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North Carolina Macular Dystrophy Phenotype in France Maps to the MCDR1 Locus

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Purpose: To determine if a family in France, which manifests an autosomal dominant macular dystrophy, has North Carolina macular dystrophy (MCDR1) and to determine its possible molecular genetic relationship with the original North Carolina family.

Methods: A family from Northern France with a macular dystrophy underwent comprehensive ophthalmic examinations and were ascertained for genetic studies. Blood collection and examinations were performed on 38 individuals. Fundus photographs with a hand held KOWA camera were obtained on affected subjects. DNA was extracted and genotyping performed using new microsatellite genetic markers, which have recently been found in the MCDR1 (North Carolina macular dystrophy) region. Standard two - point linkage and haplotype analysis was performed.

Results: Eleven individuals were found with the clinical manifestations of North Carolina macular dystrophy. Two - point linkage analysis generated a maximum peak LOD score of 4.5 with a recombination of 0% between D6S1717 and the macular dystrophy locus in the French family. The haplotype associated with the disease is, however, different from that of the original North Carolina family.

Conclusions: These findings indicate that the macular dystrophy gene in this French family maps to the same region as that of North Carolina macular dystrophy (MCDR1) locus but that independent mutations are involved. The disease in the French family is clinically and genetically similar to North Carolina macular dystrophy. Therefore MCDR1 occurs in various ethnic groups, is present world-wide, and there remains no evidence of genetic heterogeneity for this clinically distinct form of macular degeneration.

North Carolina macular dystrophy is an autosomal dominant inherited trait consisting of congenital or infantile onset of macular degeneration. The disease causing gene has been genetically mapped to chromosome 6q16 by Small and associates (1,2). It is now known as MCDR1 as named by the Human Genome Organization (MC=macular, D=dystrophy, R=retinal, 1=first macular degeneration reliably genetically mapped).

The original description of this disease by Lefler, Wadsworth, and Sidbury was of descendants of a large family, of Irish descent, which had settled in the mountains of North Carolina in the 1800's (3). This report called the disease "dominant macular degeneration and aminoaciduria." A subsequent report of the same family by Frank and associates revealed that the aminoaciduria was in fact unrelated to the macular degeneration and renamed the disease "dominant progressive foveal dystrophy"(4). Later, it was demonstrated that separate branches of this North Carolina family were inadvertently published as distinct and new clinical entities such as "central areolar pigment epithelial dystrophy" and "autosomal dominant central pigment epithelial and choroidal degeneration"(5-14).

The diversity in names given the disease in this one family reflects, in part, the wide phenotypic variability seen between individuals within the the one family. The phenotype of this disease consists of patients generally having a life-long duration of impaired central vision. Generally the disease is stable except for those who develop choroidal neovascular membranes. The visual acuity ranges from 20/20 to 20/800 with the medium visual acuity being 20/60. The funduscopic findings are also highly variable ranging from a few yellow drusen-like lesions in the central macular region to disciform scars to macular colobomas (Figure 1a-d). The peripheral retina can be variably abnormal with peripheral retinal drusen as well. Previous electroretinogram and electro oculograms were reported to be normal. Herein, we report a new family of French origins with a maculopathy that is clinically identical to the MCDR1 phenotype.

METHODS

We visited the family members at their home in Northern France (Flanders region) (Figure 2). Thirty-eight individuals from the family underwent comprehensive ophthalmic examinations and were ascertained for genetic studies after IRB approved informed consent was obtained. An extensive family history was obtained, consisting of 5 generations. Visual acuities were measured using a Snellen acuity chart and/or near vision card with a pinhole occluder. The pupils were dilated with 1% Mydriacyl. Fundus photographs were obtained using a hand held Kowa™ fundus camera. Blood samples were collected in EDTA tubes. The DNA was extracted using standard phenol-chloroform protocols.

Affectation status was determined as previously described 1-12. Three grades of severity of the maculopathy have been noted. Grade 1 consists of only fine drusen in the central maula (Figure 1a); grade 2 lesions exhibit confluent drusen and/or

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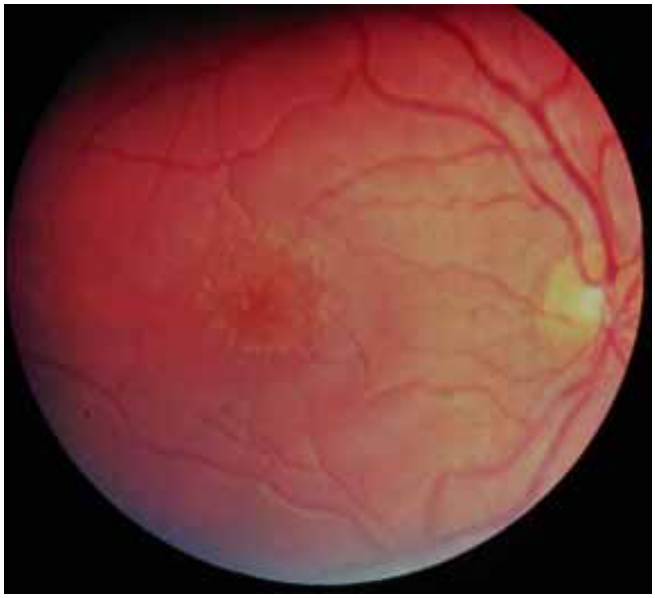

Figure 1a. Hand-held KOWA fundus photograph, individual #4027 in pedigree, right eye, 17 year old man, fine drusen-like lesions in central macula, visual acuity 20/20.

Figure 1b. Hand-held KOWA fundus photograph, individual #4022 in pedigree, 14 year old man, left eye, small coloboma-like lesion with atrophy of the retinal pigment epithelium in central macula, visual acuity 20/25.

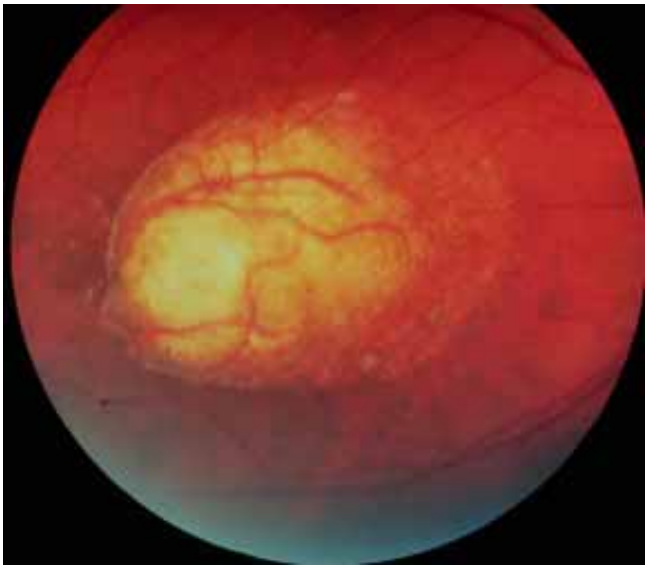

Figure 1c. Hand-held KOWA fundus photograph, individual #3030 in pedigree, 44 year old woman, right eye, large coloboma-like lesion in central macula, visual acuity 20/400

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Figure 1d. Hand-held KOWA fundus photograph, individual #3030 in pedigree, left eye, large coloboma-like lesion in central macula, visual acuity 20/400.

disciform scar; grade 3 lesion is a discrete macular coloboma or staphyloma (Figure 1b-d). Peripheral drusen are variably present. The disese is generally not progressive with the exception of those who develop choroidal neovascularization.

Polymerase chain reaction microsatellite genotyping was performed as described by Weber and May (13). The closest linked markers to MCDR1 are D6S251, D6S252, D6S275, D6S361, D6S492, D6S424, D6S300, D6S1682, D6S501, D6S249, GATAp6995, afm270xe5, D6S1716, D6S1717, D6S1565, GATAp9365, D6S1671, D6S475, D6S468, D6S283, and D6S301 as determined by previous genotyping of the original North Carolina family. These markers span a 20 centiMorgan region (cM). These same genetic markers were used in the French family. Analysis was performed by maximum likelihood estimation using the software package Linkage 5.1 setting the penetrance of MCDR1 at 95%, gene frequency at 1:10,000, and an autosomal dominant inheritance pattern. The allele frequencies for the analyzed markers were obtained from published databases (Genome Data Base and the Cooperative Human Linkage Center). Two-point linkage analysis was performed first using the sub-program Mlink (14).

RESULTS

Affected subjects in this family exhibited the full range of the

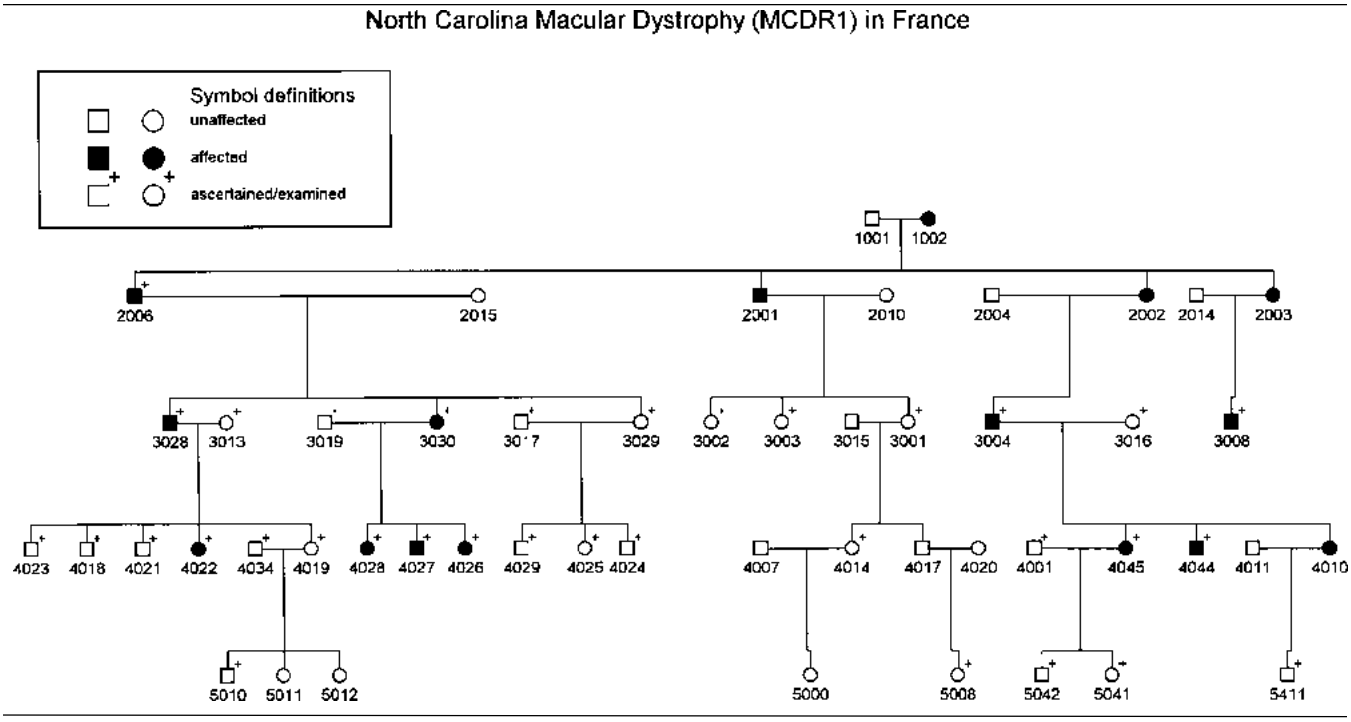

Figure 2. Pedigree of MCDR1 Frannce Family.

Table 1. Two point LOD scores of MCDR1 linked markers versus the macular dystrophy in the French family. Zmax is the maximum LOD score achieved and the theta max is the genetic distance at which that maximum LOD score is achieved.

Marker				theta			
	0	0.1	0.2	0.3	0.4	Zmax	theta max
D6S251	3.0	2.5	1.9	1.4	0.7	3.0	0.0
D6S275	1.0	1.2	1.0	0.7	0.4	1.2	0.08
D6S361	0.6	0.4	0.2	0.1	0.02	0.6	0.0
D6S492	0.13	0.1	0.09	0.06	0.04	0.1	0.0
D6S424	-0.4	2.8	2.4	1.7	0.9	2.9	0.07
D6S300	-2.3	1.5	1.4	1.0	0.5	1.5	0.12
D6S1682	-0.4	0.4	0.5	0.4	0.2	0.5	0.2
D6S501	1.8	1.4	0.9	0.5	0.1	1.8	0.0
D6S249	0.06	0.05	0.03	0.01	0.00	0.06	0.01
GATAp6-995	1.7	1.2	0.8	0.3	0.03	0.01	0.0
afm270xe-5	1.4	1.2	0.8	0.5	0.2	0.05	0.0
D6S1716	0.8	0.9	0.7	0.4	0.08	0.9	0.05
D6S1717	4.5	3.6	2.7	1.6	0.7	4.5	0.0
D6S1565	1.3	1.6	1.4	1.0	0.5	1.6	0.08
GATAp9-365	-2.1	1.7	1.5	1.1	0.5	1.7	0.11
D6S1671	-15	-0.9	0.0	0.03	0.02	0.03	0.34
D6S475	3.4	2.7	1.9	1.2	0.5	3.4	0.0
D6S468	0.2	0.9	0.9	0.8	0.4	0.9	0.17
D6S283	-3.5	0.14	0.5	0.4	0.3	0.5	0.2
D6S301	-6.3	-1.0	-0.6	-0.3	-0.1	0.03	0.4

classical findings of North Carolina macular dystrophy as described previously (5 12). This included highly variable expressivity ranging from drusen in the central macular region to disciform macular lesions to macular colobomas associated with a congenital or infantile onset of decreased central vision (Figure 1a-d). The family history revealed no evidence of emigration to the United States or genealogic connection with the American family. The American family maintains that they are of Irish heritage but their surname is French Huegenot in origin.

Microsatellite genetic markers that were tightly linked to the MCDR1 locus generated positive LOD scores or were uninformative in the French family. Significantly positive LOD scores (Zmax > 3.0, indicating odds > 1,000:1 in favor of linkage with a greater than 95% probability of linkage) were generated with the markers D6S251, D6S1717 and D6S475 (Table 1). Other closely linked markers were positive or yielded little information. Analysis of the crossover data (Table 2) shows the critical region for the MCDR1 gene to be between D6S424 and D6S1671. These meiotic break points directly overlap with the MCDR1 region but does not significantly narrow the region any further than that gained with the original North Carolina family. The haplotype associated with the disease, however, is different from that of the North Carolina family.

DISCUSSION

North Carolina macular dystrophy (MCDR1) was originally named as such because of the founder effect concentrating the mutated gene in the mountains of North Carolina. Because of its name, many clinicians and researchers have assumed that this is an extremely rare disease present in only one family in the world. Small and associates previously demonstrated that

all known individuals affected in North America with North Carolina macular dystrophy indeed did emanate from the same family in North Carolina (12).

Many of the genetic markers that were originally tightly linked to MCDR1 were not particularly informative. One exception to this was D6S251, which barely generated a significant LOD score of 3.0. Indeed, until recently, D6S249 had been the most closely linked marker in the North Carolina family but generated a maximum LOD score of only 0.06 in the French family. Therefore additional informative markers were needed in the MCDR1 region.

While such a family study containing 38 subjects would seem to be of adequate size, this is not necessarily the case. The French family contains 15 potentially fully informative meiotic events that could allow discernment of segregation of the affected allele and thus demonstrate linkage or the lack of linkage. Theoretically if every meiotic event in the family were completely informative for a given marker, the maximum possible LOD score would be 4.5. The marker D6S1717 is such a marker and generated this highly significant LOD score indicating greater than a 10,000:1 odds in favor of linkage. This single result alone is sufficient to establish linkage to the MCDR1 locus. Because D6S1717 is fully informative in this family, there is no need to attempt to capture more information by doing an additional multipoint analysis.

Table 2. Meiotic Breakpoint Analysis. UI = uninformative, I = informative, phase known, X = fully informative crossover.

Individual	#3008	5411	3030	3004
Marker				
D6S251	UI	I	UI	UI
D6S275	I	UI	UI	UI
D6S361	UI	UI	UI	UI
D6S492	UI	UI	UI	UI
D6S424	X	I	I	I
D6S300	I	I	I	UI
D6S1682	UI	UI	UI	UI
D6S501	I	UI	I	UI
D6S249	UI	UI	UI	UI
GATAp6995	I	UI	I	UI
afm270xe5	UI	UI	I	I
D6S1716	UI	UI	I	I
D6S1717	I	I	I	I
D6S1565	I	UI	UI	UI
GATAp9365	I	UI	I	I
D6S1671	UI	X	X	X
D6S475	I	UI	UI	UI
D6S468	UI	X	UI	UI
D6S283	UI	UI	UI	UI
D6S301	UI	UI	UI	UI

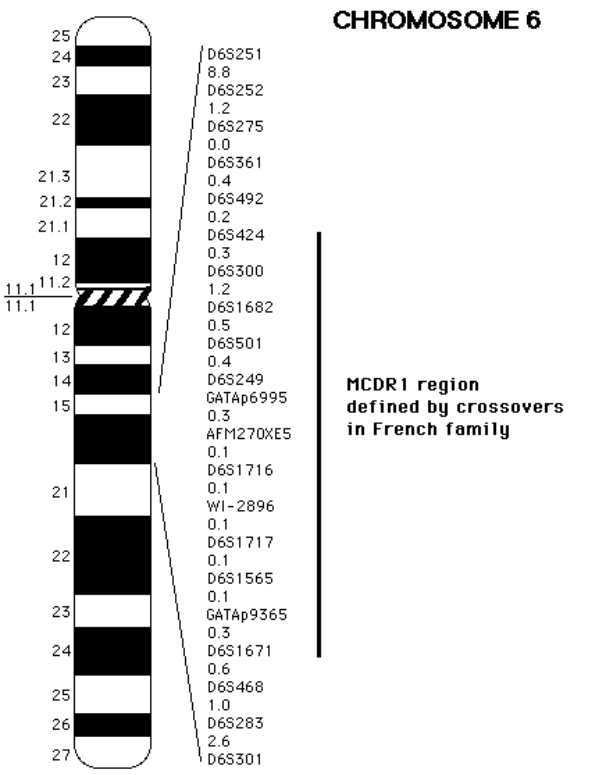

Figure 3. Ideogram of chromosome 6 showing location and genetic distances of markers in relation to the MCDR1 gene.

Our findings indicate that the gene responsible for the maculopathy in this French family maps to the MCDR1 locus (Figure 3). The clinical phenotype is also identical to that found in the North Carolina family. Our findings show no evidence of genetic heterogeneity of MCDR1. That is, all families with the MCDR1 phenotype have mapped to the same genetic locus. Haplotype analysis shows that the marker alleles on the disease-carrying chromosomes are different when comparing the North Carolina family with the French family. This suggests that the French family most likely represents an independent mutation in the MCDR1 gene. An alternative hypothesis is that the French family and the North Carolina family do have a common ancestor; however this common ancestor would have to be in the far distant past such that an ancestral crossovers flanking the disease locus had occurred.

The MCDR1 phenotype is much more prevalent than previously realized. Indeed, it should be no surprise that this disease is not limited to any one particular racial, ethnic, or geographic region. This family in France most likely represents a independent mutation in the MCDR1 gene. Understanding of the MCDR1 gene is important for several reasons. This disease seems to be macular-specific as evidenced by the funduscopic examination as well as the lack of electroretinogram and electro oculogram abnormalities. Therefore, understanding this gene will give insight into specific features of the macula in regards to its function and dysfunction. Additionally, the MCDR1 phenotype appears very similar to the very common age-related macular degeneration. Age-related macular degeneration is the most common cause of blindness in our elderly American population. Therefore,

perhaps understanding the MCDR1 gene will shed light on and contribute to management of age-related macular degeneration.

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