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Martinique Crinkled Retinal Pigment Epitheliopathy

Clinical Stages and Pathophysiologic Insights

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Purpose: To reappraise the autosomal dominant Martinique crinkled retinal pigment epitheliopathy (MCRPE) in light of the knowledge of its associated mutated gene mitogen-activated protein kinase–activated protein kinase 3 (*MAPKAPK3*), an actor in the p38 mitogen-activated protein kinase pathway.

Design: Clinical and molecular study.

Participants: A total of 45 patients from 3 generations belonging to a family originating from Martinique with an autosomal dominant MCRPE were examined.

Methods: Best-corrected visual acuity, fundus photographs, and spectral-domain optical coherence tomography (SD OCT) of all clinically affected patients and carriers for the causal mutation were reviewed at the initial visit and 4 years later for 10 of them. Histologic retinal lesions of *Mapkapk3*$^{-/-}$ mice were compared with those of the human disease.

Main Outcome Measures: The MCRPE natural history in view of *MAPKAPK3* function and *Mapkapk3*$^{-/-}$ mouse retinal lesions.

Results: Eighteen patients had the c.518T>C mutation. One heterozygous woman aged 20 years was asymptomatic with normal fundus and SD OCT (stage 0). All c.518T>C heterozygous patients older than 30 years of age had the characteristic dried-out soil fundus pattern (stages 1 and 2). Complications (stage 3) were observed in 7 cases, including polypoidal choroidal vasculopathy (PCV) and macular fibrosis or atrophy. One patient was homozygous and had a form with severe Bruch's membrane (BM) thickening and macular exudation with a dried-out soil pattern in the peripheral retina. The oldest heterozygous patient, who was legally blind, had peripheral nummular pigmentary changes (stage 4). After 4 years, visual acuity was unchanged in 6 of 10 patients. The dried-out soil elementary lesions radically enlarged in patients with a preferential macular extension and confluence. These findings are in line with the progressive thickening of BM noted with age in the mouse model. During follow-up, there was no occurrence of PCV.

Conclusions: MCRPE is an autosomal dominant, fully penetrant retinal dystrophy with a preclinical stage, an onset after the age of 30 years, and a preserved visual acuity until occurrence of macular complications. The natural history of MCRPE is in relation to the role of *MAPKAPK3* in BM modeling, vascular endothelial growth factor activity, retinal pigment epithelial responses to aging, and oxidative stress. *Ophthalmology 2016;123:2196-2204 © 2016 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

Martinique crinkled retinal pigment epitheliopathy (MCRPE) is an autosomal dominant retinal dystrophy that we clinically described in 2013 in 3 families who originated from Martinique, one of the French West Indies islands.[1,2] These 3 families have a common ancestral background (Fig 1). Specific hallmarks of the disease are the network of white retinal pigment epithelium (RPE) lines mimicking a dried and cracked soil upon fundus examination. This pattern is linked to the irregular thickness of the Bruch's membrane (BM) and the remarkable scalloped elevation of the RPE, visible on spectral domain optical coherence tomography (SD OCT) (Fig 2). Affected patients are asymptomatic until the occurrence of polypoidal choroidal vasculopathy (PCV), choroidal neovascularization, macular fibrosis, or atrophy. At the final stage, the phenotype resembles a pigmentary retinopathy with

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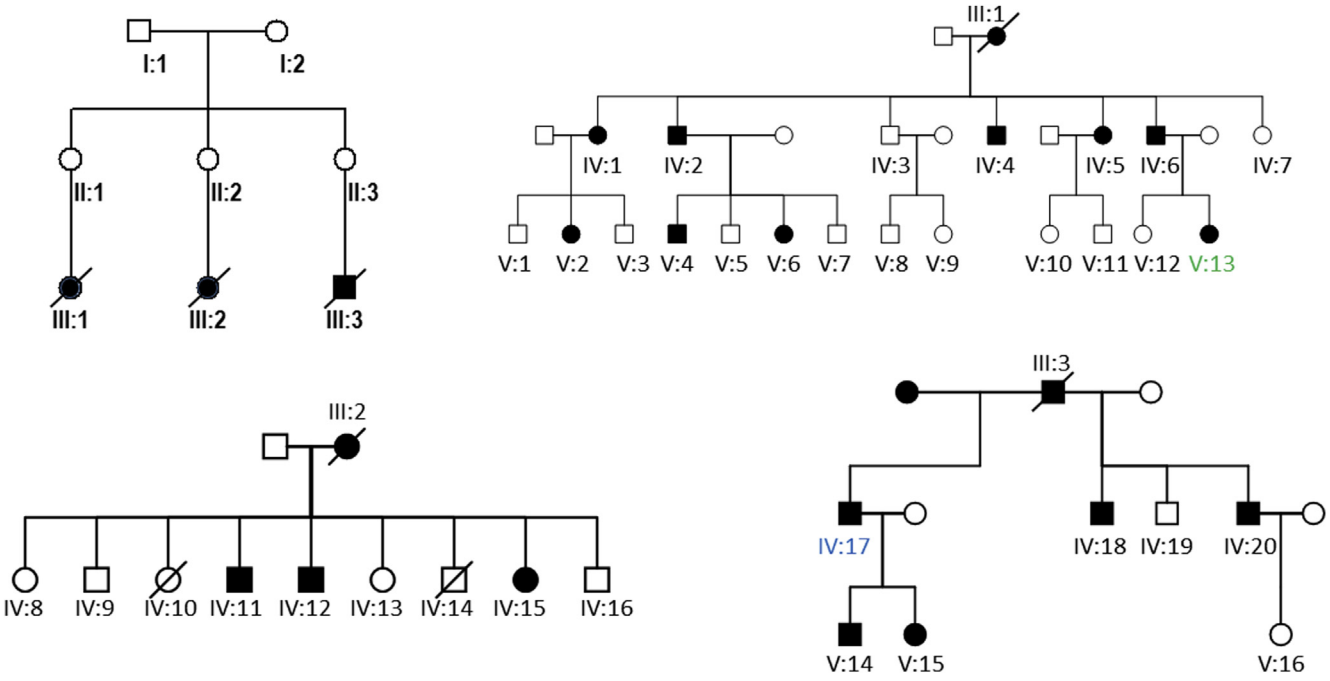

Figure 1. Pedigree of the family originating from Martinique, one of the French West Indies Islands. The dystrophy is inherited as an autosomal dominant trait. A total of 45 patients from 3 generations have been examined, and 17 affected subjects older than 30 years of age had a typical dried-out soil pattern. All affected individuals (*black symbols*) carried the c.518T>C (p.Leu173Pro) mutation (M/+) in mitogen-activated protein kinase–activated protein kinase 3 (*MAPKAPK3*). Patient IV:17 (*blue*) was homozygous for the mutation. The 12 patients aged more than 30 years with a normal fundus (*open symbols*) did not have the mutation (+/+). The 21-year-old V:13 patient (*green*) had the causal mutation and a normal fundus.

mottled pigmentations and a dried-out soil aspect at the posterior pole. No other associated symptom has ever been reported for these individuals.

Whole-exome sequencing has allowed us to identify the causal missense mutation, c.518T>C (p.Leu173Pro) in exon 8 of mitogen-activated protein (MAP) kinase–activated

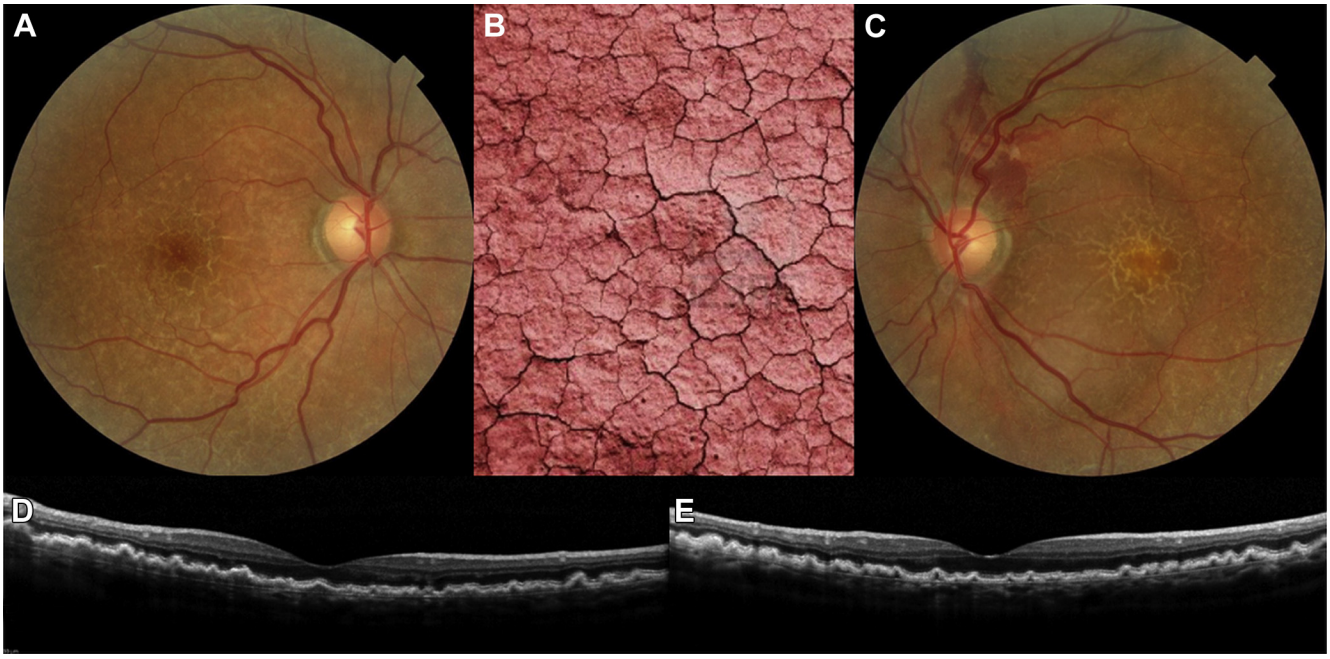

Figure 2. Typical Martinique crinkle retinal pigment epitheliopathy fundus and spectral domain optical coherence tomography (SD OCT). Fundus photographs showing the typical network of white retinal pigment epithelium (RPE) lines in (**A**) right and (**C**) left eyes resembling (**B**) dried-out soil. Note the crinkled, irregular, thickened, and scalloped elevation of the RPE as disclosed on SD OCT (**D**, **E**).