Precise phenotyping is crucial to a diagnosis of retinal disorders and to the appropriate selection of patients for clinical studies designed to evaluate treatment efficacy. To this end, multi-modal fundus imaging technologies have greatly facilitated improved understanding of the natural histories of various retinal diseases. A combination of imaging modalities can overcome the limitations of single approaches and can expand the scope of information that can be acquired. Spectral domain optical coherence tomography (SD-OCT) enables noninvasive visualization of normal and pathological retina and is a standard diagnostic tool in clinical ophthalmological diagnosis. The high-resolution images afforded by SD-OCT make it possible to discern multiple hyperreflective bands in human outer retina. Accordingly, SD-OCT has enabled fundamental insights into retinal disease processes including those impacting photoreceptor and retinal pigment epithelial (RPE) cells. For instance, in retinitis pigmentosa, termination of the hyperreflective ellipsoid zone (EZ) is used to identify the boundary between healthy and degenerated photoreceptor cells under conditions of centripetal disease progression. Intactness of the external limiting membrane (ELM) and EZ is also a strong predictor of visual improvement in eyes undergoing surgery for diabetic macular edema whereas in the setting of geographic atrophy, photoreceptor cell degeneration is connoted by loss of integrity of the ELM and EZ and by thinning of the outer nuclear layer (ONL).

Hyperreflective focal lesions that incorporate photoreceptor-attributable bands in SD-OCT images are features of some retinal diseases of varying etiology (Table). Among these are two monogenic diseases associated with white dot-like fundus lesions caused by mutations in genes encoding proteins of the visual cycle, retinol dehydrogenase 5 (RDH5) and retinaldehyde-binding protein 1 (RLBP1). Also included in this group are two retinopathies associated with disease variants in ATP Binding Cassette Subfamily A Member 4 (ABCA4) and peripherin-2/retinal degeneration slow (PRPH2/RDS); both disorders present with fundus flecks. The correlates of fundus patterning recognized as reticular pseudodrusen (RPD) in AMD also take the form of hyperreflective foci that extend radially through photoreceptor cell-attributable bands in SD-OCT scans.

Comparisons amongst white dots, flecks and RPD have not previously been considered yet structural correlates could provide insight into underlying disease mechanisms. Here we will visit similarities and differences in the fundus presentation of these lesions when viewed by near-infrared fundus autofluorescence (NIR-AF) that translates a signal of healthy photoreceptor cells.

Keywords: fundus autofluorescence, spectral domain optical coherence tomography, retina, retinal pigment epithelium, retinal disorder, scanning laser ophthalmoscopy, flecks, white-dots, reticular pseudodrusen
from melanin, short-wavelength fundus autofluorescence (SW-AF) originating in bisretinoid lipofuscin, and SD-OCT. In one case ultrawide-field pseudocolor fundus images are included. By way of illustrating the structural features of interest we present representative images together with references to the literature. We suggest that an element common to these lesions is the involvement of RPE in the pathological processes and in establishing the fundus patterning. We also propose that these lesions are the products of degenerative processes in photoreceptor cells that are preceded by RPE dysfunction.

### White Dot-Like Lesions Associated With Deficiencies in the Visual Cycle

Fundus characteristics associated with mutations in both *RLBP1*/*CRALBP* and *RDH5* are recognized in color fundus photographs by the presence of numerous discrete white dot-like lesions. Hence, in the ultrawide-field pseudocolor fundus photograph shown here (Figs. 1A, 1B), lightly pigmented puncta are prominently visible in peripheral fundus where they are organized within radial arrays of contrasting pigmentation. This pattern is established by RPE and is similar to the pattern of alternating pigmented and non-pigmented RPE cell clones detected in carriers of ocular albinism due to mutations in *GPR143/OA1*.31,32 The near-infrared fluorescence signal from melanin is also reduced (Figs 1C, 2A, 3A).

The protein product of *RLBP1* (cellular retinaldehyde binding protein [CRALBP]) and the protein (11-cis-retinaldehyde dehydrogenase) encoded by *RDH5* are both expressed in RPE cells where they function in the visual cycle to promote regeneration of 11-cis-retinaldehyde.33 Accordingly, we have demonstrated here (Figs. 2B, 3B) and previously that SW-AF intensities are reduced in patients carrying disease-causing variants in *RLBP1* and *RDH5*. Against the background of hypoautofluorescence, a fine granular autofluorescence is visible centrally in SW-AF images (Figs. 2B, 3B) in both *RLBP1*/*CRALBP*-associated and *RDH5*-associated disease (Figs. 2, 3). Target-like configurations presenting as a center and surround of contrasting intensities, are distinctly visible in the pseudocolor (Fig. 1B), NIR-AF (Figs. 1C, 2A, 3A) and SW-AF images (Figs. 2B, 3B) in both *RLBP1*/*CRALBP*-associated and *RDH5*-associated disease. Aberrations in the SD-OCT scans correspond to the dots observed in the en face images (Fig. 1D).12 As shown in Figures 1 and 2, the SD-OCT images acquired from the patients carrying mutations in *RLBP1* reveal multiple hyper-

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**TABLE. Multimodal Imaging: Shared Features of Interest**

| Clinical/Genetic Diagnosis | Expression of Protein Product | Presentation in SD-OCT Scans | Foci Presenting in En Face Images | SW-AF Signal at Foci Relative to Surround | NIR-AF Signal at Foci Relative to Surround |
|----------------------------|-------------------------------|-----------------------------|----------------------------------|------------------------------------------|------------------------------------------|
| Retinitis punctata albescens | *RLBP1*                       | RPE                         | Radial progression of hyperreflective thickening of IZ, EZ; interruption of EZ and ELM; thinning of ONL | Dots | Bright |
|                             |                               |                             |                                  | Dark center with bright surround         |                                           |
| Fundus albipunctatus        | *RDH5*                        | RPE                         | Dots                            | Bright | Dark center with bright surround         |
| Ret. Stargardt disease      |                                | Photoreceptors              | Flecks                          | Bright | Reduced or occasionally increased       |
| Pattern dystrophy           | *PRPH2/RDS*                   | Photoreceptors              | Flecks                          | Bright | Reduced or increased                     |
| RPD/AMD Complex             | Complex                       | —                           | RPD                             | Dark center with bright surround         | Dark center with bright surround         |

EZ, ellipsoid zone; IZ, interdigitation zone.
shared features in RPE-involved disorders

Figure 2. Fundus images of a 13-year-old patient carrying compound heterozygous mutations in RLBP1. (A) NIR-AF image (787 nm). (B) SW-AF (488 nm). Depigmented foci are dark in NIR-AF and SW-AF images. (C) SD-OCT scan. (D) Magnification of area in C. Images are representative of two patients.

Figure 3. Fundus images obtained from a patient (age 14 years) exhibiting mutations in RDH5/11-cis-retinol dehydrogenase. (A) NIR-AF (787 nm). (B) SW-AF (488 nm). Arrows are color-coded (yellow, green, blue, white) to indicate corresponding lesions visible in the two modalities. Depigmented foci are dark in NIR-AF and SW-AF images. (C) SD-OCT (right) with IR-R (left). The horizontal axis of the SD-OCT image is indicated in the IR-R image by the green line ending in an arrow. Corresponding foci in A and C are indicated by red arrows. The detectability of the autofluorescent puncta (B) in SW-AF images despite RDH5 deficiency and reduced availability of 11-cis-retinaldehyde is likely enabled by the use of a higher than typical sensitivity setting; by image processing that enhances contrast by stretching intensity values to span the full grayscale range (0–255); and by reduced signal attenuation by photopigment and melanin. Reflective thickenings of the IZ along with altered contours of the EZ (Figs. 1E, 2C). Outer retinal aberrations akin to those described above, together with punctate white dots in the fundus are also features of vitamin A deficiency.36,37

Diseases Exhibiting Fundus Flecks

ABCA4-related and PRPH2/RDS-associated diseases are, respectively, autosomal recessive and autosomal dominant forms of inherited retinopathies. In both cases, the disease-causing gene is expressed in photoreceptor cells and in both disorders, patients exhibit autofluorescent fundus flecks (Figs. 4A–4C, 4E–4G, 5E).2,14–21 The ABCA4 protein is involved in the handling of retinaldehyde while PRPH2/RDS plays a key role in the formation of outer segment disks.39 The brightness of flecks in ABCA4-disease is associated with elevated levels of bisretinoid lipofuscin; the latter forms in photoreceptor cells and accumulates in RPE.40,41 These fluorophores confer a dark choroid in ABCA4-affected patients undergoing fluorescein angiography and are the source of elevated SW-AF.40–42 Conversely, in the presence of PRPH2/RDS mutations a “dark choroid” in fluorescein angiograms is not observed19 and based on quantitative fundus autofluorescence measurements, SW-AF intensities are only modestly elevated in a subset of patients.43 Some flecks in both ABCA4- and PRPH2/RDS-associated diseases are accompanied by a halo of reduced SW-AF (Figs. 4A–4C, 4E–4G, 5E, orange arrow) and central older flecks.
FIGURE 5. Fundus images presenting disease features characteristic of PRPH2/RDS-associated disease. Patient age 36 years (A–D). IR-R (left) and SD-OCT (right) scans. The horizontal axis of the SD-OCT image is indicated in the IR-R image by the green line. Corresponding flecks in IR-R and SD-OCT images are indicated by arrows of the same color. (E) NIR-AF (787 nm). Corresponding flecks in A to F are indicated by colored arrows. Note flecks exhibiting hyperautofluorescence or hypoautofluorescence. Images are representative of seven patients (14 eyes).

FIGURE 6. Fundus images of RPD (age 90 years) and L-ORD (age 63 years). (A) RPD: IR-R. (B) RPD: SD-OCT. (C) RPD: SW-AF (488 nm). (D) NIR-AF (787 nm). RPD colocalize as darkened foci in SW-AF and NIR-AF and as conical-shaped lesions (orange arrows) that extend through the interdigitation zone and ellipsoid zone bands in SD-OCT scans. The central green line in A indicates the horizontal axis of the SD-OCT scan. RPD images are representative of nine patients (18 eyes). (E, F) IR-R (E) and corresponding SD-OCT image (F) of fundus of patient carrying the single missense variant S163R in CTRP5/C1QTNF5 [c.489C>A); p.(Ser163Arg)] conferring L-ORD.

Diseases Presenting With Reticular Fundus Patterns

In SW-AF and NIR-AF images RPD are readily identified as interlacing ribbons, circular or oval foci with darkened centers and a brighter annulus (Figs. 6C, 6D).

Conversely, the NIR-AF signal originating in melanin at the position of flecks in both ABCA4- (Figs. 4D, 4H) and PRPH2/RDS-associated disease (Fig. 5F) are more often hypoauflorescent than hyperautofluorescent, and the profiles are often larger in NIR-AF images than in SW-AF images (Figs. 4H, 5F). In SD-OCT images acquired from individuals having ABCA4- and PRPH2/RDS-disease, flecks co-localize with hyperreflective barrel- or pyramidal-shaped profiles (Figs. 4A–4C, 4E–4G, 5A–5D). In some cases the hyperreflectivity is limited to thickening of the IZ and EZ whereas in other cases flecks extend anteriorly through the EZ and ELM. ONL thickness decreases as the lesion expands anteriorly and progressively incorporates photoreceptor-attributable SD-OCT bands. Flecks in ABCA4-disease have been shown to originate at the level of photoreceptor cells. Accordingly, fleck hyperautofluorescence originating from impaired photoreceptor cells in the presence of PRPH2/RDS mutations might also explain the relative brightness of the flecks even as retina-wide bisretinoid lipofuscin formation is not increased with PRPH2/RDS mutations.

AF images are similarly darkened in NIR-AF images (Figs. 6C, 6D); the brighter annulus also colocalizes in the two modalities. While in SW-AF images the presence of macular pigment obscures the visibility of RPD in central-most retina, these lesions are readily visible centrally when examined with NIR-AF (Figs. 6C, 6D). RPD lesions visible in fundus images of AMD patients confer increased risk of advanced disease. As with white dots and flecks, RPD colocalize with hyperreflective lesions in photoreceptor-attributable SD-OCT bands (Fig. 6B). Some RPD lesions present as either shallow corrugations of IZ and EZ bands that may be indicative of disease beginning in outer segments or at later stages as rectangular, oval or pyramidal shaped foci that extend radially through photoreceptor cell-attributable bands progressively interrupting IZ, EZ, and ELM. RPD are associated with ONL thinning. The SD-OCT lesions corresponding to RPD in SW-AF images do not displace outer retinal layers anteriorly as would be expected of extracellular deposits. Hypertransmission of SD-OCT signal into the choroid is observed in connection with some RPD (Fig. 6B); this feature is indicative of local RPE atrophy in association with these RPD.

The SD-OCT aberrations discussed above are not limited to RPD in the setting of AMD. For instance, reticular patterning is visible in the fundus of patients with late-onset retinal degeneration (L-ORD), an autosomal dominant disorder that...
is caused by a p.Ser163Arg point mutation in the complement 1q tumor necrosis factor 5 gene (*CTR5/C1QTNF5*) that is expressed in RPE and ciliary epithelium.56–58 Spots of hypoautofluorescence surrounded by halos of slightly brighter autofluorescence in SW-AF images are considered to be the equivalent of the dot-like sub-type of RPD.

In SD-OCT scans the reticular patterns co-localize with scalloped irregularities of the IZ and EZ reflectivity bands, and in more advanced cases, with conical lesions extending through the EZ line and into the thinner ONL. (Figs. 6E, 6F). Both RPD and L-ORD are associated with abnormalities in dark-adaptation and progression to loss of RPE and photoreceptor cells.53,56,61

Another example is available from the literature. The undulations and discontinuities of the EZ band observed in SD-OCT scans in association with Sorsby fundus dystrophy have also been likened to RPD.13,62 In SW-AF images these lesions appear target- or ribbon-like.62 This autosomal dominant macular dystrophy caused by variants in the gene encoding tissue inhibitor of metalloproteinase-3 (*TIMP3*) leads to RPE cell loss.63

**COMMENTS**

Features of white dots, flecks and RPD lesions suggest that RPE are disabled or atrophied at these positions. For instance, the punctate lesions taking the form of flecks are typically hyperfluorescent in fluorescein angiograms in association with *PRPH2*/*RDS*-associated disorders.34 White dot lesions associated with mutations in *RLBP1* are also hyperfluorescent in fluorescein angiograms.64 These window defects indicate that the RPE monolayer is not fully intact. Also indicative of a breach in the RPE monolayer is evidence of hypertransmission of OCT signal into the choroid. RPD in AMD are often but not always associated with increased transmission of OCT signal into the choroid.29,48,54,55

Flecks in association with disease variants in *ABCA4* or *PRPH2*/*RDS* can be associated with hypertransmission into the choroid or the fleck can cast a shadow;2,22 the latter may be due to screening by elevated fluorophore concentrations in the outer segments. In the presence of *RLBP1*/*CRALBP* and *RDH5* mutations hypertransmission is widespread (Figs. 1–3). Reduced NIR-AF intensities in patients diagnosed with *RDH5*, and *RLBP1*/*CRALBP*-related disease are also suggestive of thinned or atrophied RPE. NIR-AF signal is substantially reduced at many but not all fleck loci in *ABCA4* and *PRPH2*/*RDS*-associated diseases (Figs. 4, 5) whereas RPD in SD-OCT scans colocalize with NIR-AF that is reduced but not absent. Reduced NIR-AF signal suggests a reduction in melanin that could be accounted for by RPE thinning. With regard to alternative interpretations, we note that the reduced NIR-AF signal is unlikely to be due to absorption by tissue anterior to the lesion. For instance, as noted above, increased transmission of signal into the choroid can be observed in SD-OCT scans in the presence of flecks, dots and RPD and in some cases the NIR-AF of flecks is even increased (Fig. 4).

**FINAL THOUGHTS**

In many forms of RP, mutations in photoreceptor-specific genes lead to retinal degeneration with widespread death of rods and cones.55–69 Yet orderly photoreceptor cell degeneration proceeds without the formation of punctate lesions in en face images nor the presence of intermittent hyperreflective foci in SD-OCT scans. Conversely, in other retinal diseases of varying etiology, photoreceptor cell-attributable bands in SD-OCT scans are interrupted intermittently by hyperreflective focal lesions. We suggest that in diseases associated with flecks, white-dots and RPD, the hyperreflective focal aberrations visible in SD-OCT scans represent degenerative changes in groups of photoreceptor cells secondary to disease processes in the underlying RPE. The hyperreflective shallow corrugations observed in the IZ and EZ bands of SD-OCT scans may be indicative of disease beginning in outer segments. These disease processes can arise because of mutations in genes whose protein product is expressed in photoreceptor cells (*ABCA4*/STGD1; *PRPH2*/RDS) yet severely impact RPE. In other cases the mutated genes are expressed in RPE (*RLBP1*/CRALBP and *RDH5*). Just as the hyperautofluorescent fundus rings in RP track the progress of photoreceptor cell degeneration, flecks, white-dots and RPD may signify photoreceptor cell degeneration in some retinal diseases involving RPE. Additional studies are warranted to determine whether the rate at which the punctate lesions extend radially and the frequency of the lesions at any given time are determined by genetic factors.

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