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RETINITIS PIGMENTOSA IN THE NAVAJO

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CLYDE FARSON,** and GARY PABALIS**

Abstract—Two types of retinitis pigmentosa have been identified in the Navajo population which are ophthalmoscopically different, and which have different clinical courses. The recessive form has a fundus appearance that reveals the grey granular surface of the exposed choroid due to retinal pigment epithelial dropout, and there is little pigment clumping even in advanced cases. Clinically, this suggests that this group has a retinal pigment epithelial dystrophy. Patients are typically blind by age 30.

The dominant form has a traditional RP fundus picture with bone spicules and large clumps of pigment, with blindness generally occurring by age 40 to 55. Both have a childhood onset with affected members easily being identified by age 6. The known frequency of the two types is 1/1878, with true incidence undoubtedly being greater.

Key words: Retinitis pigmentosa Retinal pigment epitheliopathy Fluorescein angiography Choriocapillaris Navajo

Retinitis pigmentosa (RP) is the generic name given to a set of diseases characterized by night-blindness, and a slow progressive visual field loss. Central vision is commonly preserved until advanced stages of the disease process. The diagnosis is often confirmed by an abnormal electroretinogram, constricted visual field test, and characteristic fundus changes including pigment deposits in the retina, optic atrophy, and vascular attenuation. However, these features are not always consistently present in all RP patients.

Since RP has been found in all major ethnic and racial groups, and has been reported from all parts of the world [1], it is not surprising that two forms of retinitis pigmentosa have been found in the Navajo Indian.

The first type of RP is inherited in the autosomal dominant pattern, and has been traced back three generations to a brother and sister who are still living (Fig. 1). The second variety is inherited in the autosomal recessive manner, and has been found to occur on all parts of the reservation. No evidence of the X-linked form of RP has been found in the Navajo Indian population.

MATERIALS AND METHODS

During routine eye examinations, 76 full-blooded reservation Navajo Indians have been identified with retinitis pigmentosa on the basis of the clinical examination. The patients were seen in the U.S. Public Health Service Hospitals and Clinics on the Navajo reservation in Arizona and New Mexico. Special attention was given to age, best corrected visual acuity, family history, biomicroscopy, and fundus appearance.

Electroretinography and fluorescein angiography was performed at a referral hospital in two sisters from a recessive pedigree who had RP and unilateral peripheral neovascularization [2]. Fundus photos were taken with both the Kowa portable fundus and Zeiss fundus camera. Pedigrees were prepared on the dominant family as part of a study on linkage analysis.

Statistical analysis of age and visual acuity data was undertaken with the assistance of the Department of Biomathematics, Computer Center, UCLA Center for the Health Sciences.

RESULTS

Forty-three patients, 23 females and 20 males, were identified with the autosomal recessive forms of retinitis pigmentosa. Most parents were examined and none were found to have carrier signs or any sign of retinal disease. The electroretinogram of two patients, ages 21 and 12, was

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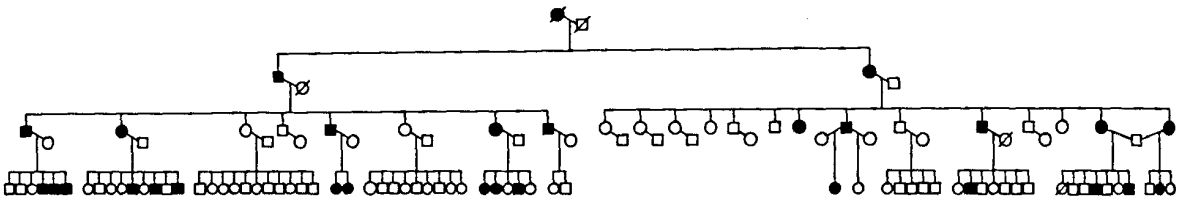


Fig. 1. (Heckenlively *et al.*) Pedigree of Navajo family with dominantly inherited retinitis pigmentosa. All affected and most unaffected members have been examined. Males are represented by squares, females by circles, affected symbol filled in, deceased shown with diagonal line through symbol.

non-recordable. Visual fields are constricted, and the maculae appear grossly normal, or have subtle retinal pigment epithelial (RPE) mottling with loss of the foveal reflex. Most patients initially are referred to the eye clinic with blurred vision and nightblindness when they are 8–14 years old. Best corrected vision is usually 6/15–6/30 (20/50–20/100) at this time. No affected patient had a visual acuity better than 6/9 (20/30). The clinical course is steady deterioration with blindness by age 30. Small posterior subcapsular cataracts are common in the advanced stages of the disease. Retinal vascular attenuation is minimally present, and on careful examination, optic nerveheads appear pink. Vitreous degeneration with condensates and clear veils are found in both the dominant and recessive RP patients, but this finding is not unusual in the Navajo population as a whole.

The autosomal recessive variety can be identified as early as five years of age, and parents report noting signs of nightblindness as early as two years of age. In the early stages, the fundus pattern is characterized by a grey granular appearance in areas of focal thinning of retinal pigment eipthelium, exposing the choroid (Fig. 2). As the disease progresses, these areas become confluent, giving an overall grey granular appearance, and the islands of intact RPE are quite noticeable. There is miminal pigment aggregation or dispersion, and bone spicules or large clumps of pigment are not seen (Fig. 3).

The process starts in the midperiphery and becomes more generalized, advancing anteriorly and posteriorly over a period of years. On fluorescein angiography, there is no blockage of the dye by the retinal pigment epithelium (Fig. 4), but the choriocapillaris is patent, relatively free

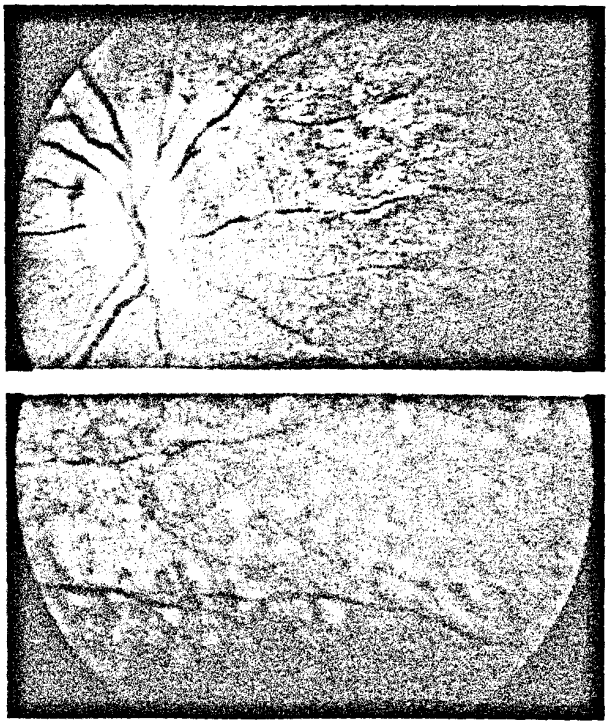


Fig. 2. (Heckenlively *et al.*) Ten-year-old Navajo girl with autosomal recessive RP demonstrating multiple areas with focal loss of retinal pigment epithelium superior temporally baring the choroid surface, and diffuse patchy loss nasal to the optic nerve.

Fig. 3. (Heckenlively *et al.*) Seventeen-year-old Navajo woman with autosomal recessive RP. Extensive loss of RPE exposing choroid gives grey granular fundus appearance. No bone spicule or pigmentary deposits are seen.

of damage. Clinically, these patients therefore have a primary retinal pigment epithelial dystrophy.

Thirty-three patients, 14 female and 19 males, with the autosomal dominant form of retinitis pigmentosa were examined from a large pedigree (Fig. 1). Only three members had better than 6/9 (20/30) vision. The pigmentary fundus changes were typical of RP, with aggregation of pigment into large clumps and/or bone spicules throughout the fundus (Figures 5a and 5b). Affected children could clearly be identified by

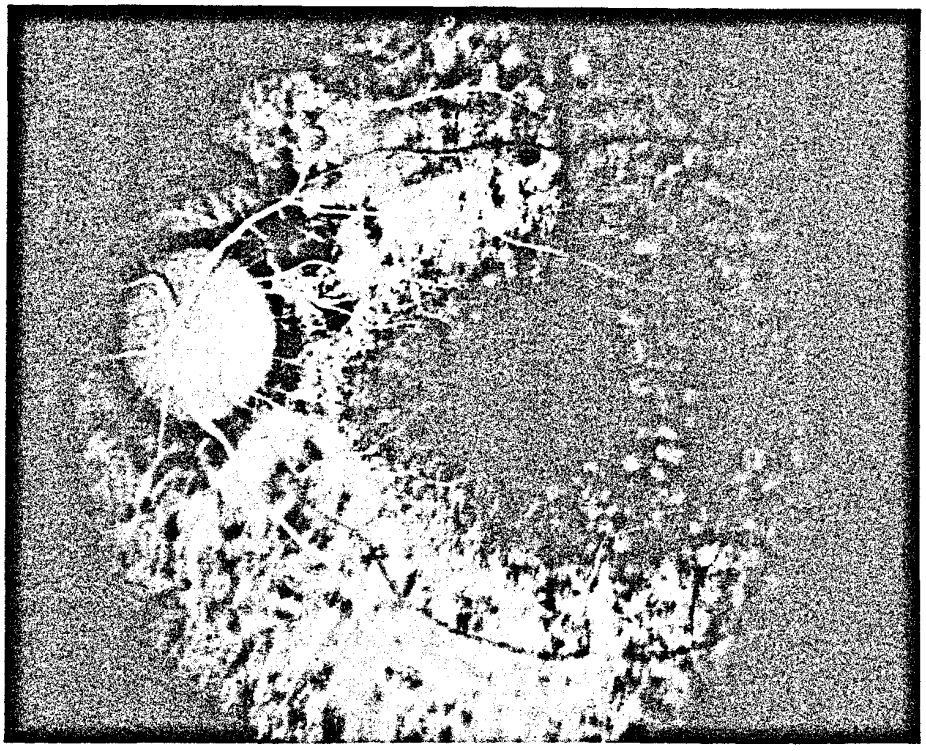
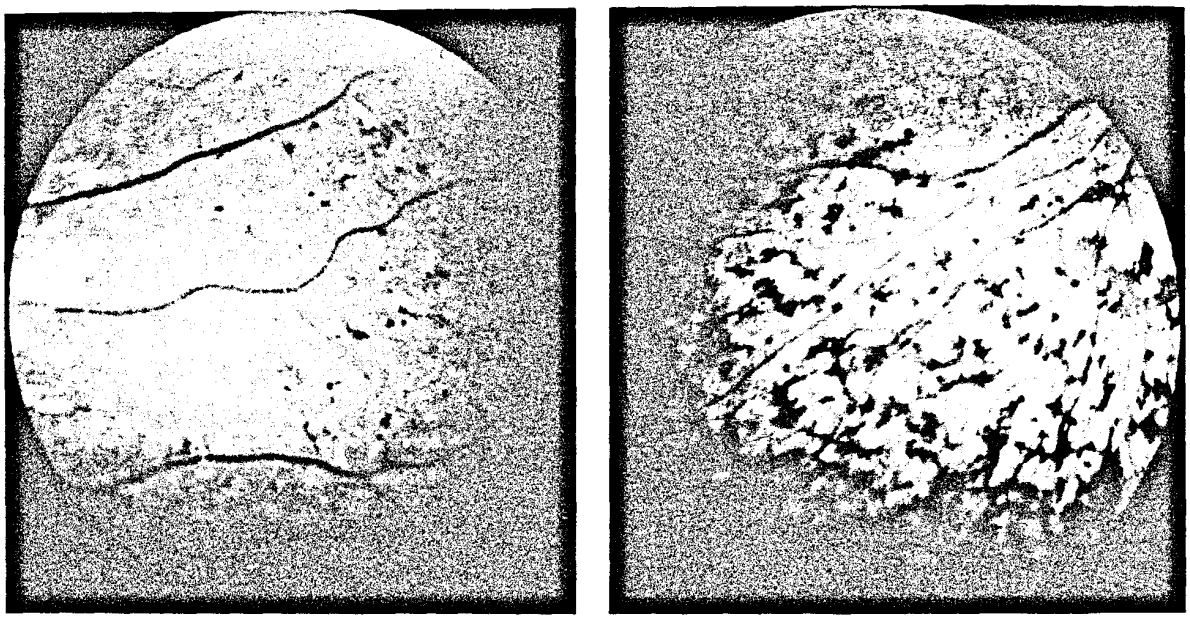


Fig. 4. (Heckenlively *et al.*) Fluorescein angiogram of 21-year-old Navajo woman with autosomal recessive RP. There is not blockage of fluorescence by the RPE, and the choriocapillaris is present in most areas. Diffuse fine pigment clumping is highlighted by the hyperfluorescent background.



Figs. 5a & 5b. (Heckenlively *et al.*) Eight-year-old Navajo boy (left) with autosomal dominant RP nasal to disc, demonstrating early pigmentary changes. Fourteen-year-old Navajo girl cousin (right) has heavy retinal pigmentary deposits.

age 5 on examination with the direct ophthalmoscope, as the pigmentary deposits can be seen nasal to the disc, and in the equator regions. Optic nerveheads usually appear pink until advanced stages of the disease. Vitreous degeneration was present in affected and unaffected family members. Pigment deposits could be seen in affected members in the anterior vitreous on biomicroscopy.

Other interesting incidental findings found in the affected and unaffected Navajo patients include high astigmatism, with the rule at 90°, commonly up to five diopters, and frequently pterygia.

The visual acuities of the recessive and dominant RP groups were compared to their ages. The data was plotted on a scattergram (Fig. 6). The two groups appear to segregate, with the recessive group demonstrating decreased visual acuities at an earlier age. An analysis of variance of the data confirms that the visual acuities differ significantly ($p < .0001$) after adjusting for age differences between the two groups. However, even though the dominant group visual acuity changes less with age than the recessive group, analysis fails to show a significant difference (regression slope 1.70 to 2.07). This suggests that the visual acuity deterioration rate is not significantly different between the two groups, but that the deterioration starts earlier in the recessive group.

The impression that the recessive group is affected at an earlier age is reinforced by looking at the mean ages of the RP clinic population; the recessives averaged 17.4 years, while the dominants averaged 29.4 years of age, suggesting that the recessive group's earlier disability encouraged them to present themselves for examination sooner.

DISCUSSION

Because the Navajo Nation is a relatively closed culture, with few marriages outside the tribe, it is reasonable to assume that the two forms of RP identified represent specific genetic entities.

This is important because it is not known how many genetic forms (i.e., specific gene loci) for RP are in existence. A careful study of retinitis pigmentosa in the Navajo population may impart a better understanding of the disease processes, because we know we are dealing with two specific types.

The possibility of different RP genes is the reason family studies are important, because it can be assumed that each affected member has the same gene defect, and secondary factors influencing the gene expression can be studied. Because dominant and X-linked genes are expressed more frequently in families, it has been more difficult to study the variability of gene expression in recessive diseases. However, the Navajos represent a unique group (simulat-

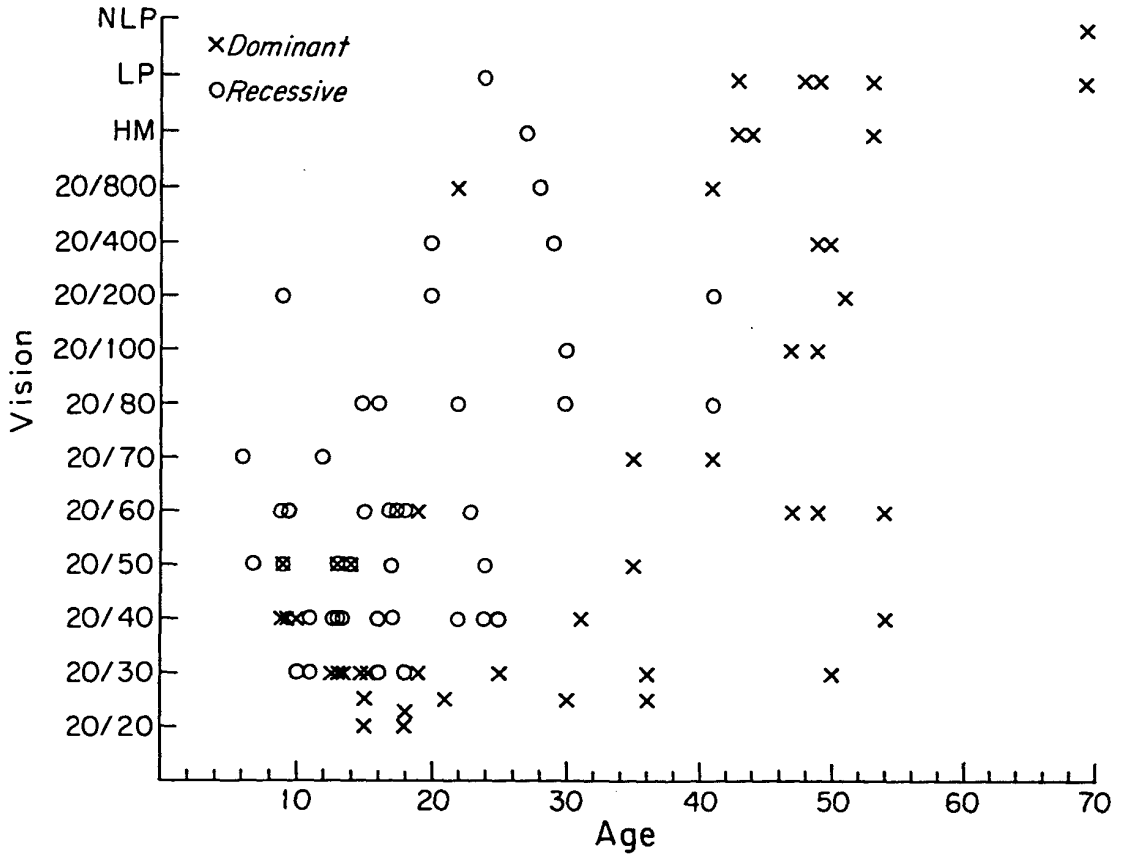


Fig. 6. (Heckenlively *et al.*) Scattergram of visual acuities plotted against age of patient for both RP groups. Each eye is plotted separately. Analysis of data confirms a significant difference of visual acuity between the groups, but once age is taken into account, the deterioration rate is not significantly different.

ing a large family) in which the heterogeneity of a recessive RP type can be studied. Secondary processes which in the past have been taken as part of the primary gene expression, can be identified. An example of this would be two recessive RP sisters who in addition to their retinitis pigmentosa had peripheral retinal neovascularization. As this change was not found in any of the other recessive RP patients, the RP and peripheral neovascularization would not be considered the result of a single gene action in these two patients.

The frequency of RP in the Navajo is higher than has been reported in other populations with 1/1878 known affected[1], compared to the usual quoted Caucasian RP frequency of 1/7000 [3]. This higher figure may be artefactual, since most Navajos eventually receive eye exams by the U.S. Public Health Service, while a large defined Caucasian population of similar size has not been reported to be examined specifically looking for the incidence of RP. However, the known Navajo RP frequency is constantly becoming greater as new cases are continuing to be found.

The childhood onset of RP in the Navajo may be influenced by environmental factors; Navajos are exposed to more sunlight than most Americans, as the skies are usually clear year round, and most of the reservation is over 5,000 feet which reduces atmospheric filtration of sunlight resulting in a tremendous midday glare. The rural lifestyle contributes to the amount of time spent outside, increasing the exposure to sunlight. Most Navajos do not wear sunglasses.

Traditional genetic counseling is being performed by trained Navajo nurses, though some patients react negatively to being counseled on risks. The problem is compounded by a tradition of large families, with 8 or more children being common. Consanguinity is less common than might be thought, as it is customary to marry outside the clan.

The statistical analysis of visual acuities with age of both groups is confirmatory evidence that the two diseases, which are ophthalmoscopically different, also act in different fashions. Interest-

[1] The 1979 Navajo census was 138,938 (Navajo Election Commission).

ingly, once the deterioration of central vision starts, the visual acuity change of the two groups is not statistically different. This is surprising in light of the fact that the diseases can be identified in both groups by age 6, and it would be expected that the deterioration rate of the dominant group would be slower than the recessive group since the visual acuity of the dominant group is better at later ages. Our data is in agreement with that of Fishman and Pearlman [4,5], in which there is a general deterioration of central vision with increasing age in RP populations. Our dominant group, like those reported by Jay and Krill [6,7] also shows later onset of central vision loss.

It is helpful to think about the retinal layer(s) of disease involvement in attempting to classify the various forms of RP. In the Navajo recessive group, the retinal pigment epithelium is diffusely lost, leaving the choriocapillaris relatively intact. In most forms of RP where the RPE is lost, the choriocapillaris frequently is missing on fluorescein angiography [8]. This suggests that in the Navajo recessive RP, the primary pathological process is in the RPE. The early dominant form has intact RPE except in areas of bone spicule formation.

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Reviewer's Comments—This is a fascinating report of two populations of Navajos, one with a dominant form of Retinitis pigmentosa and one with a recessive form. The description of the two types and the pedigrees are well documented. This is an interesting disease entity in a relatively closed population and should alert investigators to study such populations. The discussion also is most interesting and it would be fascinating to obtain pathologic specimens from these two apparently separate populations. I recommend publication of this well-written paper as is.