Phenotype of Retinitis Pigmentosa Associated With the Ser50Thr Mutation in the NRL Gene

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Background: We previously reported an Ser50Thr mutation in the NRL gene as a cause of autosomal dominant retinitis pigmentosa.

Objective: To determine the characteristic features of the autosomal dominant retinitis pigmentosa phenotype associated with the NRL Ser50Thr mutation in affected individuals from 4 related families.

Methods: Clinical records were available for 21 affected individuals; 7 underwent more extensive electrophysiologic and psychophysical testing.

Results: Night blindness was the first symptom to manifest, with onset between birth and age 16 years. Difficulty with peripheral vision was experienced between 20 and 37 years of age. Visual acuity was well preserved in younger individuals, but those older than 30 years frequently had substantial visual loss (6/36 or worse) associated with macular atrophy. Electrophysiologic testing revealed a nondetectable scotopic electroretinogram with relative preservation of the photopic electroretinogram and pattern electroretinography in the 3 youngest patients tested (aged 15-18 years). In older individuals, all components of the electroretinogram were nondetectable. Dark-adapted visual fields in younger individuals were greatly impaired, but their photopic fields remained relatively well preserved. Older patients had photopic fields limited to just a few degrees. Distinctive peripapillary chorioretinal atrophy seems to develop as the disorder progresses.

Conclusions: The NRL Ser50Thr mutation is associated with selective loss of scotopic function before age 20 years. With time, however, the photopic system becomes affected, leading to loss of the photopic visual field and of visual acuity.

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Retinitis pigmentosa (RP) (MIM No. 268000; Online Mendelian Inheritance in Man, available at: http: www.ncbi.nlm.nih.gov/omim) is the term applied to a clinically and genetically heterogeneous group of retinal degenerations that primarily affect the peripheral photoreceptors and that have an overall prevalence of approximately 1:3000. Retinitis pigmentosa is characterized by progressive loss of vision, initially manifesting as night blindness, with subsequent loss of the peripheral visual fields, and later frequently involving deterioration of central vision. Retinitis pigmentosa may be inherited as an autosomal recessive, autosomal dominant, digenic, or X-linked trait. Autosomal dominant RP (adRP) accounts for 20% to 25% of all cases of RP. Our group previously reported a Ser50Thr (S50T) mutation in the NRL gene, located at the 14q11 locus, as the cause of adRP in a 3-generation British family (designated RP251). The NRL gene encodes a basic motif–leucine zipper DNA-binding protein (NRL) that is highly expressed in the adult neural retina. NLR protein acts as a transcription factor responsible for up-regulating the activity of the promoter elements of several retina-specific genes, including rhodopsin and PDE6β (the β subunit of cyclic guanosine monophosphate–phosphodiesterase), leading to increased production of these proteins. Subsequent mutation screening of NRL in 200 apparently unrelated adRP families revealed 3 additional pedigrees (RP57, RP357, and RP3097) with the NRL S50T mutation. Haplotype analysis confirmed that all 3 of these families were related to the original family RP251, indicating the presence of a “founder effect.”

The role of NRL mutations as the cause of adRP at the 14q11 locus has since been confirmed by the identification of 2 novel NRL mutations in patients with RP.
A Pro51Leu missense mutation has been reported in a Spanish family with adRP, and a Gly122Glu mutation has been observed in a patient with simplex RP.

In this study, we define the phenotype associated with the NRL S50T mutation in family RP251 to determine whether detailed clinical, electrophysiologic, and psychophysical studies of affected individuals can demonstrate characteristic features that might aid in the identification of additional families with NRL mutations. In addition, we reviewed the clinical notes on affected individuals from families RP57, RP357, and RP3097 to ensure that the phenotype was consistent in the extended pedigree.

**METHODS**

**PARTICIPANTS**

This research was performed in accordance with the Declaration of Helsinki and was approved by the Hospital Ethics Committee of Moorfields Eye Hospital. The authors obtained informed consent for clinical and molecular genetic assessment from all participants.

Twenty-five members of the family RP251 were enrolled in the molecular genetic analysis that led to identification of the NRL S50T mutation (Figure 1). This family consisted of 14 affected individuals, 7 unaffected relatives, and 4 spouses. (DNA was not available from the deceased individual.) All 14 affected family members underwent a full ophthalmologic examination. Previous visual field test results, electrophysiologic data, and fluorescein angiograms were available for many individuals, but these investigations had not been standardized. For the purposes of this study, therefore, 7 patients were selected to represent different generations of this family, and these individuals underwent more detailed electrophysiologic and psychophysical assessment.

The 3 additional families (RP57, RP357, and RP3097) contained 13 surviving affected individuals (Figure 2). Information was obtained from clinical records that were available for 8 individuals, but they were not all reexamined.

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**Figure 1.** Pedigree of the family RP251.

**Figure 2.** Pedigrees of additional families with the NRL Ser50Thr mutation. A, Family RP357. B, Family RP57. C, Family RP3097.
Clinical and Functional Investigations

Affected patients were questioned regarding age at onset of (1) night blindness, (2) difficulty with side vision, and (3) central visual loss, if any. They then underwent measurement of distance visual acuities, slitlamp biomicroscopy of the lens, ophthalmoscopic examination of the fundus, static perimetry, electrophysiologic testing, and confocal scanning laser ophthalmoscopy (cSLO). Best-corrected distance acuity was measured for each eye recorded in the patient's clinical notes.

Psychophysical Assessment

Electrophysiologic assessment was undertaken on 7 patients from generations II and III of family RP251. Electroretinography (ERG) was performed according to the standards published by the International Society for Clinical Electrophysiology of Vision11 (including rod ERG, bright white flash mixed rod-cone ERG, and 30-Hz cone-derived flicker ERG). Pattern ERG was also performed according to International Society for Clinical Electrophysiology (ERG) was performed according to the standards published by the International Society for Clinical Electrophysiology of Vision11 (including rod ERG, bright white flash mixed rod-cone ERG, and 30-Hz cone-derived flicker ERG). Pattern ERG was also performed according to International Society for Clinical Electrophysiology of Vision standards.12

Static threshold perimetry in the dark- and light-adapted states was performed using a prototype confocal scanning laser ophthalmoscope (cSLO). Best-corrected distance acuity was measured for each eye with undilated pupils at a distance of 6 m on a Snellen chart. Electrophysiologic and psychophysical evaluations were carried out at least a week apart to ensure that bleaching of retinal photopigments did not affect the results. All imaging procedures were performed at the end of the appropriate day's tests. When possible, a comparison was made with previous examination findings recorded in the patient's clinical notes.

Electrophysiologic and Psychophysical Assessment

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Static threshold perimetry in the dark- and light-adapted states was performed using a modified Humphrey field analyzer (Allegan Humphrey, Hertfordshire, England). Photopic visual fields were performed using the standard Humphrey 30-2 protocol.

Results

The pupil was dilated with 2.5% phenylephrine hydrochloride and 1% cyclopentolate hydrochloride, and the patient underwent dark adaptation for 45 minutes. The Humphrey field analyzer was modified for use in dark-adapted conditions.13,14 An infrared source illuminated the bowl, and an infrared monitor (Phillips, Eindhoven, the Netherlands) was used to detect eye movements. Fields were recorded using central 30-2 and peripheral 30/60-2 programs and macula full-threshold tests. The target size corresponded to Goldmann size 5 for peripheral testing and to Goldmann size 3 for macular programs. Each program was performed with a red (predominant wavelength, 650 nm) and blue (predominant wavelength, 450 nm) filter in the stimulus beam.

cSLO Images

Images of autofluorescence in the central macular region were obtained using a prototype confocal scanning laser ophthalmoscope and previously published techniques.15

Description of Patients

Clinical details, including age, history of visual loss, current Snellen visual acuity, and ophthalmoscopic findings, from the 14 affected individuals in family RP251 (age range, 15-64 years) are given in Table 1. The data available for affected individuals from families RP57,
RP357, and RP3097 are also included in Table 1. The clinical features recorded for these patients were consistent with those for individuals from family RP251.

PHENOTYPE RANGE

The first symptom of retinal dystrophy observed by all affected individuals was night blindness. The age at onset of nyctalopia reported by patients from these families varied from early life to age 16 years, with approximately half indicating onset between 8 and 15 years of age. Patients often complained of difficulty with dark adaptation, especially when entering a dimly lit building on a sunny day.

Difficulty with peripheral vision commenced between 20 and 30 years of age in 6 patients and between 31 and 37 years of age in 2 patients. Asymptomatic photopic visual field defects were, however, demonstrated by static perimetry in individuals as young as 17 years.

Except for patient IV:3 from family RP57 (see the “Funduscopic Appearances” subsection), the onset of significant visual acuity loss was delayed until at least age 29 years, with 7 of 8 patients stating that this occurred between ages 30 and 40 years. There was no apparent relationship between the age at which nyctalopia was first observed and the time at which visual field loss and visual acuity loss were noticed.

Visual acuities were well preserved in patients younger than 20 years, with 7 of 8 patients having a Snellen visual acuity of 6/9 or better in both eyes. Beyond age 30 years, most patients (11 of 13) had significant loss of visual acuity (6/12 or worse) in one or both eyes. Substantial visual loss (6/36 or worse) was present in 12 of these 26 eyes and was associated with macular atrophy in most individuals. A scatterplot of age vs visual acuity in the right eye is shown in Figure 3.

Eight patients, all older than 35 years, had bilateral posterior subcapsular lens opacities or had undergone cataract extraction. Cataract contributed to reduction in visual acuity in some patients, but pseudophakic individuals frequently also had poor central vision as a result of macular atrophy.

FUNDUSCOPIC APPEARANCES

Peripheral retinal changes in younger affected individuals (<20 years) were limited to 1 or more small patches of midperipheral intraretinal pigment. More generalized peripheral pigmentation with associated atrophy of the retinal pigment epithelium, usually affecting all 4 retinal quadrants, was seen in older patients. Pigment tended to be deposited in rounded clumps more often than in classic “bone spicules.”

Patient IV:3 from family RP57 (aged 30 years) was unique in exhibiting bilateral extensive peripheral retinal telangiectasis, primarily, but not exclusively, affecting the inferior fundus. At age 19 years she was observed to have bilateral vitreous cells and haze associated with diffuse macular edema and a visual acuity of 6/24 OU. At that time, very mild peripheral telangiectasis was observed. This edema did not respond to oral prednisolone therapy, and the patient then did not attend further outpatient appointments. She was seen again at age 28 years with extensive peripheral telangiectasis giving rise to bilateral inferior serous retinal detachments that progressed to involve the macula in each eye. Initially, there was some response to treatment with oral acetazolamide (500 mg/d), but eventually she required bilateral inferior retinal cryotherapy. Despite this treatment, her maculae remained edematous and her visual acuity continued to deteriorate to 2/60 OD and 6/36 OS.

Macular edema seemed to be present, or was recorded to have occurred, in many younger patients (Table 1). However, fluorescein angiography in patients with macular thickening revealed masking of choroidal fluorescence in the foveal region associated with surrounding patches of increased fluorescence rather than foveal edema (Figure 4B). Oral acetazolamide was used in an attempt to reduce macular edema and improve visual acuity in several of these patients, but none experienced any improvement in visual function.

In older patients, the typical finding was a bull’s-eye pattern of macular atrophy (Figure 5). This was frequently associated with substantial impairment in visual acuity.

Pallor of the optic disc was observed in 7 older patients (age range, 36-64 years). In addition, a remarkable progressive atrophy of the peripapillary retina was observed, which is not a typical feature of RP. Early peripapillary atrophy was evident even in the youngest in individuals examined, and this became prominent in older individuals (Figure 6). Early peripapillary atrophy was not a reflection of severe myopia, as most patients had no significant refractive error.

PSYCHOPHYSICAL FINDINGS

Patients III:3, III:4, and III:5 from family RP251 had dark-adapted field tests performed before age 15 years. In each case, there was a significantly greater impairment of the scotopic visual field when performed with the blue filter in situ than with the red filter (Figure 7). This implies a predominant dysfunction of the rod system, consistent with the observation that nyctalopia is the initial feature of this retinal dystrophy. Photopic visual fields
in these younger family members revealed significant defects within the central 30°, but they were frequently asymptomatic. Esterman binocular visual fields in these patients were usually within the standards required for driving in the United Kingdom.

The progression of field loss in early adulthood is illustrated by Goldmann kinetic perimetry performed in individual II:4 from family RP3097 at age 26 years (Figure 8), which revealed bilateral midperipheral ring scotomata, with sparing of (1) the central 10° to 20°, (2) a thin rim of inferonasal peripheral field, and (3) the temporal periphery.

In affected individuals older than 40 years, the photopic visual fields, performed using the standard 30-2 Humphrey program, were restricted to less than 10°, indicating that photopic visual field loss initially affects the midperiphery and then progresses to include the far periphery and more of the central field.

ELECTROPHYSIOLOGIC FINDINGS

Electrophysiologic assessment was undertaken on patients II:2, II:4, II:10, III:4, III:5, III:7, and III:9 from family RP251 (aged 44, 43, 39, 18, 17, 15, and 19 years, respectively) (Table 2 and Figure 9).
Electrophysiologic testing revealed a nondetectable scotopic ERG in all 7 patients. In the 3 youngest patients tested (aged 15-18 years), there was relative preservation of the photopic ERG, 30-Hz flicker response, and pattern ERG. White stimulation under conditions of dark adaptation resulted in an ERG with a “negative” waveform, the amplitude of the a-wave exceeding that of the b-wave in all 6 eyes. The 30-Hz flicker responses were delayed and reduced in amplitude. Visual acuity was 6/6 bilaterally in individuals III:5 and III:7 and 6/12 bilaterally (owing to macular edema) in individual III:4.

Long-duration stimuli were also used to separate the “ON” and “OFF” photopic pathways in patient III:7, whose cone-mediated responses were well preserved. The ON response showed a negative waveform, whereas the OFF response was well formed and showed no unequivocal abnormality. Patient III:9 (aged 19 years) demonstrated severe reduction in the amplitude of the photopic transient and 30-Hz flicker responses. In addition, his pattern ERG was

Figure 7. Dark-adapted visual fields of patient III:5 from family RP251 performed at age 13 years with blue (450-nm) (A) and red (650-nm) (B) filters in the stimulus beam. Significantly greater impairment is observed with the blue filter in situ, implying a predominant dysfunction of the rod system.

Figure 8. Goldmann kinetic perimetry performed in individual II:4 from family RP3097 (aged 26 years) shows a midperipheral ring scotoma, with sparing of the central 10°.
markedly subnormal despite a visual acuity of 6/9 bilaterally. In older patients, all components of the ERG were nondetectable, reflecting the progressive involvement of cones in the disease process. Visual acuity in these individuals ranged from 6/9 to 4/60 (Table 1). The light rise in the electro-oculogram was grossly reduced (120%) or abolished in the 2 individuals tested (patients II:4 and III:9).

**cSLO FINDINGS**

Images from cSLO of the macula in younger patients revealed a bright ring of increased autofluorescence around the fovea, which persists until the development of macular atrophy (Figure 10). In older patients, areas of hyperautofluorescence on cSLO images corresponded to areas of macular atrophy observed on funduscopy, confirming the loss of photoreceptor cells.

### DEFINING THE NRL S50T PHENOTYPE

Many of the clinical features of the retinal dystrophy associated with the NRL S50T mutation are similar to those observed in patients with RP due to mutations in *rhodopsin*, *peripherin-RDS*, or other, as-yet-unidentified, genes. Classically, the first symptom of RP is nyctalopia, with later onset of problems relating to visual field loss, and, last, variable reduction of central vision. Visual field loss typically begins in the midperiphery rather than in the far periphery. Peripheral intraretinal pigment migration is associated with retinal pigment epithelium atrophy. Except for a few geographically limited forms of RP (sectorial RP), the scotopic ERG usually becomes severely reduced during the course of the disease.

Several features of the phenotype associated with the NRL S50T mutation may, however, serve to distinguish it from other forms of RP:

1. In younger family members, electrophysiologic testing typically demonstrates a remarkable preservation of cone function at a time when rod function is severely compromised.

2. The negative waveform of the dark-adapted maximal (bright white flash) ERG response is well recognized in certain disorders such as X-linked retinoschisis but is unusual among RP phenotypes. Since the first 10 to 12 milliseconds of the a-wave is generated in relation to photoreceptor hyperpolarization, whereas the b-wave arises in the inner retina, the relative preservation of the a-wave in this dystrophy is of particular interest.

The relatively greater reduction in b-wave amplitude suggests inner retinal dysfunction and may represent a direct effect of the NRL mutation, mediated by its expression in other cells of the neural retina, or an indirect effect due to loss of rods.

Histologic studies of human retinas affected by RP have demonstrated that rods, amacrine cells, and horizontal cells may all undergo neurite sprouting in regions with significant photoreceptor loss. When neurite sprouting occurs, most rod neurites bypass the dendrites of horizontal and bipolar cells, the normal targets of rod axons in the outer plexiform layer, and directly contact the hypertrophied processes of Müller cells, which have undergone reactive gliosis in response to photoreceptor cell death, and the somata of amacrine cells. These changes in retinal neuronal circuitry may contribute to the ERG abnormalities observed in RP and in some instances to the development of an ERG in which the b-wave is of lower amplitude than the a-wave.

3. The development of macular thickening seems to be a natural stage in the progression of this dystrophy. Although a proportion of patients with RP will develop cystoid macular edema, fluorescein angiographic findings indicate that this is not the mechanism by which macular thickening arises in these individuals.

4. A striking bull’s-eye pattern of macular atrophy, with attendant loss of visual acuity, more typical of that seen in cone-rod dystrophies, is observed in older individuals.

5. Peripapillary chorioretinal atrophy, similar to that seen in high myopia but not a common feature of inherited retinal dystrophies, occurs with disease progression. Histologic analysis of age-related peripapillary atrophy has demonstrated degeneration of the retinal pigment epithelium–Bruch membrane complex, with concomitant loss of rod photoreceptors, which resembles the degeneration that may be found in the macula and periphery of aging eyes.

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**Table 2. Results of Electrophysiologic Assessment in 7 Patients From Family RP251**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Scotopic</th>
<th>Maximal</th>
<th>30-Hz Flicker</th>
<th>Photopic</th>
<th>Pattern</th>
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<tr>
<td>II:2</td>
<td>44</td>
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<tr>
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<tr>
<td>II:10</td>
<td>39</td>
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<td>0/0</td>
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<td>0/0</td>
</tr>
<tr>
<td>II:14</td>
<td>18</td>
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<td>115/95</td>
<td>80/60</td>
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<td>Delayed/delayed</td>
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<td>Delayed/delayed</td>
<td>5.0/4.0</td>
<td>0.6/0.9</td>
</tr>
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</table>

**Abbreviations:** ERG, electoretinography; L, left; R, right.
Atrophy is also observed in the macular and peripapillary regions in myopia and in the peripapillary region alone in chronic glaucoma. Progressive peripapillary chorioretinal atrophy in patients with the NRL S50T mutation may, therefore, be mirroring the atrophic changes occurring in the macula and retinal periphery.

Each of these features may well be found in isolation in patients with retinal dystrophies due to other ge-
Before the development of molecular classifications, adRP was classified according to the pattern of photoreceptor degeneration. Type 1 or diffuse adRP is characterized by diffuse loss of rod function with relative preservation of cone function in the early stages of the disease. Patients frequently seek care early, with night blindness evident before age 10 years. Further visual symptoms and retinal pigmented changes, however, may be delayed for 10 to 20 years after the onset of disease. There is good evidence that loss of visual sensitivity in the early stage of disease is due to cell dysfunction rather than cell death. In contrast, type 2 or regional adRP, which is more common, displays regional or patchy loss of rod function accompanied by concomitant loss of cone function in the affected areas. Type 2 adRP has a variable age of onset and may rapidly progress to develop symptomatic visual field loss. In this form of RP, loss of function can be explained by cell death or loss of outer segments. The NRL S50T phenotype would clearly be defined as a type 1 adRP according to this classification.

For patients living in relatively wealthy, industrialized societies, where populations are often concentrated in artificially illuminated towns and cities, the early onset of night blindness may have a minimal impact on employment prospects (with the exception of the Armed Services) and other activities. However, visual field loss occurs relatively early in patients affected by the NRL S50T mutation dystrophy, resulting in failure to conform to legal requirements for driving between ages 20 and 30 years. This may be particularly disabling if the individual lives in a remote area or relies on a car for work. The apparently inevitable loss of cone function and visual acuity observed in older patients will have the greatest effect on employment and leisure activities.

Comparison with published data on the RP phenotypes associated with other genotypes may be misleading, but the NRL S50T mutation phenotype seems to be more severe in terms of visual acuity loss than that seen with the most common well-characterized RP-causing mutation, rhodopsin Pro23His.

**MOLECULAR BIOLOGY OF NRL S50T: A MECHANISM FOR DISEASE?**

The S50T mutation exchanges a serine residue for the related amino acid threonine at position 50 in 1 of 2 highly conserved regions of the transactivation domain of the NRL protein. This may alter NRL’s activity, specificity, or ability to interact with other transcription factors. In vitro, a significant increase in the transactivation of the rhodopsin promoter has been observed with the mutant NRL S50T protein, suggesting that the NRL S50T mutation may result in increased transcription of rhodopsin, and possibly of other photoreceptor genes, in vivo. Because rhodopsin is the major structural protein of rod outer segments, and overexpression of rhodopsin has been shown to cause photoreceptor cell death, this may be the mechanism by which the NRL S50T mutation initiates retinal degeneration.

The subsequent loss of cone function may be due to the breakdown of a structural or physiological dependence on the rods. Alternatively, it may result from an inability of the retinal pigment epithelium to deal with the increased amounts of rhodopsin and other proteins contained in phagocytosed rod outer segments. The ring of increased autofluorescence observed in cSLO images may lend support to the latter hypothesis.

Mutations in the cone-rod homeobox gene (CRX) encoding another transcription factor, which functions synergistically with NRL in regulating rhodopsin promoter activity, have been shown to cause autosomal dominant cone-rod dystrophy (CORD2) and recessive Leber congenital amaurosis. NRL protein is expressed primarily in rods, whereas CRX is present in rods and cones. This expression pattern may determine that the NRL S50T mutation produces a rod-cone dystrophy, manifesting with nystagmus due to early severe loss of rod function, whereas CRX mutations cause cone-rod phenotypes initially manifesting with loss of visual acuity.

**SUMMARY**

Four ancestrally related families with the NRL S50T mutation have so far been identified. This mutation causes a severe progressive retinal dystrophy affecting first the rod and subsequently the cone photoreceptors (rod-cone dystrophy). Rod function, as assessed by electrophysiologic and psychophysical testing, is profoundly impaired in the first 2 decades of life, at a time when cone function remains relatively well preserved. Significant loss of cone function occurs as the disorder progresses, and in older individuals, all components of the ERG are undetectable. Patients almost invariably develop macular thickening, frequently together with a mild reduction in visual acuity, between ages 15 and 30 years. As the disease progresses, a substantial loss of visual acuity (6/36 or worse) is usually observed, typically in association with the development of a bull’s-eye pattern of macular atrophy. Peripheral intraretinal pigment formation is sparse, even in the later stages of the disease. Distinctive peripapillary choriotrebral atrophy develops as the dystrophy progresses.
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