His	(36)
Dudakova <i>et al</i> (2019)	24	190	Ile-Thr	(2)
Orr <i>et al</i> (2007), Nickerson <i>et al</i> (2010)	25	232	Asn-ser	(7,36)
Riebeling <i>et al</i> (2003), Nickerson <i>et al</i> (2010)	26	233	Asn-His	(29,36)
Weiss <i>et al</i> (2007), Riebeling <i>et al</i> (2003), Nickerson <i>et al</i> (2010)	27	236	Asp-Glu	(8,29,36)
Weiss <i>et al</i> (2010)	28	240	Asp-Asn	(37)

Wibaut in 1924 (3) and, finally, the molecular basis of SCCD has been correlated with UBIAD1, which is located on chromosome 1 p36 (7-9). Following this, scientists and ophthalmologists across the world continued to report new cases of SCCD.

Increasingly, UBIAD1 point mutations leading to SCCD were also identified (Table I). The present review has investigated 28 point mutations of UBIAD1 that cause SCCD through a literature search and the details are demonstrated in Table I. The mutation hot spot in UBIAD1 was on 102 (N102S), which had been demonstrated in a number of SCCD-affected families (7-9,22,33-38). Similarly, the occurrence of SCCD is higher in European and North American countries compared with other countries and regions associated with this gene defect,

including Asia and Africa. Prevalence of SCCD is also reported in the Chinese Han and Japanese populations (22,36,38,39). To further understand this gene, Dong *et al* (40) constructed an SCCD mouse model with N100S mutation by CRISPR-Cas9 gene editing to further clarify the pathogenesis and treatment of SCCD. The UBIAD1 mutant mouse line that was created carried a mis-sense mutation N100S, corresponding to the human UBIAD1 N102S mutation.

The genetic basis of SCCD has been demonstrated since 2007, but the mechanism of SCCD formation is still elusive. The present study next illustrates the functions of UBIAD1 to build a connection between abnormal lipid metabolism and the pathogenesis of SCCD.

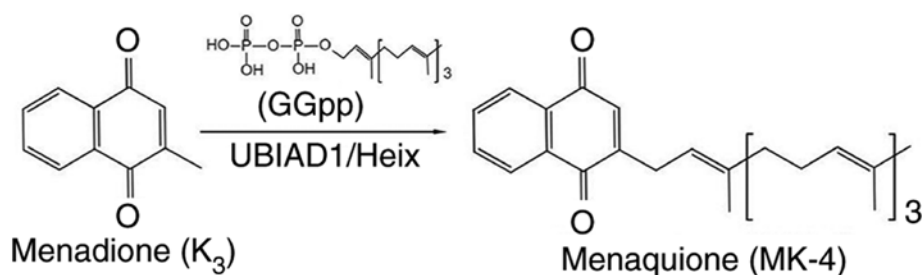


Figure 2. UBIAD1/Heix is a vitamin K₂ biosynthesis enzyme. The schematic shows the conversion of menadione to MK-4. UBIAD1, UbiA Prenyltransferase Domain Containing 1; MK-4, menaquinone-4.

4. Subcellular localization and functions of UBIAD1

Subcellular localization of UBIAD1. The GFP-UBIAD1 fusion protein vector was transfected into a human osteosarcoma cell line MG-63 to investigate the sub-cellular localization of UBIAD1. The results revealed endoplasmic reticulum (ER) localization, but not Golgi (41). Nickerson *et al* (36) also confirmed mitochondrial sub-localization of UBAID1, but not ER, in cultured corneal cells. To support their results, immunofluorescence was performed to ensure wild-type and mutated UBIAD1 (N102S) localization in excisional human corneal stromal cells. Similarly, Vos *et al* (42) reported an orthologous protein of UBIAD1 in *Drosophila* that was localized in the mitochondria, which supported the result of Nickerson *et al* (36). Mugoni *et al* (43) also indicated that UBIAD1 was a non-mitochondrial localization prenyltransferases that synthesized CoQ10 in the Golgi. Subsequently, Wang *et al* (44) demonstrated that RPWS residues of UBAID1 proteins were Golgi retention signal peptides. In mice N2A cells, the UBIAD1 protein was also localized in the mitochondria, ER and Golgi (45).

Jiang *et al* (46) examined the subcellular localization of wild-type UBIAD1 and the SCCD-associated mutants in CHO-K1 cells. They revealed that wild-type UBIAD1 is preferentially localized at Golgi, whereas the SCCD-associated mutants exhibited a diffused distribution and were dominantly sequestered in the ER. Fredericks *et al* (47) in his study concluded that the UBIAD1 protein was localized in the mitochondria, ER and Golgi apparatus with different functions and exhibited species specificity.

Tumor suppressor. The UBIAD1 is encoded by the *UBIAD1* gene and is involved in significant physiological processes *in vivo*. A previous study demonstrated that UBIAD1 inhibited cell proliferation of transitional cell carcinoma (10). McGarvey *et al* (11) transduce exogenous UBIAD1 constructs into two prostate carcinoma cell lines (LNCaP and PC-3), which markedly decrease cell proliferation by 80%. Fredericks *et al* (48) also demonstrated that UBIAD1 expression decreases in one third of bladder cancer samples through gene microarray analysis. In constructing bladder carcinoma nude-mouse model, UBIAD1 expression was induced, which inhibits tumor occurrence and development. In another study, mutated UBIAD1 did not bind to APOE which causes abnormal cholesterol levels *in vivo* (12). Elevated cholesterol levels also regulated cancer cell apoptosis and proliferation, thus distorting the balance maintained by intracellular

UBIAD1 (48). Therefore, although UBIAD1 played important roles in bladder tumor suppression, the mechanism remains to be elucidated.

UBIAD1 as a novel CoQ10 and vitamin K2 biosynthetic enzyme. The *UBIAD1* gene encodes a prenyltransferase containing 338 amino acids, with a molecular weight of 36.83 kDa (7,11). Nakagawa *et al* (41) decreases UBIAD1 expression in human cells using siRNA, which largely suppresses the conversion of deuterium-labeled vitamin K derivatives to deuterium-labeled menaquinone-4 (MK-4). To establish UBIAD1 function, Nakagawa *et al* (41) also infected insect cells sf9 with UBIAD1 baculovirus and detected deuterium-labeled MK-4 formed from vitamin K derivatives. Furthermore, Nakagawa *et al* (41) first identified UBIAD1 as an MK-4 biosynthesis enzyme in humans (Fig. 2), which suggests that vitamin K did not only existing in plant form, phyloquinone (PK), but also in bacterial form (MK-4).

Heix (Heixuedian), is an orthologous protein of UBIAD1 in *Drosophila melanogaster*, composed of 359 amino acids with a molecular weight of 39.22 kDa (42). Following Heix mutation, a black dot phenotype lymphoma appeared in the 3rd to 4th instar larvae in *Drosophila* (49,50). UBIAD1 localizes at the mitochondria and converts vitamin K₁ to K₂, which is a significant cofactor in eukaryotic blood coagulation and an electronic carrier binding to the cell membrane in bacteria (43). By contrast, vitamin K₂ is necessary and sufficient for electron transport in *Drosophila* mitochondria (42). Therefore, when Heix is mutated, mitochondria dysfunction arise. However, supplementation with vitamin K₂ rescues mitochondrial dysfunction (42). Heix is also a dosage-sensitive modifier of pink1, which is mutated in Parkinson's disease, as it affects mitochondrial function. Additionally, Heix converts menadione to vitamin K₂ in *Drosophila* (Fig. 2) (42).

Mugoni *et al* (43) found that UBIAD1 is a non-mitochondrial localized prenyltransferase and it catalyzed CoQ10 synthesis on the Golgi membrane. Reduced expression of UBIAD1 in vascular cells could decrease antioxidant CoQ10 cytoplasmic content, resulting in reactive oxygen species (ROS)-mediated lipid peroxidation. Similarly, the inhibition of endothelial nitric oxide synthase (eNOS) can prevent UBIAD1-dependent oxidative damage, revealing the crucial role of UBIAD1 and CoQ10 in nitric oxide (NO) signaling and cardiovascular system.

To further broaden UBIAD1 function, Mugoni *et al* (43) used zebrafish to investigate intracellular roles of the UBIAD1 ortholog gene, *Barolo* (*Bar*). The zebrafish cardiovascular

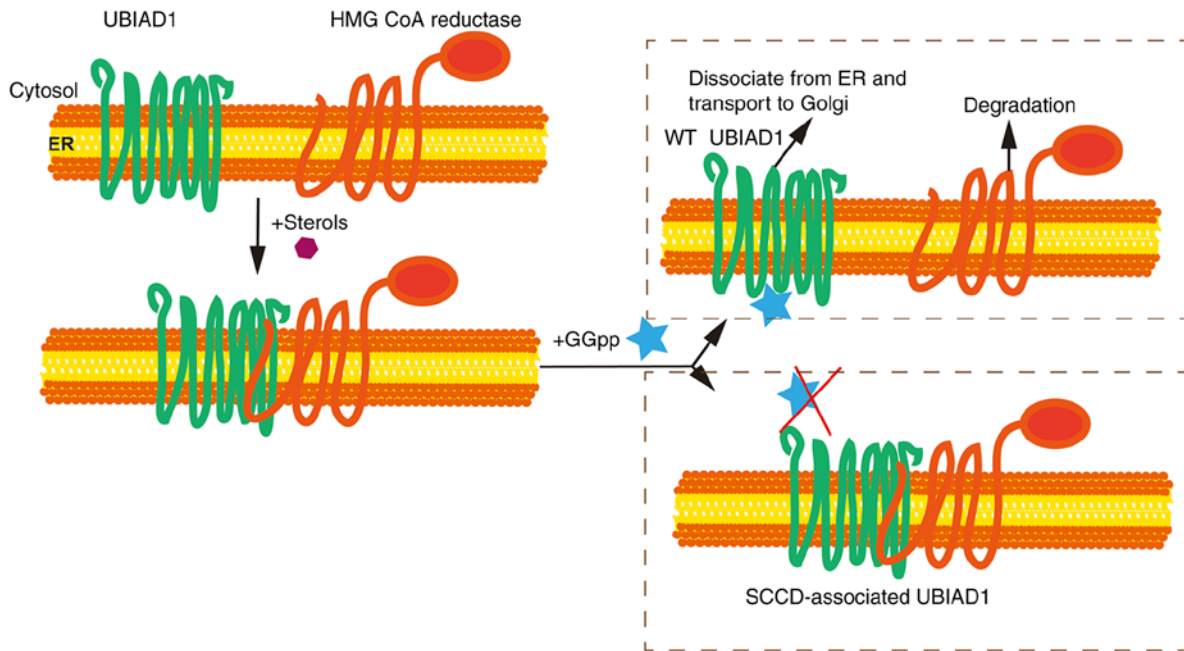


Figure 3. Putative roles of UBIAD1 in sterol-accelerated degradation of HMGCR. In sterol-deprived cells, HMGCR and UBIAD1 localize at ER membrane, independently. The intracellular accumulation of sterols in ER membranes triggers the binding of reductase to UBIAD1. GGpp promotes HMGCR degradation by binding to UBIAD1. UBIAD1 then dissociates from HMGCR in ER membrane and is transferred to the Golgi. The conformation change of mutated UBIAD1 causes SCCD in the cornea and led to the sequestration of HMGCR in the ER membrane. HMGCR retention causes a consistent synthesis of cholesterol *in vivo*, which leads to excess accumulation of cholesterol in the cornea and finally SCCD. UBIAD1, UbiA Prenyltransferase Domain Containing 1; HMGCR, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase; ER, endoplasmic reticulum; GGpp, geranylgeranyl diphosphate; SCCD, Schnyder's crystalline corneal dystrophy; WT, wild-type.

system fails after *Bar* is mutated, resulting from oxidative stress and ROS-mediated cell damage. Further study also demonstrated that UBIAD1 is a CoQ10 biosynthesis enzyme localized at the Golgi apparatus, which regulates ROS levels and the redox status in vertebrate cardiovascular system. Therefore, increasing oxidative stress causes heart and vascular cell apoptosis, as well as cardiovascular system failure when UBIAD1 is deficient (43).

Involvement of UBIAD1 in cellular lipid metabolism. When UBAID1 mutates, cholesterol and lipids accumulate abnormally in the cornea, leading to SCCD disease, indicating that UBIAD1 is involved in lipid metabolism in cells (7-9,16,17,19,46). The over-expression of UBIAD1 decreases cholesterol levels in 293 cells and cannot interact with the APOE protein after point mutation, which causes the abnormal metabolism of intracellular cholesterol (48). Fredericks *et al* (47,51) also constructed a cell line model based on a castration-resistant prostate cancer cell LNCap-C81 to reveal the association between UBIAD1 and steroid synthesis. Intracellular cholesterol synthesis rate, content and correlated enzymes increased when UBIAD1 was deficient. By contrast, the down-regulation of UBIAD1 resulted in mitochondrial damage and considerable cholesterol storage in hepatocellular carcinoma cells, which indicated the crucial role of UBIAD1 in mitochondrial function (52). Preliminary functional studies of UBIAD1 also focused on cell morphology and biochemical parameter change after abnormal expression of UBAID1 (10-12,41,43,48,52).

Schumacher *et al* (53-55) demonstrated that sterols stimulates UBIAD1 binding to HMG CoA reductase, which is a

cholesterol biosynthetic enzyme and subject to sterol-accelerated, endoplasmic reticulum-associated degradation (ERAD) augmented by the non-sterol isoprenoid geranylgeraniol. Geranylgeraniol then inhibits UBIAD1 binding of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMGCR) that promotes reductase degradation and transport of UBIAD1 from the ER to Golgi. This mutation results in a conformation change of mutated UBAID1, thereby inhibiting the binding of GGpp to UBIAD1 mutants, which prevents HMGCR degradation and dissociation of UBIAD1, thus contributing to consistent synthesis and accumulation of cholesterol *in vivo* (Fig. 3). HMGCR is an important rate-limiting enzyme in the cholesterol and non-sterol isoprenoid biosynthetic pathway, which is regulated by cholesterol feedback. Mevalonic acid is produced through the reduction of HMG CoA, which forms farnesyl pyrophosphate through a series of reactions and is a substrate in the biosynthesis of GGpp and cholesterol (Fig. 4) (56).

The UbiA superfamily of proteins is a collection of trans-membrane prenyltransferases that catalyze the biosynthesis of a number of crucial molecules, such as, ubiquinones, menaquinones, plastoquinones, hemes, chlorophylls, vitamin E and structural lipids (57). These vital compounds serve as electron and proton carriers for cellular respiration and photosynthesis. They also serve as antioxidants to decrease cell damage and as structural components of microbial cell membranes, which indicates that the UbiA superfamily of proteins is involved in significant physiological processes and human diseases (57). Compared with the Golgi localization of wild-type UBIAD1, SCCD-associated mutants are dominantly detained in the ER and compete with insulin-induced gene 1 (INSIG1) for

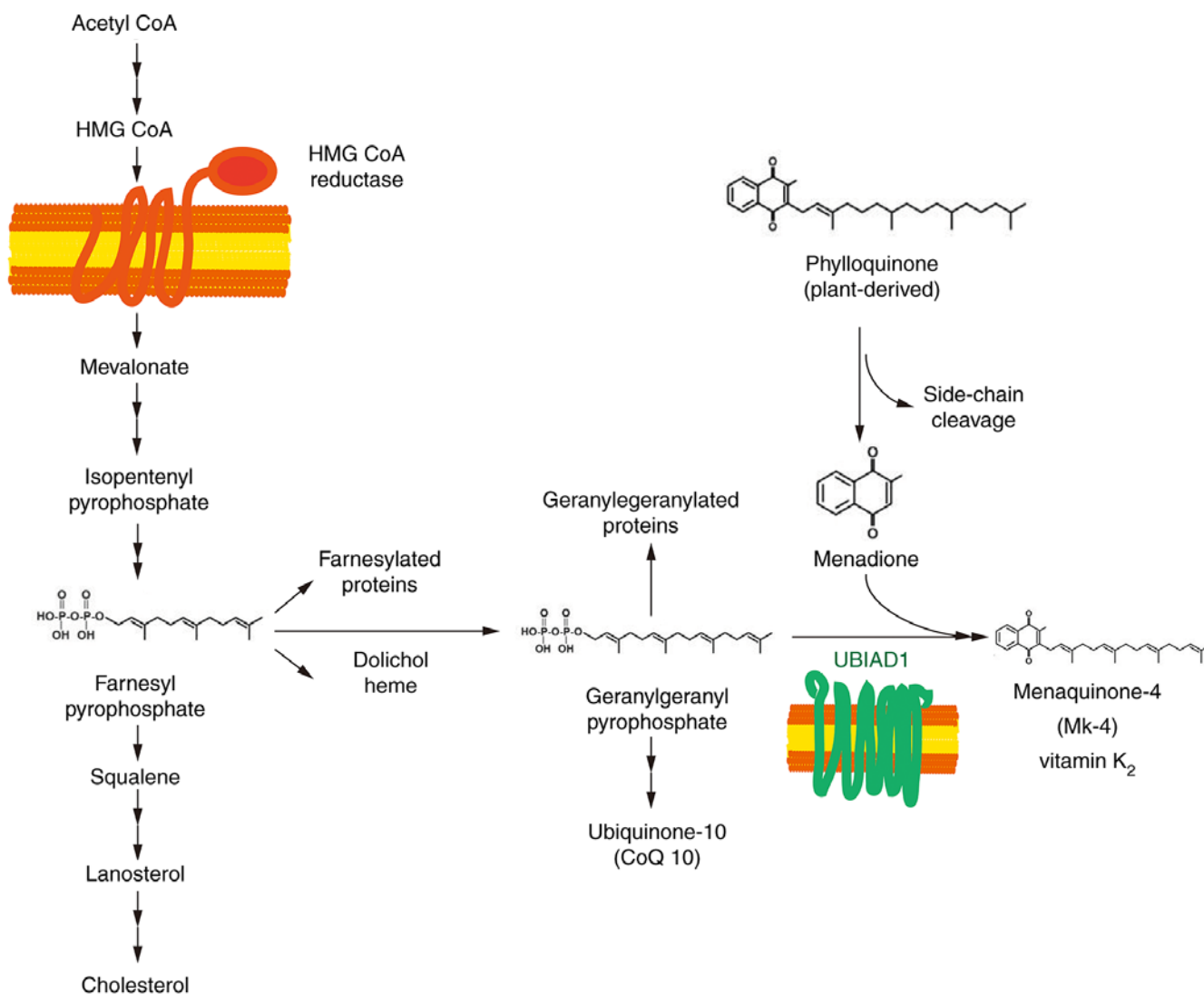


Figure 4. Schematic of cholesterol and Mk-4 biosynthesis in mammalian cells. HMG, 3-hydroxy-3-methyl-glutaryl; Co A, coenzyme A; UBIAD1, UbiA Prenyltransferase Domain Containing 1.

HMGCR binding, hence preventing HMGCR from degradation and increasing the biosynthesis of cholesterol (46). INSIG1 encodes for a probable six trans-membrane domain protein of 277 amino acids. Sterols then induce the ER-anchored INSIG1, which competes with UBIAD1 to bind HMGCR. Also, INSIG1 is associated with E3 ubiquitin ligase, which ubiquitinates HMGCR, eventually leading to the degradation of HMGCR (46).

Jiang *et al* (46) constructed heterozygous *Ubiad1* G184R (*Ubiad1*^{G184R/+}) knock-in mice that exhibited an elevated expression of HMGCR in various tissues. The aged *Ubiad1*^{G184R/+} mice, which exhibited identical clinical characteristics with patients with SCCD, demonstrated corneal cholesterol accumulation and opacification. These results indicated that SCCD-associated mutants impede its ER-to-Golgi transport and stabilize its interaction with HMGCR. This disturbed transport then increases cholesterol biosynthesis, causing excess accumulation of cholesterol in the cornea and, eventually, SCCD. Previous studies have demonstrated that GGpp triggers the release of UBIAD1 from HMGCR, allowing ERAD and ER-to-Golgi transport of UBIAD1 (53-55). A

SCCD-related mice model affirms the physiological significance of UBIAD1 in cholesterol homeostasis and demonstrates the inhibition of HMGCR ERAD, contributing to SCCD pathogenesis (46,58). Similarly, Jun *et al* (59) establishes a biochemical assay for UBIAD1-mediated synthesis of MK-4 in isolated membranes and intact cells. The results reveal that mutated UBIAD1 exhibited reduced Mk-4 biosynthetic activity compared with wild-type UBIAD1.

Sequestration in the ER, therefore, protects SCCD-associated UBIAD1 from autophagy and allows intracellular accumulation of the mutated protein, which magnifies the inhibition of HMGCR ERAD. The results of Jun *et al* (59) further broaden the understanding of SCCD pathogenesis and limit the efficacy of cholesterol-lowering statin therapies.

5. Conclusion

Mutations in UBIAD1, which synthesizes vitamin K₂ (subtype menaquinone-4, MK-4) and CoQ10, account for the rare autosomal dominant genetic disorder SCCD, also known as SCD. It also regulates eNOS activity based on its antioxidant

abilities (36-38). Progressive opaqueness of the cornea, due to the aberrant accumulation of cholesterol, is one of a number of symptoms of SCCD (1,13-25). French ophthalmologists Van Went and Wibaut in 1924 (3) first described SCCD. In the following years, a number of SCCD-affected families were reported across the world (13-18,20,23,28-31,60-86).

The search for the pathogenesis and molecular basis of SCCD lasted for decades until 2007, when three teams uncovered the conundrum due to UBIAD1 mutations (7-9). The pathogenesis of SCCD was then investigated and clarified by consistently exploring the functions of UBIAD1. From research, it was identified that UBIAD1 regulates HMGCR through GGpp in cholesterol biosynthesis and metabolism of significant componential molecules (46,53,54,56,58,59,87,88). UBIAD1 is also a critical tumor suppressor in the urinary system (11,44,47,48,51,88) and regulates cell proliferation through the ras signaling pathway (88). UBIAD1 homologous proteins are widely expressed in bacteria and eukaryotes and play vital roles in different intracellular physiological processes.

The present review clarified the pathogenesis and functions of the SCCD-associated gene UBIAD1, therefore guiding effective diagnosis and treatment of the inherent eye disease.

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Authors' contributions

JX and LL wrote and revised the manuscript. JX critically revised and corrected the manuscript. JX and LL conceived the idea for the review, collected and interpreted the studies included, reviewed the manuscript and contributed significantly to the writing the manuscript. Both authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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