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Grk1 Missense Mutations in Type II Oguchi Disease: A Literature Review

Theodore Edward Margo[1], Frank Sungping Chen[2], Yu-Jiun Chen[1] and Ching-Kang Chen[1,3*]

[1]*Department of Molecular Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229, USA*

[2]*Division of Otolaryngology, PeaceHealth Medical Group, Eugene, Oregan, OR 97401, USA*

[3]*Department of Ophthalmology, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229, USA*

Abstract

Oguchi disease is a rare form of congenital stationary night blindness resulting from arrestin-1 (SAG) or rhodopsin kinase (GRK1) loss-of-function mutations. Unlike other congenital nyctalopias, patients with Oguchi disease can reach the dark-adapted state, albeit only after several hours of sustained darkness exposure. The mechanism underlying rhodopsin kinase dysfunction in Oguchi disease remains understudied. Previous research utilized the Grk1 knockout mice to reveal its role in phototransduction, the process that transduces light into neuronal signals in rod and cone photoreceptors. By studying Grk1 missense mutations via a knock-in approach, a more complete picture of the Oguchi disease mechanism involving GRK1 may be readily harvested. We summarize here the current knowledge on the Type II Oguchi disease with Grk1 missense mutations by focusing on the interaction of GRK1 with other proteins, and how these interactions influence dark adaptation. We call for more detailed analyses of GRK1 missense mutations in animal models, particularly V380D and L157P, to reveal novel disease mechanisms to gain further insight onto GRK1's action and function.

Keywords: GRK1; GRK7; Oguchi disease; Phototransduction; Rhodopsin phosphorylation; Electroretinography (ERG), Congenital Stationary Night Blindness (CSNB); Mizuo-Nakamura phenomenon; Retinitis Pigmentosa (RP)

Clinical features and diagnosis of human Oguchi disease

In 1907, a Japanese ophthalmologist known as Dr. Chuta Oguchi described a case of night blindness with delayed dark adaptation [1]. Over several decades, the disease was further characterized to be congenital, stationary, and globally distributed in regions including Japan, China, India, Europe, Pakistan, and Egypt [2-7]. Patients typically reported a decrease in night vision but retained normal daytime visual acuity and color vision. Slit lamp examination revealed a peculiar metallic-gray or golden-brown fundus discoloration, which normalized after a prolonged period of dark adaptation. This so-called Mizuo-Nakamura phenomenon differentiates this disease from other congenital nyctalopias [2,8]. Oguchi disease is also peculiar in patients' ability to fully dark-adapt when they stay long enough in the dark. Currently, it is classified as a form of congenital stationary night blindness (CSNB). However, its definitive status as stationary has been challenged as disease progression to photoreceptor loss has been documented in animal models and some patients [3,9-11].

The diagnosis of Oguchi disease may be suspected based on the Mizuo-Nakamura phenomenon and patient history but must be differentiated from other CSNBs and/or confirmed through electroretinography [12] or DNA sequencing [13]. The electroretinogram (ERG) measures retinal light responses to brief flashes. It consists of an a-wave and a b-wave, the former of which directly depends on the health and function of rod and cone photoreceptors. ERG is recordable in Oguchi disease patients following an extensive period of dark exposure. ERG performed under a normal condition in a clinic usually showed a much-reduced rod response [6,12]. In general, ERG studies showed that rod photoreceptors in Oguchi disease patients are present but reliable recordings require four times longer than normal period of dark adaptation. Importantly, once dark-adapted, rod-mediated ERG responses in most Oguchi disease patients are comparable to healthy controls [6,12]. Cone-mediated ERG responses can be isolated from those from rods using proper background light exposure and recording settings and most Type-II Oguchi disease patients showed normal cone-derived ERG.

Genetic basis of human Oguchi disease

Oguchi disease is inherited in an autosomal recessive manner, and mutations are localized to one of two genetic loci [14]. Visual arrestin, also known as the S-antigen (SAG) or arrestin-1, was the first locus identified, and occurred frequently in the Japanese population [4,15-19]. Pathology associated with SAG mutations constitutes the Type I Oguchi disease. Interestingly, there was one reported case with an autosomal dominant inheritance [16]. The Type II Oguchi disease results from mutations in the rhodopsin kinase (Grk1) gene. It is primarily associated with patients of European descent [4,19]. While missense mutations at either locus produce pathology, base deletion and frameshift mutations at these genes are more commonly encountered [8,15].

While both types of Oguchi disease are regarded as stationary, this notion is currently under scrutiny because retinitis pigmentosa (RP), a relentlessly progressive retinal

disease, has also been associated with SAG and GRK1 mutations [16,20]. RP begins with progressive loss of peripheral eyesight, leading to tunnel vision, and eventually total blindness. Though rare, adults with Oguchi disease can demonstrate a similar progressive retinal degeneration to that typically found in early-stage RP patients, which may include a shared golden fundal discoloration like the Mizuo-Nakamura phenomenon [17]. The association between RP and Oguchi disease suggests the latter is capable of a slow but sure progression to irreversible retinal damage in humans. Several additional studies have documented conspicuous organizational changes within human and mouse retinas after intense light exposure [10,21]. Among these reported findings are shortened rod outer segments, reversibly hyper-reflective outer segment regions, and thinning of the parafoveal outer nuclear layer in the human retina [10,21]. Rod intensity changes suggest that rod cells are the primary site of pathology and the culprit responsible for the observed fundus changes associated with disease. Despite its categorization as a CSNB, structural changes in the retina may still develop over time [21]. RP may also present with nyctalopia, and Type I Oguchi patients later developing RP have been reported [12,16]. The newfound convolution between these two clinical entities and the presence of retinal structure changes begs again the question of whether Oguchi disease is truly a stationary pathology.

It is necessary to understand the recovery phase of phototransduction, particularly the deactivation of photoexcited rhodopsin, to comprehend the absence of normal dark adaptation in Oguchi disease patients [10,22]. Metarhodopsin II is the active intermediate responsible for the elevation of the visual threshold in Oguchi disease [23]. When the retina is devoid of light stimulation, both rods and cones undergo rapid adaptational processes in efforts to regain light sensitivity, a process known as dark adaptation. Retinal light sensitivity improves one-thousand-fold within a few minutes in the dark in healthy individuals, during which recovery is mediated mainly by cones. In contrast, rods are slower to dark adapt and require approximately 30 minutes in normal individuals, during which light sensitivity increases further by several orders of magnitude. A rod becomes sensitive again to dim light only after complete dark adaptation [12] that allows nearly all activated rhodopsin molecules to be silenced and regenerated. This is because rods are easily saturated with <4% of activated rhodopsin lingering in the system [12,23,24].

Phototransduction

Human rods are known for decades that they detect single photons. Phototransduction, composed of a cascade of biochemical reactions taking place in the photoreceptor outer segment, is the signaling pathway behind this amazing feast. It occurs when a photon strikes a rhodopsin molecule and transforms the covalently bound chromophore 11-cis-retinal into an all-trans form. Photoisomerization of the chromophore triggers conformational changes in the rhodopsin molecule, leading to the adoption of the active Metarhodopsin II configuration. Rhodopsin is a G-protein-coupled receptor composed of the apoprotein opsin and the bound chromophore [25]. Once activated, it stimulates the heterotrimeric G-protein transducin by catalytically facilitating the exchange of GTP for GDP on the transducin α subunit, which in turn binds the inhibitory γ subunit of phosphodiesterase 6. The resulting disinhibition of the near-perfect enzyme phosphodiesterase 6 [26] leads to a rapid decline in intracellular cGMP concentration and the closure of cGMP-gated channels situated on the outer segment plasma membranes, resulting in a rapid membrane hyperpolarization and hence a neuronal signal that is relayed to subsequent retinal neurons.

GRK1 mutations, like those in arrestin-1, cause profound delays in rod recovery because the shut-off of activated rhodopsin is impaired [27]. Rhodopsin phosphorylation by GRK1 enables steric capping of phosphorylated rhodopsin by SAG to prevent further transducin activation. Because they work in tandem, damage to either the Grk1 or the arrestin-1 gene results in the same recovery defect [28]. It is worth mentioning that in Oguchi disease, complete photoreceptor recovery is still achievable, if these patients stay in the dark long enough to regenerate all activated rhodopsin to regain light sensitivity. The Metarhodopsin II tends to persist until the photoisomerized all-trans retinal spontaneously dissociates from it, a natural decay process that takes minutes to occur. To ensure timely rhodopsin deactivation and prevent oversaturation of phototransduction, activated rhodopsin in normal individuals is phosphorylated at its carboxyl terminus by GRK1 [29] and then followed by the binding of SAG to prevent it from activating transducin. Thereafter, all-trans retinal dissociates from opsin, reduced to retinol and then reisomerized and recycled in the adjacent pigmented epithelium (RPE) through a process called the visual cycle [30]. This faster deactivation mechanism of Metarhodopsin II occurs within a hundred milliseconds and trumps its slow natural decay, which takes ~900 seconds [10,27], and hence alleviates its profound negative effect on the recovery of rod sensitivity [12,31]. However, this slow decay is likely responsible for the lengthy characteristic of dark adaptation found for all Oguchi disease patients. It is noteworthy here that there are other forms of congenital night blindnesses originating from mutations in other components of the phototransduction cascade, and each has its own unique determining features [3,12,32].

The focus on GRK1

This review centers on GRK1 and not SAG for two reasons. First, SAG has already been the subject of a large body of research and reviews. Gurevich, for instance, has synthesized the current understanding of the roles and mutations of visual arrestin [33,34] in Type I Oguchi disease. Second, GRK1 remains enigmatic regarding its activation, catalytic activity, and intracellular targeting. Additionally, the roles of its posttranslational modifications are understudied and incompletely understood. We believe that the many disease-causing missense mutations identified thus far in Type II Oguchi disease patients hold the key to additional insights into GRK1's roles in photoreceptors.

GRK1 is a serine/threonine kinase and a member of the G-protein-coupled receptor kinase family [35]. It performs the phosphorylation of photoexcited rhodopsin and is required for the timely recovery of phototransduction [10,36]. The human Grk1 gene is located on chromosome 13q34, measures 563 amino acids in length and has been sporadically investigated for the pathophysiology behind Oguchi disease [8,36-38]. GRK1 contains three domains [35], namely, the central kinase domain that is responsible for catalytic activity, the N-terminal

regulator of G-protein signaling homology (RH) domain that presumably facilitates rhodopsin binding [13,39] and the short C-terminal domain, which contains a CaaX motif directing GRK1 prenylation and subsequent modifications important for membrane affinity and intracellular compartmentalization [40,41]. Currently, several aspects of GRK1's physiological functions are appreciated. Under normal conditions, it phosphorylates activated rhodopsin, a readily assayable activity allowing detailed biochemical characterizations [42-44]. Rhodopsin, a G protein-coupled receptor and the initiator of phototransduction, is GRK1's prime target in rod photoreceptors. The phosphorylation of Metarhodopsin II reduces its ability to activate transducin, and the subsequent binding of arrestin to phosphorylated rhodopsin quenches its downstream signaling [8,28]. GRK1 activity is inhibited by recoverin at the photoreceptor membrane in a calcium dependent manner [44-47]. Though not strictly necessary for activation of the phototransduction cascade, recovery of phototransduction is much prolonged in GRK1's absence [10], and photoreceptors become prone to light damage in both transducin-dependent and transducin-independent manners [48,49].

Just like transducin, GRK1 is also activated by photoexcited rhodopsin but its importance in human Oguchi disease is unstudied. When assaying kinase activity using a rhodopsin C-terminal peptide as a substrate, GRK1 activation was discovered as the kinase activity toward the peptide substrate increased tremendously when proteolytically truncated membrane bound rhodopsin without its C-terminal Ser/Thr phosphorylation sites was present [50,51]. The Tesmer group has studied the activation mechanism structurally by exploring the interactions between G protein-coupled receptor kinases and G protein-coupled receptors and determined that GRK1 can assume an active conformation when associated with negatively charged membrane lipids and/or activated rhodopsin [52,53]. Thus, as recoverin inhibits GRK1, rhodopsin activates it, while the surrounding transducin competes with it (for activated rhodopsin). Tesmer's conclusions are supported by the successful docking of GRK1's N-terminus into a structural cleft in the activated rhodopsin, where it reorganizes into an alpha helix [53]. In addition, acidic and basic residues on GRK1 and rhodopsin, respectively, could stabilize this active configuration [53]. We want to point out here that a missense mutation at either of these sites could theoretically disrupt the GRK1-rhodopsin complex and decrease GRK1 activity, resulting in a phenotype somewhat mimicking Oguchi disease. However, it is noteworthy that these structure-based studies of GRK1 activation used a recombinant bovine GRK1 truncated at residue 535 lacking much of the C-terminal domain and the CaaX box. A 4bp deletion near this truncation site in humans causes Oguchi disease [8]. When the mutant human GRK1, designated as HRKS536(4-bp del), was ectopically expressed in the COS7 cells, it exhibited barely measurable light-dependent kinase activity toward rhodopsin [54]. The structural study of GRK1 activation would benefit greatly from using a full-length recombinant or purified native GRK1.

Though human type II Oguchi disease arises from poor or no GRK1-mediated phosphorylation of rhodopsin, GRK1 itself has been noted to undergo phosphorylation. In mice, GRK1's phosphorylation by protein kinase A decreases its kinase activity for rhodopsin, which typically occurs under scotopic conditions. Interference with this process causes a delayed dark adaptation, somewhat phenocopying Oguchi disease [55]. As the pathologic mechanism of type II Oguchi disease remains poorly understood, all aspects of GRK1 regulation by other binding partners and/or kinases that phosphorylate it should be considered in future investigations.

In humans, GRK7 is found alongside GRK1 in cones, but not in rods [56]. Mice lack a Grk7 gene and express only GRK1 in both rods and cones [57]. Mice that carry a mutation removing the PKA-dependent phosphorylation site Ser21 do not demonstrate a delayed dark adaptation in cones [55]. In contrast, cone recovery is greatly delayed in the GRK1 knockout mice [58]. These findings suggest GRK1 may have a peripheral or a replaceable role in the recovery of cone phototransduction in humans [19,27].

Unsolved mysteries of GRK1

Despite the ample research conducted on Type II Oguchi disease, some points remain obscure. Most relevantly, we do not understand how each specific GRK1 missense mutations disrupts its phosphorylation of rhodopsin. Hypotheses regarding this issue have evolved over decades from the general concept of a metabolic versus neurologic etiology, all the way to the structural changes proposed for GRK1 molecule with a disease-causing mutation [2,13,24]. One overly simplified hypothesis stated that these mutations disrupt GRK1's catalytic activity toward activated rhodopsin [54]. Other speculated dysfunctions, such as insults to GRK1's stability and/or ability to bind activated rhodopsin (in the missense mutation of the N-terminal RH domain), have not been explored at all.

Recoverin is a neuronal calcium sensor in the retina that inhibits GRK1 in its calcium-bound state [28,44,59]. It decreases the phosphorylation of rhodopsin by binding and inhibiting GRK1, resulting in a slower deactivation of rhodopsin in darkness. In bright light and when intracellular calcium concentration decreases, recoverin releases GRK1 and increases the phosphorylation of rhodopsin [28,46,59]. In the dark, the interaction between GRK1 and recoverin somewhat mimics the dysfunctional state of mutant GRK1 found in type II Oguchi disease. Such a mimicry can conceivably be augmented in a constitutively active recoverin mutant mouse that phenocopies some if not all reported GRK1 knockout phenotypes. However, defects in recoverin's regulation of GRK1 activity are unlikely to be pathological as the recoverin knockout mice do not show an Oguchi disease-like ERG or morphological phenotypes, despite other functional abnormalities were nonetheless noted [60-63].

Other than a report showing that the ability of the V380D GRK1 mutant to phosphorylate activated rhodopsin is completely disrupted [54], there are no reports of new pathologic mechanisms. Previous investigations using the knockout approach established GRK1 as the sole kinase responsible for light-dependent rhodopsin phosphorylation and deactivation [9,10,64]. Current literature supports the notion that GRK7 alone can support timely cone recovery in the absence of GRK1 in humans. However, cones are also affected in some Oguchi disease patients, demonstrated, for instance, in a report of two Japanese siblings with Pro391His Grk1 mutations [19]. Research in zebrafish has also shown GRK7 knockdown to flagrantly impair cone response recovery and dark adaptation [55,65]. Granted that we do not appreciate a

clinically significant impact on cone function in most Oguchi disease patients, GRK7 likely compensates significantly for GRK1 dysfunction. Further, it is possible that GRK1 and GRK7 might interact in a way that mutations in GRK1 could undermine GRK7 activity resulting in impaired cone recovery. Alternatively, due to the potential for rod cell death in Type II Oguchi disease [10], cone functional changes could be due to the absence of surrounding rod support precipitating into nearby cones' dysfunction or death. This phenomenon is well-known in RP as a bystander effect [66]. Additional information on GRK1's activity in cone cells could determine if future research is necessary into cone-function in type II Oguchi disease.

The clinically defining signature of Oguchi disease, the Mizuo-Nakamura phenomenon, remains also incompletely understood. The peculiar fundal color change was speculated to be due to excess extracellular potassium in the retina [15] and decreased Müller glial activity. It is currently unclear how or if GRK1's dysfunction bears any responsibility for the Mizuo-Nakamura phenomenon, though it notably remains present in Oguchi disease caused by arrestin-1 mutation as well. Despite the absence of a systemic investigation, one report indicates a fundal color change was not observed in GRK1 deficient mice [12]. This observation combined with their increased vulnerability to light-induced retinal damage could reasonably suggest that the Mizuo-Nakamura phenomenon does not occur in mice due to physiological differences between the two species [3,10]. GRK7 could also be the key to further investigation into the physiology behind this peculiar fundal color change seen in human patients, given its absence in mouse cones, but not human cones [67]. Of note, the Mizuo-Nakamura phenomenon is observed in other CSNBs such as X-linked cone rod dystrophy and X-linked retinoschisis [20].

Further work, by focusing on specific pathologic missense mutations in GRK1, may clarify its mechanism of dysfunction and open the door for novel treatments of not only the rare Oguchi disease, but also the relatively more common and progressive retinitis pigmentosa involving mutations in the rhodopsin gene. Therefore, we tabulate below current known GRK1 missense mutations and propose a study in the mouse model utilizing the latest genome editing technology to better characterize its abnormal function in Oguchi disease.

Known GRK1 missense mutations and disease mechanisms

We focus on missense mutations here for several reasons. Firstly, they may cause phenotypic change without disabling the protein completely, allowing greater insights to be gleaned. With a single amino acid change, the tertiary structure of GRK1 may be preserved, altering only a certain aspect of GRK1 activity but still causing a sufficient pathological consequence. In contrast, the more frequently seen frameshift or nonsense mutations often result in nonfunctional or truncated GRK1, which provide less insight. Secondly, nonsense mutations often suffer from nonsense mediated decay, in which mRNAs containing premature stop codons are preferentially degraded [68], leading to a decreased protein concentration to augment the impact already imparted by the mutation.

Table 1 lists all twelve currently known GRK1 missense mutations. All but one of the known GRK1 missense mutations localize to the kinase domain, the region responsible for GRK1 catalytic activity. The V380D mutation has been tested in the CO7 cell and determined to have no detectable catalytic activity. Mutations in this kinase domain are thus hypothesized to disrupt tertiary structure and consequently catalytic activity [13]. The sole RH domain mutation, Leu157Pro (L157P), may interrupt interaction of GRK1 with rhodopsin, likely secondary to proline-kinking [13], with the potential to affect catalytic activity and/or GRK1 activation by rhodopsin.

Protein variant	Domain	Reference
L157P	RGS	Mucciolo et al, 2018 (Mucciolo, Sodi et al. 2018)
G199R	Kinase	Poulter et al, 2021 (Poulter, Gravett et al. 2021)
L208P	Kinase	Teke et al, 2016 (Teke, Citirik et al. 2016)
R316S	Kinase	Wei et al, 2023 (Wei, Li et al. 2023)
R332W	Kinase	Poulter et al, 2021 (Poulter, Gravett et al. 2021)
E362K	Kinase	Poulter et al, 2021 (Poulter, Gravett et al. 2021)
A377P	Kinase	Godara et al, 2012(Godara, Cooper et al. 2012)
V380F	Kinase	Poulter et al, 2021 (Poulter, Gravett et al. 2021)
V380D	Kinase	Yamamoto et al, 1997; Godara et al, 2012 (Yamamoto, Sippel et al. 1997, Godara, Cooper et al. 2012)
P391H	Kinase	Hayashi et al, 2007 (Hayashi, Gekka et al. 2007)
R438C	Kinase	Poulter et al, 2021 (Poulter, Gravett et al. 2021)
L463P	Kinase	Wei et al, 2023 (Wei, Li et al. 2023)

Table 1: Known disease-causing Grk1 missense mutations.

Retinitis pigmentosa, the leading cause of blindness in those younger than 60 years old [69], frequently is characterized by mutations found in phototransduction proteins. Understanding the Oguchi disease mechanism could open significant doors in therapy for what currently is a relentlessly progressive, irreversible, and incurable blinding disorder. We, therefore, advocate for GRK1 missense mutations in type II Oguchi disease to be studied further, preferably in animal models with novel genome-editing techniques [70]. Results from such studies can be compared with published GRK1 knockout data [10,48,49] to uncover novel insights concerning GRK1's mysteries inside rod and cone photoreceptors. We expect that phenotypes for various Grk1 missense mutations to be dependent on their domain-localizations, with a disruption of the kinase domain that inactivates the kinase to differ from those due to disruption of the RH domain responsible for interaction with the substrate rhodopsin. To this end, we have begun to generate the V380D and L157P knock-in mouse models and plan to study the phenotypic differences among the two and the GRK1 knockout mice. Preliminary findings using the V380D knock-in mice show that this mutation affects GRK1's expression in the retina (Chen CK et al. Invest. Ophthalmol. Vis. Sci. 2024; 65(7):6199), which suggests that protein stability plays a hitherto unappreciated role in the pathologic mechanism of Type-II human Oguchi disease.

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***Corresponding author:** Ching-Kang Jason Chen, PhD, FARVO, Departments of Molecular Medicine and Ophthalmology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, MC-8257, San Antonio, TX 78229-3900, Tel: 210-562-4135; Email: chenc10@uthscsa.edu

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