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Mapping of a macular drusen susceptibility locus in rhesus macaques to the homologue of human chromosome 6q14-15

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Abstract

Rhesus macaques (*Macaca mulatta*) are a natural model for retinal drusen formation. The present study aimed at clarifying whether chromosomal regions homologous to candidate genes for drusen formation and progression in humans are also associated with a drusen phenotype in rhesus macaques. Some 42 genetic markers from seven chromosomal regions implicated in macular degeneration syndromes in humans were tested for whether they identified homologous, polymorphic sequences in rhesus DNA. This was found to be the case for seven markers, all of which were subsequently screened for the presence of potentially disease-predisposing alleles in 52 randomly chosen adult animals from the Cayo Santiago population of rhesus macaques (Caribbean Primate Research Center, PR, USA). The high drusen prevalence expected in the Cayo Santiago colony was confirmed in our sample in that 38 animals were found to have drusen (73%). Logistic regression analysis revealed that some alleles of the rhesus homologue of anonymous human marker *D6S1036* were consistently over-represented among affected animals. Of two candidate genes located in the respective region, allelic variation in one *(IMPG1)* showed strong association with drusen formation. We conclude that one or more genes located at the rhesus homologue of human 6q14-15 are likely to play a role in retinal drusen formation, a finding that represents a first step towards the identification of genetic factors implicated in macular drusen formation in rhesus macaques. This is an important tool for the separation of genetic and environmental factors which must occur before satisfactory management methods can be developed.

Keywords: retina; drusen; ageing macular dystrophy; disease susceptibility; *Macaca mulatta*

1. Introduction

The aetiology and pathogenesis of age-related human macular degeneration (AMD), a major cause for visual impairment in the elderly population, are not well understood. Strong evidence for a genetic contribution to this condition is provided, for example, by the fact that monozygotic twins show strong concordance for AMD, and several genes implicated in early onset forms of macular degeneration have been reported (Gorin et al., 1999; Crabb et al., 2002). In the opinion of several authorities, an initial obligatory symptom and a hallmark of the disease is the formation of drusen, deposits on Bruch's membrane probably derived from the retinal pigment epithelium (Sarks et al., 1999; Hageman et al., 2001; Stone et al., 2001). Association studies such as that on patients from the Beaver Dam Eye Study (Wisconsin, USA) recently identified candidate regions for drusen formation on several human chromosomes, including nos. 5, 6, 12, and 15 (Schick et al., 2003; Seddon et al., 2003). An earlier affected sib-pair analysis yielded evidence for candidate genes on chromosomes 5 and 10 (Weeks et al., 2000). It is likely that, at least in part, these results reflect genetic heterogeneity between and within the populations studied.

It has been known for some time that rhesus macaques (*Macaca mulatta*) represent a natural model for retinal

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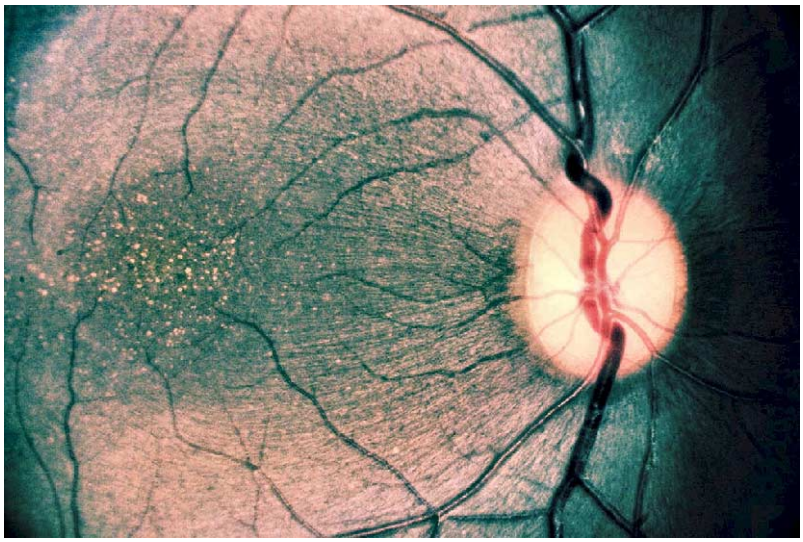

Fig. 1. Fundus photograph of the left eye of a rhesus macaque, showing punctate, coalesced and soft macular drusen with some pigment changes. The photograph is of Cayo Santiago female T69, age 14 years (49 human years).

drusen formation (Stafford, 1974; El-Mofty et al., 1978). Clinically and ultrastructurally, rhesus drusen (Fig. 1) closely resemble human pathology (Ishibashi et al., 1968; Ulshafer et al., 1987; Olin et al., 1995) and, in progressed disease, they may be associated with mildly reduced visual function as measured by electrophysiological means (Engel et al., 1988; Dawson et al., 1989). Drusen formation is usually a relatively rare condition in rhesus macaques, affecting not more than 6% of the aging animals in US primate facilities (Bellhorn et al., 1981; Stafford et al., 1984). Extensive work by one of us (W.W.D.) who investigated this condition in the free-ranging colony of rhesus macaques on Cayo Santiago (CS), Puerto Rico, revealed, however, that almost 60% of the animals living there are affected. Both the prevalence and the severity of drusen on CS increase linearly with age (Hope et al., 1992). As to the causes of the high prevalence, it has been speculated that environmental (diet, light exposure) and genetic factors may both play a role (Hope et al., 1992). A genetic component had to be invoked to explain the significant differences in drusen prevalence observed between different lineages of ancestry on the island.

The CS colony, and all animals derived from that population, are descendants of the 409 animals transferred from India to the Caribbean in 1938 by American zoologist R.A. Carpenter. No new animals have been introduced since then. After 1956, all CS monkeys became individually identified and daily census records were constantly maintained. Animals regularly removed to ensure a constant colony size are housed in large outdoor corrals at the Sebana Seca facility of the Caribbean Primate Research Centre (CPRC) on mainland Puerto Rico. These animals include social group M in which the present work has been performed. Owing to human negligence during World War II, the CS population went through a bottleneck of only 115 animals. Given that the founder population was initially small and became drastically reduced later on, any locus heterogeneity involved in the causation of a particular phenotype is likely to be small on CS, thus rendering the colony particularly suitable for genetic association studies.

We screened a randomly selected subset of CS-derived animals for the presence and severity of retinal drusen formation and assessed the association of the phenotype with allelic variation at markers from chromosomal regions homologous to candidate genes for drusen formation (and possible progression to AMD) in humans.

This is the first study in a subhuman primate aiming at identifying a genetic contribution to macular drusen formation.

2. Methods

2.1. Animals

The study group comprised 52 animals aged 7–22 years. These animals were randomly selected from Cayo Santiago (CS)-derived social group M, maintained at the Sebana Seca field station of the Caribbean Primate Research Centre (CPRC) on mainland Puerto Rico. Since the foundation of the CS colony, the approximately 900 animals residing on the island at any time have only been subjected to behavioural studies. Occasionally, social groups such as group M have, however, been moved to the mainland field station intact to be used for special scientific projects. The study group was randomly subdivided into an initial focus sample of 34 animals (group I), used for exploratory analysis, and a second sample of 18 animals (group II) that served as means of independent verification for any