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Clinical Spectrum of Chromosome 6–linked Autosomal Dominant Drusen and Macular Degeneration

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- **PURPOSE:** To describe the clinical phenotype and the intrafamilial variation in retinal findings in a North American family with an autosomal dominant drusen disorder that maps to chromosome 6q14.
- **METHODS:** Ophthalmic examinations were carried out on participating family members. Fundus photographs were obtained whenever possible. Electroretinography was performed on the proband and her father. Blood was drawn for DNA analysis.
- **RESULTS:** Twelve family members had drusen and/or atrophic macular degeneration. The disease in asymptomatic young adults is characterized by fine drusen that are

See also pp. 197–202.

most conspicuous in the macula. The proband presented at 3 years of age with atrophic maculopathy and drusen. Her cousin was found to have atrophic macular lesions and drusen in the first year of life. Two older affected individuals have reduced vision from cicatricial and atrophic macular changes. The gene for the disease was mapped to chromosome 6q14 and appears to be adjacent to but distinct from the locus for North Carolina macular dystrophy.

- **CONCLUSIONS:** There is extreme variability in the clinical expression of this dominant form of drusen and macular degeneration. Most young adults have fine macular drusen and good vision. Affected infants and children may have congenital atrophic maculopathy and drusen. There is historical evidence of progression of the disease in late adulthood with moderate visual loss.

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THE DESCRIPTION OF INHERITED FORMS OF DRUSEN and macular degeneration goes back to at least 1875 when Hutchison and Tay¹ described three sisters with posterior pole drusen. These authors gave one of the earliest surviving descriptions of the disease that we now know as macular degeneration. In 1899, Doyne² described a family in which five of eight members had “bad sight.” He subsequently reported on three families carrying the same disorder, which he later called “honeycomb choroiditis.”³ In 1925, malattia leventinese, the clinical findings of which resemble those of Doyne honeycomb choroiditis, was detailed by Vogt⁴ in several Leventine Valley (Switzerland) families. Molecular genetic studies have proved that Doyne honeycomb retinal dystrophy and malattia leventinese are the same disease.^{5–8} Using careful genealogical sleuthing, Small⁹ found that another dominant retinal drusen and macular degeneration disorder, North Carolina macular dystrophy, had been described under different names in several branches of a large family. The disease was apparently inherited from three founding Irish brothers who lived in the late eighteenth and early nineteenth centuries.⁹ The responsible gene, MCDR-1, was mapped to chromosome 6q14-q16,¹⁰ and several European and South American families with this condition were also mapped to the same region.^{11–14} Klein and associates¹⁵ mapped a gene for age-related macular degeneration to 1q25-q31 in a large kindred. Sorsby macular dystrophy, another type of inherited macular degeneration, maps to chromosome 22 and results from mutations in the TIMP-3 gene.^{16,17} Lastly, a dominant form of Stargardt-like macular dystrophy was mapped to chromosome 6q.^{18,19} We present the clinical characteristics of a Pennsylvania family with a dominant drusen and atrophic macular degeneration that maps to 6q14 and appears to be genetically distinct from North Carolina macular dystrophy.²⁰

FIGURE 1. Pedigree of family with dominant drusen and macular degeneration. Squares = males; circles = females; filled squares and circles = affected; and open squares and circles = not affected.

SUBJECTS AND METHODS

INFORMED CONSENT WAS OBTAINED FROM ALL PARTICIPANTS or their guardians, and 27 family members and spouses were examined by the authors. Two members were examined by other ophthalmologists. These evaluations included, at a minimum, visual acuity on a near card and a dilated fundus examination. Fundus photographs were obtained on most patients using a portable fundus camera. An electroretinogram was performed on the proband and her father using a standardized protocol.²¹

Blood samples were collected, DNA was extracted, and gene mapping was performed using standard techniques and linkage analysis. The results of the mapping studies are reported in the companion article by Kniazeva and associates.²⁰

RESULTS

• **CASE REPORT:** The index patient (IV-4 in Figure 1) was noted by her mother to have inward deviation of the left eye shortly after 1 year of age. She was given glasses at the age of 2, and at age 3, with worsening of the esotropia, she was first examined by a pediatric ophthalmologist. Her visual acuity at age 3 years was RE: 5/30 and LE: 3/30 using Allen cards. Her anterior segment examination was normal, and there were no iris transillumination defects. Atrophic changes were noted in the macular area of both eyes, and she was referred for further evaluation. Ophthalmoscopy showed a lightly colored fundus with bilateral areas of geographic atrophy in the posterior pole and some drusen between the temporal vascular arcades (Figure 2). In each eye, the optic nerve head was normal and retinal vessels were of normal caliber. The peripheral fundus was pale and did not show any pigmentary changes. The patient was managed with optical correction of her partially accommodative esotropia. The retinal appearance

FIGURE 2. Proband (IV-4) at age 4 years. Posterior pole in the left eye. A prominent area of chorioretinal atrophy is present temporal to the fovea. A few drusen can be seen along the superior edge of the atrophic lesion.

remained unchanged over a 4-year follow-up, and visual acuity at the age of 7 years was RE: 20/40 and LE: 20/50. She developed a fine nystagmus with no specific pattern.

• **FAMILY STUDY:** There was a strong family history of retinal abnormalities. The proband's father, uncles, and other members of her family were said to have a retinal disorder that did not, for the most part, affect their vision. The family was primarily of Dutch and Irish origin, with some Native American ancestry through the oldest affected individual (I-2).

Twelve individuals were found to have numerous drusen and/or atrophic macular degeneration (Table 1). Seventeen, including spouses, had a normal retinal examination. Nine other family members declined to participate in the study. Six of the affected patients were females, and six were males. There were a nearly equal number of male (17)

TABLE 1. Clinical Characteristics of Family Members in a Pedigree of Autosomal Dominant Drusen and Macular Degeneration

Pedigree Identifier	Age/Sex	Affected	Visual Acuity	Fundus and Other Ocular Abnormalities
I:2	91/F	Yes	20/200 both eyes	Geographic atrophy and some drusen in macula and fundus periphery both eyes; vascular abnormalities in RE suggestive of old central retinal vein occlusion
II:2	Deceased/F	Yes	Unknown	Drusen (by history)
II:3	63/M	Yes	20/20 RE; 20/60 LE	Drusen both eyes, some confluent; subretinal fibrosis RE
II:10	61/F	Yes	20/20 both eyes	Diffuse fine drusen in posterior pole both eyes
III:1	30/F	Yes	20/20 both eyes	Fine drusen in posterior pole and radially arranged drusen in fundus periphery of both eyes
III:2	34/M	Yes	20/20 both eyes	Fine drusen in posterior pole both eyes
III:3	34/M	Yes	20/20 both eyes	Fine drusen in posterior pole both eyes
III:5	38/M	Yes	20/20 both eyes	Fine drusen in posterior pole both eyes
III:9	41/F	No	20/20 both eyes	Normal
III:10	F	No	20/20 both eyes	Normal
III:12	38/F	Yes	20/20 both eyes	Fine drusen in posterior pole both eyes
III:13	36/M	Yes	20/20 both eyes	Macular and peripheral fine drusen both eyes
III:14	30/F	No	20/20 both eyes	Normal
IV:1	1/M	Yes	Good fixation both eyes	Atrophic macular lesions with fine drusen both eyes
IV:2	5/F	No	20/30 both eyes	Normal
IV:3	2/M	No	Good fixation both eyes	Normal
IV:4	8/F	Yes	20/60 RE; 20/70 LE	Macular geographic atrophy both eyes; few drusen both eyes;
		Proband		nystagmus; esotropia
IV:5	19/M	No	20/20 both eyes	Normal
IV:6	17/M	No	20/20 both eyes	Normal
IV:7	10/F	No	20/20 both eyes	Normal
IV:8	14/F	No	20/20 both eyes	Normal

and female (15) offspring in the pedigree. The disease did not skip generations, and no clinically unaffected family members transmitted the disease to their offspring. There was male-to-male transmission of the trait. The inheritance of the disease trait thus appeared to be autosomal dominant.

The youngest affected individual (IV-1) was 7 months old at the time of diagnosis. His parents were not aware of any visual difficulties. Ophthalmoscopy revealed bilateral central areas of mild atrophy of the retinal pigment epithelium as well as some fine drusen. The child was reexamined at 18 months of age and was found to have good fixation and no nystagmus. There was no change in the appearance of the macular lesions (Figure 3).

The oldest patient (I-2) was examined on her ninetieth birthday. She had visual acuity of approximately 20/200 and had bilateral diffuse geographic atrophy of the posterior pole. No drusen were present. There were shunt vessels suggestive of an old central retinal vein occlusion in her right eye. Despite our efforts, we could not retrieve old medical records, but she reported that her vision was good until her sixties.

Twelve of the 27 other individuals (44%), including the proband's father and three of his siblings, had numerous fine yellowish drusen of the macula and posterior pole (Figure 4). In some patients the drusen extended in a radial

FIGURE 3. The right eye of patient IV-1 at the age of 18 months. There is a central area of choriocapillaris and retinal pigment epithelium atrophy as well as numerous very fine drusen in the macula.

fashion into the mid-peripheral part of the fundus (Figure 5). Two older family members (II-3 and II-10) had areas of geographic macular atrophy and some submacular fibrosis

FIGURE 4. The right eye of the proband's father (III-3) at the age of 34 years, with numerous fine drusen arranged in a circular fashion around the fovea and scattered between the arcades.

FIGURE 5. Radially arranged drusen in the periphery of the right eye of patient III-1 at the age of 28 years.

in the left eye of II-3 (Figure 6). Several affected family members were unaware of their retinal disease, and some wore glasses or contact lenses for the correction of refractive errors.

The proband (IV-4) and her father (III-3) underwent electroretinography. The father's scotopic and photopic tracings were completely normal. The proband's electroretinogram was recorded at the age of 5 years. The scotopic B-wave amplitude was at the lower end of normal and had a normal latency. The photopic B-wave amplitude recorded with a 30-Hz flicker stimulus was slightly reduced to 57 microvolts (normal, >80 microvolts) but had a normal latency. Scanning laser ophthalmoscopy was used to determine fixation and showed a horizontal area of sight

FIGURE 6. (Top) The left eye of patient II-3 at age 63 years. Numerous, sometimes confluent fine drusen are present. Vision is normal in this eye. (Bottom) Macula of the right eye of patient II-3. There are confluent drusen and an inferonasal area of subretinal fibrosis. Visual acuity is reduced to 20/60.

within the macular lesion in the right eye. This was surrounded by a dense scotoma. In the left eye, fixation was within a vertical region in the temporal aspect of the macula.

DISCUSSION

THIS FAMILY HAS PROVIDED AN INTERESTING AND RARE opportunity to observe the expression of a retinal disease over four generations. This dominant type of drusen characterized by fine drusen in most young adults, and by atrophic maculopathy in some infants and elderly individuals, shares several features with North Carolina macular dystrophy, a disease that maps to an adjacent chromosomal locus and that is associated with macular degeneration in older as well as very young individuals.⁹ We attribute the unusual occurrence of atrophic maculopathy in two infants to the variable expressivity of this autosomal dominant gene. Choroidal neovascularization was not observed in any patient, but one of the older individuals (II-3) had

subretinal fibrosis that may have been the result of regressed neovascularization. Unfortunately, fluorescein angiography could not be obtained in this older person, who refused further work-up.

The family in the present report shares some characteristics with several previously described retinal drusen syndromes. The phenotype appears to be most closely related to North Carolina macular dystrophy, which like this disease, is inherited in an autosomal dominant fashion with complete penetrance and variable expressivity. It has its onset in infancy or childhood and appears to be stable in early adulthood. Drusen are found in the fundus periphery and in the central macula. In the present family, the drusen are very fine in all patients, whereas they can be of various sizes in North Carolina macular dystrophy. The present family is also of Irish descent and may theoretically be descended from the founders of the family with North Carolina macular dystrophy. In contradistinction to North Carolina macular dystrophy, the present syndrome appears to have less variability in phenotype and may be more progressive than North Carolina macular dystrophy if the presence of macular degeneration in older individuals and good vision in the majority of younger patients is taken as evidence of progression. Our linkage analysis studies reported in the companion article by Kniazeva and associates²⁰ provide significant evidence that the loci for the two diseases are adjacent but distinct. The occurrence of atrophic maculopathy in infants and very young children has been reported in North Carolina macular dystrophy and in Doyme hereditary macular dystrophy.^{9,22} The present type of drusen with macular degeneration should be considered in the differential diagnosis of the child with atrophic maculopathy. Examination of the child's parents, even if they are asymptomatic, might show the presence of drusen.

We have historical evidence that the oldest patient has experienced progressive loss of vision with increasing age, but we have not been able to review written documentation of these events. Proof that the present family has a distinct form of dominant drusen and macular degeneration came from genetic linkage analysis. Although the gene responsible mapped to the same region of chromosome 6q as MCDR-1 and the gene for autosomal dominant Stargardt disease type 3,^{9,19} there was significant evidence from haplotype and linkage analysis studies that it was distinct from these two disorders. For this most important reason, we conclude that we are describing a clinically and genetically distinct form of drusen and macular degeneration.

There is extreme variability in the clinical expression of this disease. Most young adults have fine macular drusen and good vision. Affected infants and children may have congenital atrophic maculopathy and drusen, and there may be slight progression of the disease in late adulthood with moderate visual loss.

REFERENCES

1. Hutchison J, Tay W. Symmetrical central choroidoretinal disease occurring in senile persons. *R London Ophthal Hosp Rep* 1875;8:231-244.
2. Doyme RW. A peculiar condition of choroiditis occurring in several members of the same family. *Trans Ophthal Soc UK* 1899;19:71.
3. Doyme RW. A note on family choroiditis. *Trans Ophthal Soc UK* 1910;30:93-95.
4. Vogt A. Die Ophthalmoskopie im rotfreien Licht. In: Graefe A, Saemisch T, editors. *Handbuch der gesamten Augenheilkunde. Untersuchungsmethoden*, 3rd ed. Berlin: Leipzig, Verlag von Wilhelm Engelmann, 1925:1-118.
5. Gregory CY, Evans K, Wijesuriya SD, et al. The gene responsible for autosomal dominant Doyme's honeycomb retinal dystrophy (DHRD) maps to chromosome 2p16. *Hum Molec Genet* 1996;5:1055-1059.
6. Heon E, Piguet B, Munier F, et al. Linkage of autosomal dominant radial drusen (malattia leventinese) to chromosome 2p16-21. *Arch Ophthalmol* 1996;114:193-198.
7. Edwards AO, Klein ML, Berselli CB, et al. Malattia leventinese: refinement of the genetic locus and phenotypic variability in autosomal dominant macular drusen. *Am J Ophthalmol* 1998;126:417-424.
8. Stone EM, Lotery AJ, Munier FL, et al. A single EFEMP1 mutation associated with both malattia leventinese and Doyme honeycomb retinal dystrophy. *Nat Genet* 1999;22:199-202.
9. Small KW. North Carolina macular dystrophy: clinical features, genealogy, and genetic linkage analysis. *Trans Am Ophthalmol Soc* 1998;96:925-961.
10. Small KW, Weber J, Roses A, Perciak-Vance P. North Carolina macular dystrophy (MCDR-1). A review and refined mapping to 6q14-q16.2. *Ophthalmic Genet* 1993;14:143-150.
11. Holz FG, Evans K, Gregoary CY, Bhattacharya S, Bird AC. Autosomal dominant macular dystrophy simulating North Carolina macular dystrophy. *Arch Ophthalmol* 1995;113:178-184.
12. Rabb MF, Mullen L, Yelchits S, Udar N, Small KW. A North Carolina macular dystrophy phenotype in a Belizean family maps to the MCDR1 locus. *Am J Ophthalmol* 1998;125:502-508.
13. Pauleikhoff D, Sauer CG, Muller CR, Radermacher M, Merz A, Weber BH. Clinical and genetic evidence for autosomal dominant North Carolina macular dystrophy in a German family. *Am J Ophthalmol* 1997;124:412-415.
14. Small KW, Puech B, Mullen L, Yelchits S. North Carolina macular dystrophy phenotype in France maps to the MCDR1 locus. *Mol Vis* 1997;3:1.
15. Klein ML, Schultz DW, Edwards A, et al. Age-related macular degeneration: clinical features in a large family and linkage to chromosome 1q. *Arch Ophthalmol* 1998;116:1082-1088.
16. Weber BH, Vogt G, Pruett RC, Stohr H, Felbor U. Mutations in the tissue inhibitor of metalloproteinases-3 (TIMP3) in patients with Sorsby's fundus dystrophy. *Nat Genet* 1994;8:352-356.
17. Wijesuriya SD, Evans K, Jay MR, et al. Sorsby's fundus dystrophy in the British Isles: demonstration of a striking founder effect by microsatellite-generated haplotypes. *Genome Res* 1996;6:92-101.
18. Stone EM, Nichols BE, Kimura AE, Weingeist TA, Drack A, Sheffield VC. Clinical features of a Stargardt-like dominant

- progressive macular dystrophy with genetic linkage to chromosome 6q. *Arch Ophthalmol* 1994;112:765–772.
19. Kniazeva MF, Chiang MF, Cutting GR, Zack DJ, Han M, Zhang K. Clinical and genetic studies of an autosomal dominant cone-rod dystrophy with features of Stargardt disease. *Ophthalmic Genet* 1999;20:71–81.
 20. Kniazeva M, Traboulsi EI, Stefko ST, et al. A new locus for dominant drusen with macular degeneration maps to chromosome 6q14. *Am J Ophthalmol*. Forthcoming.
 21. Marmor MF. An updated standard for clinical electroretinography. *Arch Ophthalmol* 1995;113:1375–1376.
 22. Evans K, Gregory CY, Wijesuriya SD, et al. Assessment of the phenotypic range seen in Doyme honeycomb retinal dystrophy. *Arch Ophthalmol* 1997;115:904–910.

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