Molecular Vision 2026; 32:451-463 <http://www.molvis.org/molvis/v32/451>
Received 5 August 2025 | Accepted 22 September 2026 | Published 25 September 2026

© 2026 Molecular Vision

North Carolina macular dystrophy: Haplotype analysis of 31 families shows single founders for each mutation and provides age estimates for two recurrent variants

Kent W. Small,[1,2] Joanna Im,[1,2] Jessica Avetisjan,[1,2] Fadi Shaya,[1,2] Amber Diaz,[1,2] Arpier Haritoonian,[1,2] Uma Udar,[1,2] Nitin Udar,[1,2] Emmanuelle Génin,[3] Monique J. Leys,[4] Thomas A. Rice,[5] Richard Alan Lewis,[6] Elise Heon,[7] Paul Bernstein,[8] Gregory T. Rognon,[8] Adrienne Scott,[9] Todd Schneiderman,[10] David Wilson,[11] Klaus Rohrschneider,[12] Steve Agemy,[13] Daniel F. Kiernan,[14] Johannes Birtel,[15] Peter Charbel Issa[16, 17]

[1]Macula and Retina Institute, Glendale and Los Angeles, CA; [2]Molecular Insight Research Foundation, Glendale and Los Angeles, CA; [3]French Institute of Health and Medical Research, Paris, France; [4]West Virginia University, Department of Ophthalmology and Visual Sciences, Morgantown, WV; [5]Palo Alto, CA; [6]Baylor College of Medicine, Houston, TX; [7]The Hospital for Sick Children, SickKids, Toronto, ON, Canada; [8]University of Utah, Moran Eye Center, Salt Lake City, UT; [9]Wilmer Eye Institute, Johns Hopkins Medicine, Baltimore, MD; [10]Northwest Retina Center, Silverdale, WA; [11]Capital Vision Services, Chambersburg, PA; [12]University of Heidelberg, Heidelberg, Germany; [13]Retina Consultants, New York, NY; [14]Retina Partners of Florida, Lakeland, FL; [15]Oxford Eye Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; [16]Department of Ophthalmology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [17]Department of Ophthalmology, Technical University of Munich, School of Medicine and Health, TUM University Hospital, Munich, Germany

Purpose: North Carolina macular dystrophy (NCMD/MCDR1) is an autosomal dominant congenital macular disorder with highly variable expressivity. 48 NCMD families have been identified by Small et al., 15 of which have been identified with the V1 mutation (chr6:99593030G>T) and 21 with the V2 mutation (chr6: 99593111G>C). Our study aims to determine whether V1 families indicate a common founder effect, and whether V2 families descend from a distinct, secondary founder.

Methods: NCMD was diagnosed through exams or review of records. With IRB approval and consent, DNA from blood or saliva was genotyped using 19 short tandem repeat (STR) markers from the MCDR1 region (5.4 Mb). 61 individuals were genotyped: 22 subjects with V1 and 39 subjects with V2. Ages of V1 and V2 mutations were estimated using haplotype-based EstiAge analysis.

Results: Families with the V1 mutation all showed a unique haplotype across the entire 5.4 Mb region, while families with the V2 mutation shared a separate unique haplotype across the same MCDR1 region. V1 was estimated to be approximately 150 years old (95% CI, 100–375 years), while V2 was estimated to be approximately 725 years old (95% CI, 525–1,025 years), aligning with predictions based on geographic origins of mutations and the presence of additional recombinatorial events in V2.

Conclusions: The shared 5.4 Mb genomic region creating the haplotype in V1 families indicates a most recent common ancestor or founder (MRCA), all of which are in the United States. Families with the V2 mutation all share another unique MRCA. About a third of these families are American and two thirds European. The V2 haplotype shows ancestral combinatorial events within the 5.4 Mb region, indicating a more genealogically distant common ancestor compared to V1, as supported by mutation age estimates. V1 and V2 thus define two founder mutations at MCDR1, with V2 appearing older by haplotype decay. Beyond these, most reported NCMD variants remain private and are often de novo.

North Carolina macular dystrophy (NCMD) is a rare autosomal dominant, fully penetrant disorder affecting macular development. The disease is a congenital, non-progressive maculopathy with highly variable expressivity ranging from scattered drusen to chorioretinal coloboma-like defects in the macula, typically affecting both eyes symmetrically [1-3]. NCMD, in its most severe grade 3 form, is characterized by posterior bowing and absence of the choroid, choriocapillaris, and the retinal pigment epithelial layer at birth. Frequently, a patient's vision is better than would be predicted based on macular funduscopic appearance. Visual symptoms are variable, with about two thirds of patients having mild or mild-to-moderate central vision impairment. About a third of the patients are asymptomatic, while a few exhibit severe central vision impairment, typically due to choroidal neovascular membrane (CNVM) formation [2,4].

The name of this entity was given by Gass in his atlas after the founder effect of the large family first reported in 1971 [5]. This name is now considered a misleading misnomer,

Correspondence to: Kent W. Small, Molecular Insight Research Foundation, 411 North Central Ave. Suite 115 Glendale, CA 91203; email: kentsmall@hotmail.com

as over 70 families have been reported worldwide [1,2,6-29]. NCMD is also a misnomer in that "dystrophy" implies progression and this disease is generally not progressive, although mild growth of atrophic lesions has been described in a single subject [26]. Interestingly, the severity of the disease in affected individuals across six generations in the original family was highly variable [1,2,30]. In 1991, Small et al. re-ascertained the original NCMD family and classified subjects into 3 grades, characterized by a few drusen in the central macular region (grade 1), confluent drusen in central macular region (grade 2), and macular coloboma (grade 3), with visual acuities ranging from 20/20 to 20/60 in grades 1 and 2, and from 20/40 to 20/200 in grade 3 [1].

A hallmark of NCMD is variable expressivity (Figure 1). This feature has contributed to this one disease within a singular family to be split into many different disease names such as Lefler Wadsworth Sidbury "Syndrome," dominant macular degeneration and aminoaciduria, dominant progressive foveal dystrophy, central areolar pigment epithelial dystrophy, central pigment epithelial and choroidal degeneration, and caldera maculopathy [13,31-37]. Phenocopies of NCMD include age-related macular degeneration, Best's vitelliform maculopathy, toxoplasmosis, fovea plana, benign yellow dot maculopathy (BYDM), and dominant drusen [38-42]. Peripheral drusen presence was claimed by some researchers to be a distinctive feature of NCMD to differentiate NCMD from BYDM [41]. Using ultra-widefield photography, Small et al. reported peripheral drusen in about half of the affected subjects [30].

Using genetic linkage, Small et al. mapped NCMD to chromosome 6 in 1990 and the locus was named MCDR1 by the Human Genome Organization (MC=macula, D=dystrophy, R=subtype retinal to distinguish it from corneal macular dystrophy 1=1st macular dystrophy mapped in the human genome) [43]. The causative mutations remained elusive until 2016 when Small et al. performed whole-genome sequencing and identified 3 non-coding point mutations and two tandem duplications in the DNase I hypersensitivity site DHS6S1, on chromosome 6q16, upstream of the PRDM13 gene, in the MCDR1 locus [7]. Small et al. also found a tandem duplication on chromosome 5 involving another DNase I site and the IRX1 gene (MCDR3). PRDM13 is a member of a large family of helix-loop-helix DNA binding proteins that play key roles in controlling gene expression during retinal development [44]. Presumed mutations, either single nucleotide variants (SNVs) or duplication structural variants, have been demonstrated in many NCMD families from different ethnicities, as summarized in Table 1. To date, 20 NCMD variants have been identified at the MCDR1 and MCDR3 loci; variants V1 and V2 account for 72.8% of NCMD cases, whereas most other alleles have been described in single families [7-29].

The first mutation we found in 2015, now referred to as "V1" (variant 1) is the first SNP (single nucleotide polymorphism; chr6:99593030G>T) identified in the original large NCMD family (family 765) [7]. The second SNP we found, now referred to as V2 (chr6:99593111G>C), was originally identified in a large French family in collaboration with Bernard Puech. Over the decades, many NCMD families have been ascertained by Small and our consortium and identified with the V1 or V2 mutation. Herein, we wanted to determine if each V1 and V2 mutation had its own unique most recent common ancestor (MRCA), and therefore, its own founder mutation.

METHODS

Subjects for this study were selected from our large data set of 512 NCMD subjects from 66 families. Of this data set, 140 individuals from 15 families were identified with V1, and 77 individuals from 21 families were identified with V2. At least one affected subject was chosen from each NCMD family with either a V1 or V2 mutation. Some families required two to four subjects to be selected to determine phase. In total, we analyzed 61 subjects from 32 unrelated V1 and V2 families: 22 individuals carrying V1 (14 families) and 39 individuals carrying V2 (18 families).

All affected subjects had been previously examined by one of the authors or had medical records reviewed for confirmation of NCMD diagnosis. Informed consent and IRB approval was obtained on all subjects. All tenets of the Declaration of Helsinki were adhered to in sample collection and data analysis for this study. Blood or saliva was obtained for DNA extraction and sequencing. Our genotyping and sequencing protocol has been previously published [7]. We genotyped 61 affected NCMD subjects with 19 short tandem repeats (STRs) from the MCDR1 locus (5.4 megabases [Mb]) to evaluate for shared genomic regions and haplotypes and thus a common founder effect (Figure 2). Eight of the STRs were developed in our laboratory and the remaining were available in the public database.

V1 and V2 founder mutation ages were estimated using the EstiAge program [45]. For each variant, we generated EstiAge input files from phased STR haplotypes, specifying recombination fractions for markers on each side and encoding the shared ("ancestral") haplotype. Because reliable population-based allele frequencies were not available for these loci, ancestral allele frequencies were set to a default value of 0.10 on all markers, and one additional censoring

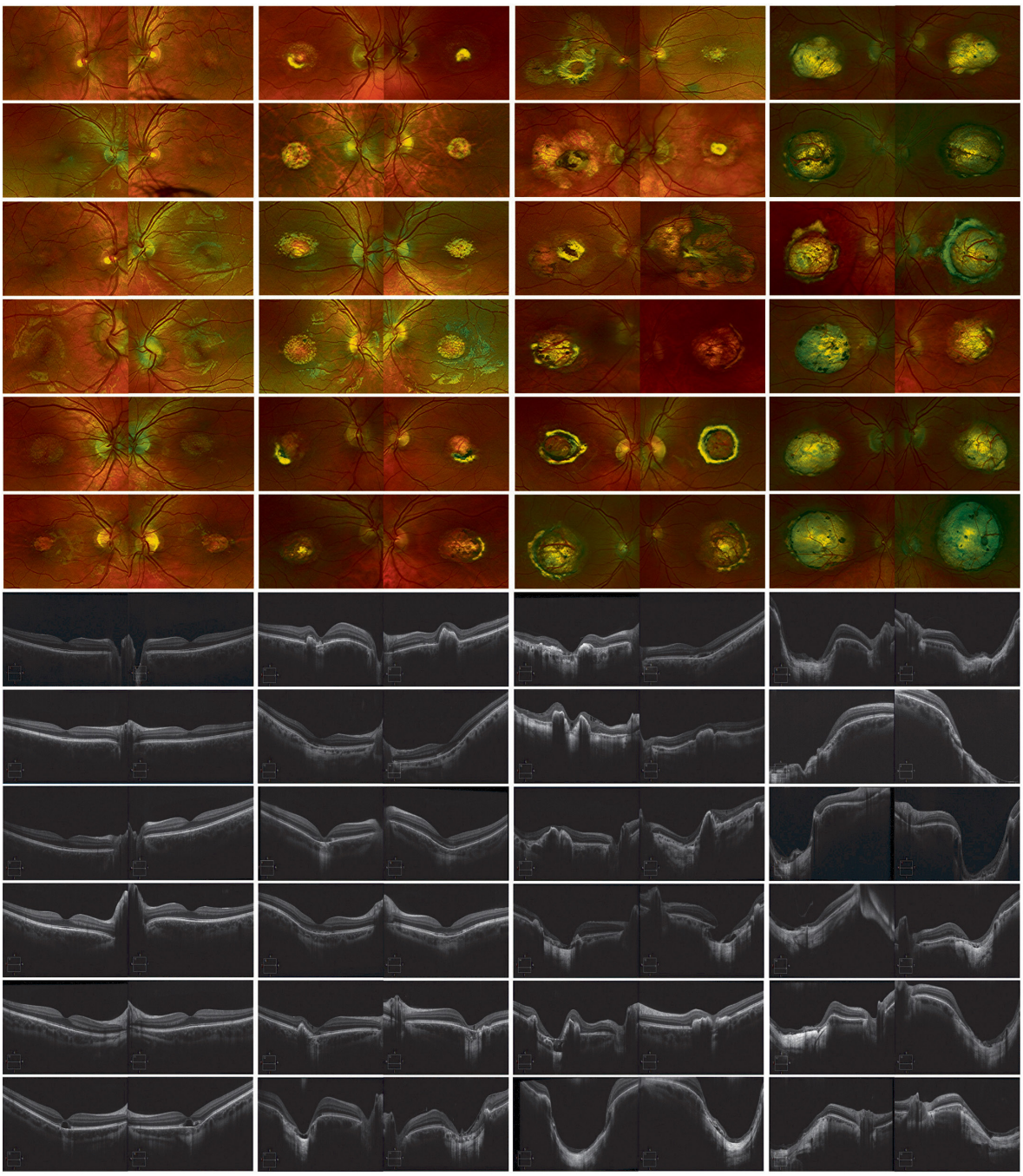


Figure 1. Retinal imaging of V1 family: Composite montage of color fundus photographs (upper panels) and corresponding optical coherence tomography (OCT) B-scans (lower panels) of 24 affected members from the original 765 V1 pedigree. Images are aligned by subject, with right and left eyes shown side-by-side within each panel.

Table 1. North Carolina macular dystrophy PRDM13 variant discovery.

Variant #	Type of Variant	Chromosomal Position (hg38)	Nucleotide Change	Phenotype	Origin of Mutation	Author, Journal, Publication Date (Ref #)
MCDR1 locus (PRDM13), chromosome 6q16						
V1	SNV	chr6:99593030	G>T	NCMD	US	Small KW et al. Ophthalmol. 2016[7]
V2	SNV	chr6:99593111	G>C	NCMD	US/Europe	Small KW et al. Ophthalmol. 2016[7]
V3	SNV	chr6:99593164	C>T	NCMD	China	Small KW et al. Ophthalmol. 2016[7]
V4	Tandem DUP	chr6:99572329–99695430	123,101 bp DUP	NCMD	Belize	Small KW et al. Ophthalmol. 2016[7]
V6	Tandem DUP	chr6:99548350–99617261	69,912 bp DUP	NCMD	US	Bowne SJ et al. Mol Vis. 2016[8]
V7	Tandem DUP	chr6:99536433–99634822	98,389 bp DUP	NCMD	France	Manes G et al. Hum Mol Genet. 2017[9]
V10	SNV	chr6:99598928	T>C	PBCRA	UK	Silva RS, et al. Hum Mutat. 2019[15]
V11	SNV	chr6:99598907	A>C	CPPCRH	China/ Egypt	Silva RS et al. Hum Mutat. 2019[15], Small KW et al. Retina. 2022[16]
V12	SNV	chr6:99593098	A>C	Possible NCMD	Georgia	Namburi P et al. Mol Vis. 2020[10]
V13	Tandem DUP	chr6:99560265–99616492	56,228 bp DUP	NCMD	Turkey	Small KW et al. Mol Vis. 2021[11]
V14	SNV	chr6:99593030	G>C	NCMD	Mexico	Small KW et al. J Vitreoretin Dis. 2023[17]
V15	Tandem DUP	chr6: 99,484,588-99619234	134,646 bp DUP	NCMD	China	Wu S et al. Graef Arch Clin Ex Ophth 2022[12]
V16	SNV	chr6:99599064	A>G	NCMD	Czech Republic	Sompele SV, Liskova P, Small KW, et al. Am J Hum Genet. 2022[14]
V17	SNV	chr6:99598914	T>C	NCMD	Korea	Seo Y, Small KW, et al. Mol Vis. 2024[18]
V18	SNV	chr6:99598926	G>A	NCMD	Korea	Seo Y, Small KW, et al. Mol Vis. 2024[18]
V19	Tandem DUP	chr6: 99,577,641-99679722	102,081 bp DUP	NCMD	Mexico	Chacon-Camacho OF, Small KW, et al. Mol Vis 2024[27]
V20	Tandem DUP	chr6:99983358–100082211dup	98,853 bp DUP	NCMD	Italy	Spedicati et al., 2025[29]
V21	SNV	chr6:99593161	T>C	NCMD	US	Small KW, et al., Publication Pending
MCDR3 locus (IRX1), chromosome 5p21						
V5	Tandem DUP	chr5:3587787–4485914	898,126 bp DUP	NCMD	Denmark	Small KW et al. Ophthalmol. 2016[7]
V8	Tandem DUP	chr5:4391264–4436422	45,158 bp DUP	NCMD	Europe	Cipriani V et al. Sci Rep. 2017[28]
V9	Tandem DUP	chr5:4396814–4440329	43,515 bp DUP	NCMD	Europe	Cipriani V et al. Sci Rep. 2017[28]

Detailed characterization of all identified genetic variants associated with North Carolina Macular Dystrophy, including chromosomal positions, nucleotide changes, and origin of mutation.

Table 2. Haplotype analysis STR markers.

Marker	Hg38 Distance from Gene	Hg38 Distance from Mutation
D6S501	2,222,977	2,209,233
D6S249	1,936,853	1,923,106
D6S1716	1,310,350	1,296,606
NU23	438,829	425,085
NU20	416,501	402,757
D6S1717	381,487	367,743
D6S1565	316,856	303,112
D6S2112	205,593	191,849
V1	13,744	0
PRDM13	0	−13,744
NU27-GA	−247,033	−260,777
NU-27-TTTC	−247,309	−261,053
NU31	−266,127	−279,871
D6S1671	−500,946	−514,690
D6S475	−549,444	−563,188
D6S283	−2,305,245	−2,318,989

STRs in the MCDR1 region showing the distances between the markers. Primers available upon request.

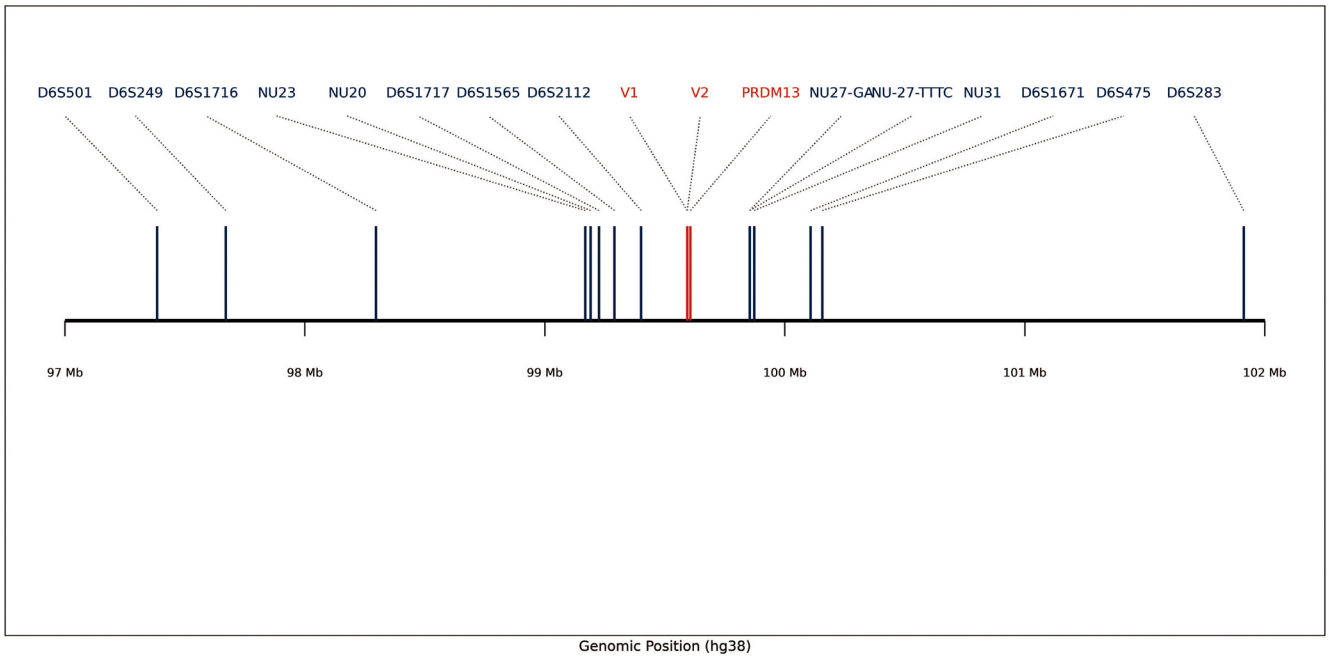


Figure 2. Genomic Context of Haplotype Markers: Our haplotype markers (blue), the V1 and V2 mutations, and the PRDM13 gene (red), along with their positions on chromosome 6.

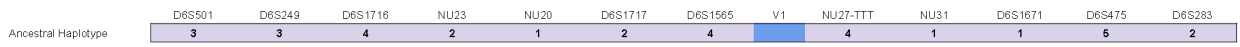


Figure 3. Hypothetical ancestral haplotype for the North Carolina macular dystrophy V1 variant: Schematic representation of the inferred ancestral STR haplotype associated with the V1 mutation, showing the allele pattern across markers in the MCDR1 region. The position of the V1 variant is indicated in blue.

marker was added on each side at recombination fraction 0.5 with unknown ancestral alleles (-1) to account for continued sharing at the most distal markers. We assumed a random-mutation model with a microsatellite mutation rate of 0.001 per locus per generation, as assumed in previous EstiAge simulations [45] and supported by established models of haplotype decay and mutation rate [46,47].

RESULTS

The STRs we used in the MCDR1 region and the genomic distances between the markers are noted in Table 2. We chose STRs within a 5.4 megabase region spanning MCDR1. Several of these were the original STRs used by Small et al. to map NCMD by linkage in 1990 [43]. A few of these STRs that we developed were uninformative in our families, especially in the V2 families. The V2 families' individuals were less informative than the V1 individuals. Therefore, additional V2 family members were genotyped to determine phase. Genotyping identified 1 misdiagnosed family (n=4) in the V1 cohort, and a lone misdiagnosed V2 subject (n=1). After variant verification, 13 V1 families (n=18) in the V1 group and 18 V2 families (n=38) were included in the haplotype analysis.

A unique shared haplotype was found for the V1 subjects and families throughout the entire MCDR1 genomic region (Figure 3). Eleven of the STRs were highly informative in the V1 families (Table 3). A different shared unique haplotype was found for the V2 subjects and families (Table 4). An ancestral crossover apparently occurred in the Utah, German, and Oxford families at D6S475, going telomeric (Figure 4). Using EstiAge, the V1 founder mutation was estimated to have arisen approximately 150 years ago (95% CI, 100–375 years). The V2 founder mutation was estimated at approximately 725 years ago (95% CI, 525–1,025 years).

DISCUSSION

Before NCMD was mapped by linkage by Small et al. in 1990, extensive genealogy studies were performed by Small on the original Lefler Wadsworth Sidbury family [1]. Multiple branches of the family were found to have been reported as unique clinical disease entities. The considerable variable expressivity of the phenotype of NCMD contributed significantly to this confusion. Even without molecular genetics, genealogical methods alone suggested a common founder for the original NCMD families as previously reported by Small et al. [48]

With current molecular genetic methods, we are now able to demonstrate that all V1 families available to us have an MRCA in the US. The shared haplotype region encompasses at least 5.4 Mb, suggesting a rather recent ancestral common founder. Additionally, the individuals and families with the V2 mutation also have a different unique shared haplotype, indicating another MRCA. Some of these are Americans and most are European (UK, French, German, Dutch, Italian). All 16 other reported mutations have been reported only in single families (i.e., private mutations).

Haplotype data that does not conform to the V1 and V2 haplotypes are noted in light gray in Table 3 and Table 4. Most noteworthy is family 777. In Table 3, it becomes apparent that all affected members in this family that have been tested possess genotypes and haplotypes that are distinct from other identified V1 and V2 subjects. The family was originally found to have what appeared to be a V1 mutation on the spherograms. However, family members maintained that their genealogy traced their origins to Mexico, and explicitly not to the United States. Upon discovering this, the family was re-sequenced by the Sanger method for the V1 mutation. This resulted in identification of a different mutation at the V1 nucleotide position (chr6:99593030G>C).

Our haplotype analysis found another error. Oxford family D subject DI:1 was found to have a haplotype that was not consistent with the segregation of the shared affected haplotype (dashed box in Table 4). Subsequent Sanger sequencing of the subject's DNA revealed that he did not have the V2 mutation. This subject was 78 years old at the time of examination and his macular phenotype is consistent with the diagnosis of AMD. Hence, the current analysis corrects an error in the previous manuscript [7].

Genotyping data and DNA sequencing data are subject to errors. In Table 3 and Table 4, the genotypes indicated by empty boxes represent data where the alleles could not be reliably interpreted. Much of the DNA used in this study is quite old, contributing to some of these issues. Some samples gave no reliable results and were excluded from our analysis.

Table 3. V1 Haplotype.

V1 Family-Subject #	Origin	D6S501		D6S249		D6S1716		NU23		NU20		D6S1717		D6S1565		NU27-TTT		NU31		D6S1671		D6S475		D6S283	
702–1824104	OH	3	3	3	6	4	4	2	2	1	2	2	8	4	4	4	2	1	1	1	4	5	3	2	1
702–1765	OH	3	3	3	6	4	3	2	2	1	1	2	5	4	4	4	4	1	1	1	5	5	8	2	1
702–1766	OH	3	5	3	6	4	3	2	3	1	4	2	2	4	6	4	4	1	1	1	10	5	5	2	1
702–1767	OH	3	3	6	6	4	3	2	2	1	4	2	6	4	6	4	4	1	1	1	10	5	5	2	1
702–1768	OH	3	3	3	6	4	4	2	2	1	2	2	8	4	4	4	2	1	1	1	4	5	3	2	1
704–17338008	WV	3	3	3	6	4	4	2	2	1	4	2	3	4	3	4	6	1	5	1	2	5	5	2	1
705–19078000	TX	3	3	3	6	4	2	2	2	1	4	2	2	4	6	4	1	1	7	1	3	5	7	2	1
715–22731	WV	3	3	3	6	4	4	2	2	1	4	2	3	4	3	4	4	1	1	1	10	5	4	2	2
720–2895329	WA	3	3	3	6	4	4	2	2	1	1	2	3	4	4	4	4	1	6	1	10	5	7	2	1
765–8051881672	NC	3	3	3	6	4	3	2	2	1	2	2	7	4	6	4	4	1	2	1	3	5	5	2	1
765–8051	NC	3	3	3	6	4	3	2	2	1	4	2	7	4	6	4	5	1	3	1	10	5	5	2	2
768–48139	TX	3	3	6	6	4	4	2	1	1	1	2	5	4	5			1	1	1	9	5	8	2	1
772–10348000	SC	3	4					2	4											1	4			2	1
773–1332100	OH	3	3	3	6	4	5	2	2	1	1	2	5	4	5	4	4	1	1	1	10	5	8	2	1
777–1730	NY	2	4	3	4	1	3	2	2	1	1	3	5	3	6	5	1	1	3	10	4	5	4	2	2
777–1731	NY	3	4	3	3	2	3	2	2	1	4	2	5	4	6	5	5	2	3	10	10	5	13	2	2
777–1732	NY	3	4	3	3	4	3	2	2	1	1	5	5	5	6	4	5	6	3			5	5	2	2
777–1733	NY	3	4	3	3	6	3	2	2	1	4	3	5	3	6	5	5	1	3	10	11	5	7	2	2
785–11941	WI	3	3	3	6	4	3	2	2	1	1	2	3	4	4	4	6	1	6	1	8	5	2	2	2
790-KSA2310	PA	3	3	1	6	4	3	2	2	1	4	2	2	4	1			1	2	1	10	1	5	2	2
1193–368101	IL	3	3	3	6	4	2	2	2	1	2	2	3	4	3	4	2	1	3	1	9	5	5	2	1
1292–12361002	NC	3	3	3	6	4	2	2	2	1	1	2	7	4	5	4	4	1	1	1	7	5	3	2	1
Affected Allele		3		3		4		2		1		2		4		4		1		1		5		2	

V1 affected subjects and families with down coded genotypes of the most informative short tandem repeats; organized by family and subject number, place of origin, and STRs.

Table 4. V2 haplotype.

V2 Family#-Subject #	Origin	D6S 501		D6S 249		D6S 1716		NU23		NU20		D6S 1717		D6S 1565		NU27-TTT		NU31		D6S 1671		D6S 475		D6S 283	
718–2442–1	CA	2	3	1	1	4	3	2	2	4	3	3	3	3	4	2	3	3	6	4	1	11	5	2	2
731–682–1	CA	2	3	4	1	4	3	2	2	4	3	7	3	5	4	4	3	1	6	10	1	7	19	2	2
769–40260	FR	2	3	1	1	7	3	2	2	1	3	5	3	6	4	4	3	3	6	1	1	5	17	2	2
769–727–4045	FR	3	3	1	1	3	3	2	2	3	3	7	3	3	4			6	6	6	1	8	17	2	2
769–726–4044	FR					4	3					3	3	8	1			1	3	6	1			2	2
771–363–8005	WV, USA	1	4	4	1	4	3	2	2	4	3	3	3	4	4	2	3	6	6	5	1	4	17	4	2
771–1949–8001	WV, USA	1	3			4	3	2	2	4	3	4	3	3	4	1	3	3	6	8	1	3	17	2	2
771–364–7004	WV, USA	1	3			4	3	2	2	4	3	2	3	4	4	6	3	6	6	10	1	7	17	2	2
775–2339–1	Germany	1	3	5	1	4	3	2	2	3	3	2	3	6	4	2	3	3	6	4	3	7	8	2	2
775–2392–9003	Germany	1	3	1	1	4	3	2	2	4	3	2	3	3	4	4	3	3	6	4	9	7	5	2	2
778–135–108	WV, USA	1	3					2	2	1	4	2	2	2	4			1	6					2	2
778–126–1	WV, USA					4	3							3	4										
778–134–107	WV, USA	4	5			1	3	2	2	4	3	3	3	5	4	4	3	6	6	3	1	8	17	2	2
783-KSA2246	UT, USA	8	8	1	1	3	3	2	2					3	4	3	3	5	6	4	1	3	7	1	2
783-KSA2264	UT, USA	8	3	1	1	3	3	2	2	4	3	2	3	4	4	1	3	6	6	8	4	19	7	2	2
783–1391	UT, USA	8	8	1	1	3	3	2	2	3	3	3	3			3	3	5	6	4	1	3	7	1	2
784–1505–1	MD, USA	5	3	1	1	4	3	2	2	4	3	8	7	6	6	4	3	6	6	10	1	5	17	2	2
787–644	TX, USA	9	3	1	1	2	3	2	2	4	3	2	3	6	4	2	3	1	6	3	1	7	17	2	2
787–644–1	TX, USA	4	3			4	3	2	2	4	3	2	3	6	4	1	3	7	6	3	1	7	17	2	2
788–1805	Germany	2	4	1	1			2	2	4	3	2	3	4	4	2	3	3	6	8	1	11	3	2	2
788–1801–9000	Germany	2	2	6	1	4	3	2	2	1	3			6	4			6	6	1	1	11	5	2	2
788–1802–8000	Germany	2	3	1	1	4	3	2	2	1	3	2	3	4	4			1	6	10	1	11	5	2	2
789–710	California	8	9	1	1	4	3	2	2	3	3	8	3	6	4	6	3	6	6	4	1	7	13	2	2
1574-D4593	Toronto	3	3			4	3	2	2	3	3	2	3	5	4			6	6	5	1	7	17	2	2
1574–12738	Toronto	3	3	5	4	2	3	2	2	1	3	4	3	4	4	7	3	2	2	2	1	7	17		
1574–12739	Toronto	8	3	5	1	2	3	2	2	4	3	3	3	2	4	1	3	2	6	11	1	3	17	2	2
1574–12741	Toronto	3	3	5	1	3	3	2	2	4	3	2	3	4	4	5	3	2	6	1	1	3	17	2	2
1–11-A1.2	Oxford	8	3	3	1	3	3	2	2	4	3	2	3	6	4	5	3	6	6	9	1	7	17	2	2
1–12-A11.1	Oxford	8	3	3	1	3	3	2	2	4	3	2	3	6	4	2	3	4	6	3	1	1	17	2	2
1–13-B1.1	Oxford	4	4	8	1	2	3	2	2	1	3	4	3	6	4	5	3	6	6	1	1	5	13	2	2
1–14-B11.2	Oxford	4	3	1	1	2	3	2	2	1	3	2	3	4	4			2	6	2	1	5	13	2	2
1–15-B111.1	Oxford	4	9	1	1	2	3	2	2	4	3	2	3	4	4	3	3	4	6	7	1	1	13	2	2

V2 Family#-Subject #	Origin	D6S 501		D6S 249		D6S 1716		NU23		NU20		D6S 1717		D6S 1565		NU27-TTT		NU31		D6S 1671		D6S 475		D6S 283	
1–16-C1.2	Oxford	8	8	3	1	1	3	2	2	1	1	4	3	4	4	5	3	1	6	4	1	11	5	2	2
1–17-C11.1	Oxford	8	3	3	1	3	3	2	2	4	3	3	3	4	4	6	3	2	6	6	1			2	2
1–18-D1.1	Oxford	4	9	9	9	1	2	2	2	4	4	7	5	4	4	2	1	1	5	3	3	3	13	2	6
1–19-D11.1	Oxford	9	3	5	9	2	3	2	2	4	3	5	3	4	4	2	3	1	6	3	1	3	17	2	2
1–20-D111.1	Oxford	3	3	5	1	1	3	2	2	4	3	3	3	3	4	3	3	3	6	9	1	7	17		
1–21-E1.1	Oxford	4	3	1	1	2	3	2	2	3	3	7	3	4	4	1	3	4	6	3	1			2	2
1–22-F1.1	Oxford	3	3	1	1	1	2	2	2	4	3	8	3	1	4	5	3	8	6	1	1	19	17	2	2
Affected Allele		3		1		3		2		3		3		4		3		6		1		17		2	

V2 affected subjects and families with down coded genotypes of the most informative short tandem repeats; organized by family and subject number, place of origin, and STRs.

Molecular Vision 2026; 32:451-463 <http://www.molvis.org/molvis/v32/451>

© 2026 Molecular Vision

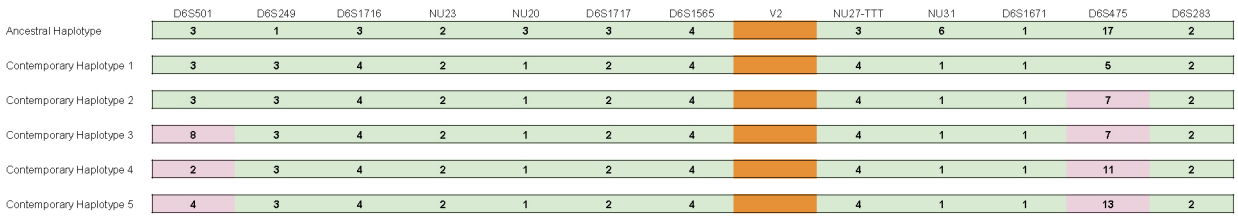


Figure 4. Hypothetical ancestral haplotype and contemporary haplotypes for the North Carolina macular dystrophy V2 variant: Schematic representation of the inferred ancestral short tandem repeat (STR) haplotype associated with the V2 mutation (top row) and representative contemporary haplotypes identified in V2 carriers (rows below), showing the allele pattern across markers in the MCDR1 region. The position of the V2 variant is indicated in orange; red-shaded cells indicate marker alleles that differ from the inferred ancestral haplotype.

A couple of haplotype inconsistencies highlighted in light gray suggest either genotyping errors or double crossovers. The latter would be statistically highly improbable within such a small genomic region.

Coalescence theory would suggest that the common genomic regions shared by V1 families and V2 families are relatively large (>5 Mb). The larger the shared DNA segment, the more recent the mutation along with fewer opportunities for ancestral recombinant events. Thus, the most recent common ancestor is likely relatively recent. Because we did not perform whole genome sequencing due to cost, we are unable to precisely define the most recent common ancestor or generate an ancestral recombination graph [49]. The V2 mutation appears to be older than the V1 due to the detected ancestral recombinatorial events in the German families 775 and 788, Utah family 783, and Oxford family B at D6S475 (solid outlined boxes in Table 4). The more preceding generations present, the greater the likelihood of an ancestral recombinatorial event occurring. Our findings indicate an ancestral founder mutation occurring further back in time. Therefore, the V2 European mutation appears “older” than the V1 mutation and perhaps originated in Germany. The genealogical finding that all V1 mutations reported thus far have been only in Americans, also suggesting that this V1 mutation is more recent. Consistent with these expectations, EstiAge analysis (see Results) supported a substantially more recent origin for V1 than for V2. The comparatively young age of V1 is consistent with the exclusively American genealogic origins of all V1 families, while the older V2 estimate is compatible with the variant’s broader European distribution.

Haplotype analysis in other published NCMD families, that were not available to us for this study, would be useful in identifying further founder effects. Two different families with tandem duplications have been reported in China. Sequencing the break points precisely and performing haplotype analysis would determine whether these two families are related or not. In one of these families as described by Wu et al., the boundaries were defined and published, while the duplication reported by Zhu et al. did not define the margins of the duplication [12,13]. Therefore, it is not possible for other researchers to determine potential genealogical ties between these two Chinese families. The mutational uncertainty highlighted by these two families emphasizes the importance of precise genomic characterization of mutations.

Another NCMD example where haplotype analysis might be useful would be the two families with congenital posterior polar chorioretinal hypoplasia (CPPCRH) both carrying the same SNP (chr6:99598907 A>C) [15,16]. Like NCMD, CPPCRH is a congenital macular maldevelopment disease; however, its clinical severity is markedly greater. Additionally, while the family reported by Silva et al. was Asian and the family reported by Small et al. was Egyptian, there remains a possibility that these two families also have a shared haplotype in the region, which can be determined by haplotype analysis [15,16].

All V1 (chr6:99,593,030 G>T) subjects studied to date are members of the same extended family, and the same is true for are all V2 (chr6:99,593,111 G>C) subjects. The two mutations lie only 81 bp apart within the same DNase I hypersensitive enhancer, 12.7 kilobases upstream of PRDM13. Therefore, the expected recombination distance between the two variants is on the order of 10^{-4} centimorgans. Given this insignificant distance, they effectively segregate as alternative alleles at a single locus.

Ultimately, our data support a two-class model of NCMD variation: two founder alleles at MCDR1 (V1 and V2) that account for the majority of reported families, and a long tail of ultra-rare variants each observed in single or few, unrelated families. For these latter variants, the available pedigrees and absence of recurrence across families are also consistent with private, often de novo, events. Family-based whole genome sequencing studies have demonstrated that on average,

approximately 74.5 de novo germline SNVs occur in a single subject's genome. Are these de novo germline mutations truly random, or are certain sites subject to selective pressures? One could argue that these mutations are selected against since NCMD is so rare. That is, would NCMD be more common if these mutations in non-coding genomic regions were truly random? This would support our theory that the NCMD mutations are caused by genomic architectural changes, allowing for the point mutations in the DNase1 sites. Perhaps "bulky lesions" characterized by DNA helix distortion cause nucleotide excision repair errors, leading to these SNVs [50,51]. De novo CNVs are sensitive to local genomic architecture as well [52]. The unique nature of NCMD and the importance of its private de novo mutations remain critical areas for future research.

ACKNOWLEDGMENTS

Financial Support: None Commercial Relationships: none Conflict of Interest Disclosure: Kent W. Small, MD: US Patent No 10 973 855 B2 Previous Poster Presentation: Small KW, Haritoonian A, Avetisjan J, Shaya F, Diaz A, Im J, Udar U, Udar N, Leys MJ, Rice TA, Lewis RA, Puech B, Heon E, Bernstein P, Rognon GT, Scott A, Schneiderman T, Wilson D, Rohrschneider K, Agemy S, Kiernan D, Birtel J, Charbel Issa P. North Carolina Macular Dystrophy, Haplotype Analysis of 31 Families Shows Single Founders for Each Mutation. ARVO 2025: i3: imagining innovation and intelligence in vision science; 2025 May 4–7.

This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits reusers to copy and distribute the material in any medium or format in unadapted form only, for noncommercial purposes only, and only so long as attribution is given to the creator. CC BY-NC-ND includes the following elements: BY: credit must be given to the creator. NC: Only noncommercial uses of the work are permitted. ND: No derivatives or adaptations of the work are permitted.

REFERENCES

1. Small KW, Killian J, McLean WC. North Carolina's dominant progressive foveal dystrophy: how progressive is it? Br J Ophthalmol 1991; 75:401-6. [PMID: 1854692].
2. Small KW. North Carolina macular dystrophy, revisited. Ophthalmology 1989; 96:1747-54. [PMID: 2622620].
3. Small KW. North Carolina macular dystrophy: clinical features, genealogy, and genetic linkage analysis. Trans Am Ophthalmol Soc 1998; 96:925-61. [PMID: 10360311].
4. Bakall B, Bryan JS 3rd, Stone EM, Small KW. Choroidal neovascularization in North Carolina macular dystrophy responsive to anti-vascular endothelial growth factor therapy. Retin Cases Brief Rep 2021; 15:509-13. [PMID: 30383557].
5. Agarwal A, Gass JDM. Gass' Atlas of Macular Diseases. 5th ed. Edinburgh: Elsevier Saunders; 2012.
6. Lefler WH, Wadsworth JAC, Sidbury JB Jr. Hereditary macular degeneration and amino-aciduria. Am J Ophthalmol 1971; 71:224-30. [PMID: 5100467].
7. Small KW, DeLuca AP, Whitmore SS, Rosenberg T, Silva-Garcia R, Udar N, Puech B, Garcia CA, Rice TA, Fishman GA, Héon E, Folk JC, Streb LM, Haas CM, Wiley LA, Scheetz TE, Fingert JH, Mullins RF, Tucker BA, Stone EM. North Carolina macular dystrophy is caused by dysregulation of the retinal transcription factor PRDM13. Ophthalmology 2016; 123:9-18. [PMID: 26507665].
8. Bowne SJ, Sullivan LS, Wheaton DK, Locke KG, Jones KD, Koboldt DC, Fulton RS, Wilson RK, Blanton SH, Birch DG, Daiger SP. North Carolina macular dystrophy (MCDR1) caused by a novel tandem duplication of the *PRDM13* gene. Mol Vis 2016; 22:1239-47. [PMID: 27777503].
9. Manes G, Joly W, Guignard T, Smirnov V, Berthemy S, Bocquet B, Audo I, Zeitz C, Sahel J, Cazevieille C, Sénéchal A, Deleuze JF, Blanché-Koch H, Boland A, Carroll P, Geneviève D, Zanlonghi X, Arndt C, Hamel CP, Defoort-Dhellemmes S, Meunier I. A novel duplication of PRMD13 causes North Carolina macular dystrophy: overexpression of PRDM13 orthologue in drosophila eye reproduces the human phenotype. Hum Mol Genet 2017; 26:4367-74. [PMID: 28973654].
10. Namburi P, Khateb S, Meyer S, Bentovim T, Ratnapriya R, Khramushin A, Swaroop A, Schueler-Furman O, Banin E, Sharon D. A unique *PRDM13*-associated variant in a Georgian Jewish family with probable North Carolina macular dystrophy and the possible contribution of a unique *CFH* variant. Mol Vis 2020; 26:299-310. [PMID: 32476814].
11. Small KW, Van de Sompele S, Nuytemans K, Vincent A, Yuregir OO, Ciloglu E, Sariyildiz C, Rosseel T, Avetisjan J, Udar N, Vance JM, Pericak-Vance MA, De Baere E, Shaya FS. A novel duplication involving *PRDM13* in a Turkish family supports its role in North Carolina macular dystrophy (NCMD/MCDR1). Mol Vis 2021; 27:518-27. [PMID: 34526759].
12. Wu S, Yuan Z, Sun Z, Zhu T, Wei X, Zou X, Sui R. A novel tandem duplication of PRDM13 in a Chinese family with North Carolina macular dystrophy. Graefes Arch Clin Exp Ophthalmol 2022; 260:645-53. [PMID: 34427740].
13. Zhu Z, Zou H, Li C, Tong B, Zhang C, Xiao J. The possible pathogenesis of macular caldera in patients with North Carolina macular dystrophy. BMC Ophthalmol 2022; 22:447-[PMID: 36402981].
14. Van de Sompele S, Small KW, Cicekdal MB, Soriano VL, D'haene E, Shaya FS, Agemy S, Van der Snickt T, Rey AD, Rosseel T, Van Heetvelde M, Vergult S, Balikova I, Bergen AA, Boon CJF, De Zaeytijd J, Inglehearn CF, Kousal B,

Leroy BP, Rivolta C, Vaclavik V, van den Ende J, van Schooneveld MJ, Gómez-Skarmeta JL, Tena JJ, Martinez-Morales JR, Liskova P, Vleminckx K, De Baere E. Multi-omics approach dissects cis-regulatory mechanisms underlying North Carolina macular dystrophy, a retinal enhanceropathy. Am J Hum Genet 2022; 109:2029-48. [PMID: 36243009].

15. Silva RS, Arno G, Cipriani V, Pontikos N, Defoort-Dhellemmes S, Kalhoro A, Carss KJ, Raymond FL, Dhaenens CM, Jensen H, Rosenberg T, van Heyningen V, Moore AT, Puech B, Webster AR. Unique noncoding variants upstream of PRDM13 are associated with a spectrum of developmental retinal dystrophies including progressive bifocal chorioretinal atrophy. Hum Mutat 2019; 40:578-87. [PMID: 30710461].

16. Small KW, Tawfik CA, Udar N, Udar U, Avetisjan J, El-Aidy LA, Shaya FS. Congenital posterior polar chorioretinal hypoplasia: Expansion of the clinical spectrum, mutation and its association with PRDM13. Retina 2022; 42:2379-87. [PMID: 36007168].

17. Small KW, Van de Sompele S, Avetisjan J, Udar N, Agemy S, De Baere E, Shaya FS. New noncoding base pair mutation at the identical locus as the original NCMD/MCDR1 in a Mexican family, suggesting a mutational hotspot. J Vitreoretin Dis 2023; 7:33-42. [PMID: 37008391].

18. Seo Y, Joo K, Lee J, Diaz A, Jang S, Cherry TJ, Bujakowska KM, Han J, Woo SJ, Small KW. Two novel non-coding single nucleotide variants in the DNase1 hypersensitivity site of *PRDM13* causing North Carolina macular dystrophy in Korea. Mol Vis 2024; 30:58-66. [PMID: 38601016].

19. Pauleikhoff D, Sauer CG, Müller CR, Radermacher M, Merz A, Weber BHF. Clinical and genetic evidence for autosomal dominant North Carolina macular dystrophy in a German family. Am J Ophthalmol 1997; 124:412-5. [PMID: 9439376].

20. 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-.

21. Rohrschneider K, Blankenagel A, Kruse FE, Fendrich T, Völcker HE. Macular function testing in a German pedigree with North Carolina macular dystrophy. Retina 1998; 18:453-9. [PMID: 9801043].

22. Reichel MB, Kelsell RE, Fan J, Gregory CY, Evans K, Moore AT, Hunt DM, Fitzke FW, Bird AC. Phenotype of a British North Carolina macular dystrophy family linked to chromosome 6q. Br J Ophthalmol 1998; 82:1162-8. [PMID: 9924305].

23. Michaelides M, Johnson S, Tekriwal AK, Holder GE, Bellmann C, Kinning E, Woodruff G, Trembath RC, Hunt DM, Moore AT. An early-onset autosomal dominant macular dystrophy (MCDR3) resembling North Carolina macular dystrophy maps to chromosome 5. Invest Ophthalmol Vis Sci 2003; 44:2178-83. [PMID: 12714659].

24. Rosenberg T, Roos B, Johnsen T, Bech N, Scheetz TE, Larsen M, Stone EM, Fingert JH. Clinical and genetic characterization of a Danish family with North Carolina macular dystrophy. Mol Vis 2010; 16:2659-68. [PMID: 21179233].

25. Kim SJ, Woo SJ, Yu HG. A Korean family with an early-onset autosomal dominant macular dystrophy resembling North Carolina macular dystrophy. Korean J Ophthalmol 2006; 20:220-4. [PMID: 17302207].

26. Birtel J, Gliem M, Herrmann P, Neuhaus C, Holz FG, MacLaren RE, Scholl HPN, Charbel Issa P. North Carolina macular dystrophy shows a particular drusen phenotype and atrophy progression. Br J Ophthalmol 2022; 106:1269-73. [PMID: 33785507].

27. Chacon-Camacho OF, Flores-Lagunes LL, Small KW, Udar N, Udar U, Diaz A, Arce-González R, Molina-Garay C, Martínez-Aguilar A, Montes-Almanza L, Garcia-Martinez F, Gudiño A, Matsui-Serrano R, Fest-Parra S, Alaez-Verson C, Shaya F, Zenteno JC. A novel *PRDM13* gene duplication causing congenital North Carolina macular dystrophy phenotype in a Mexican family. Mol Vis 2024; 30:400-8. [PMID: 39959174].

28. Cipriani V, Silva RS, Arno G, Pontikos N, Kalhoro A, Valeina S, Inashkina I, Audere M, Rutka K, Puech B, Michaelides M, van Heyningen V, Lace B, Webster AR, Moore AT. Duplication events downstream of IRX1 cause North Carolina macular dystrophy at the MCDR3 locus. Sci Rep 2017; 7:7512-[PMID: 28790370].

29. Spedicati B, Pasquetti D, Santin A, Zampieri S, Morgan A, Lenarduzzi S, Nardone GG, Paccagnella E, Cappellani S, Diplotti L, Pensiero S, Parentin F, Gasparini P, Battaglia Parodi M, Girotto G. Hidden in the Genome: The First Italian Family with North Carolina Macular Dystrophy Carrying a Novel *PRDM13* and *CCNC* Duplication. Biomedicines 2025; 13:1904-[PMID: 40868158].

30. Small KW, Wiggins R, Udar N, Silva-Garcia R, Avetisjan J, Vincent A, Shaya FS. North Carolina macular dystrophy: Long-term follow-up of the original family. Ophthalmol Retina 2022; 6:512-9. [PMID: 35151913].

31. Frank HR, Landers MB 3rd, Williams RJ, Sidbury JB. A new dominant progressive foveal dystrophy. Am J Ophthalmol 1974; 78:903-16. [PMID: 4440724].

32. Dobbie JG, Fetkenhour CL, Shoch D. Central areolar pigment epithelial (cape) dystrophy. Trans Am Ophthalmol Soc 1975; 73:141-52. [PMID: 1246802].

33. Fetkenhour CL, Gurney N, Dobbie JG, Choromokos E. Central areolar pigment epithelial dystrophy. Am J Ophthalmol 1976; 81:745-53. [PMID: 937428].

34. Leveille AS, Morse PH, Kiernan JP. Autosomal dominant central pigment epithelial and choroidal degeneration. Ophthalmology 1982; 89:1407-13. [PMID: 7162784].

35. Hermsen VM, Judisch GF. Central areolar pigment epithelial dystrophy. Ophthalmologica 1984; 189:69-72. [PMID: 6472809].

36. Khurana RN, Sun X, Pearson E, Yang Z, Harmon J, Goldberg MF, Zhang K. A reappraisal of the clinical spectrum of North Carolina macular dystrophy. Ophthalmology 2009; 116:1976-83. [PMID: 19616854].

37. Small KW, Agemy S, Shaya FS. Terminology of MCDR1: What's in a Name? JAMA Ophthalmol 2016; 134:355-6. [PMID: 26914342].

38. Small KW, Jampol LM, Bakall B, Small L, Wiggins R, Agemy S, Udar N, Avetisjan J, Vincent A, Shaya FS. Best vitelliform macular dystrophy (BVMD) is a phenocopy of North Carolina macular dystrophy (NCMD/MCDR1). Ophthalmic Genet 2022; 43:307-17. [PMID: 34895015].

39. Small KW, Tran EM, Small L, Rao RC, Shaya F. Multimodal Imaging and functional testing in a North Carolina macular disease family: Toxoplasmosis, Fovea Plana, and torpedo maculopathy are phenocopies. Ophthalmol Retina 2019; 3:607-14. [PMID: 31043363].

40. Small KW, Vincent AL, Knapper CL, Shaya FS. Congenital toxoplasmosis as one phenocopy of North Carolina Macular Dystrophy (NCMD/MCDR1). Am J Ophthalmol Case Rep 2019; 15:100521[PMID: 31367689].

41. Kiraly P, Birtel J, Ong AY, Ruan C, Fischer MD, Charbel Issa P. Extended phenotypic spectrum of benign yellow dot maculopathy. Eye (Lond) 2025; 39:1547-52. [PMID: 39984697].

42. Charbel Issa P, De Silva SR, Pfau K, Birtel J. Differential diagnosis of age-related macular degeneration. Klin Monbl Augenheilkd 2025; 242:7-21. [PMID: 39820891].

43. Small KW, Weber JL, Roses A, Lennon F, Vance JM, Pericak-Vance MA. North Carolina macular dystrophy is assigned to chromosome 6. Genomics 1992; 13:681-5. [PMID: 1639395].

44. Watanabe S, Sanuki R, Sugita Y, Imai W, Yamazaki R, Kozuka T, Ohsuga M, Furukawa T. Prdm13 regulates subtype specification of retinal amacrine interneurons and modulates visual sensitivity. J Neurosci 2015; 35:8004-20. [PMID: 25995483].

45. Genin E, Tullio-Pelet A, Begeot F, Lyonnet S, Abel L. Estimating the age of rare disease mutations: the example of Triple-A syndrome. J Med Genet 2004; 41:445-9. [PMID: 15173230].

46. Slatkin M, Rannala B. Estimating allele age. Annu Rev Genomics Hum Genet 2000; 1:225-49. [PMID: 11701630].

47. Ellegren H. Microsatellite mutations in the germline: implications for evolutionary inference. Trends Genet 2000; 16:551-8. [PMID: 11102705].

48. Small KW, Hermsen V, Gurney N, Fetkenhour CL, Folk JC. North Carolina macular dystrophy and central areolar pigment epithelial dystrophy. One family, one disease. Arch Ophthalmol 1992; 110:515-8. [PMID: 1562260].

49. Nielsen R, Vaughn AH, Deng Y. Inference and applications of ancestral recombination graphs. Nat Rev Genet 2025; 26:47-58. [PMID: 39349760].

50. Porubsky D, Dashnow H, Sasani TA, Logsdon GA, Hallast P, Noyes MD, Kronenberg ZN, Mokveld T, Koundinya N, Nolan C, Steely CJ, Guarracino A, Dolzhenko E, Harvey WT, Rowell WJ, Grigorev K, Nicholas TJ, Goldberg ME, Oshima KK, Lin J, Ebert P, Watkins WS, Leung TY, Hanlon VCT, McGee S, Pedersen BS, Happ HC, Jeong H, Munson KM, Hoekzema K, Chan DD, Wang Y, Knuth J, Garcia GH, Fanslow C, Lambert C, Lee C, Smith JD, Levy S, Mason CE, Garrison E, Lansdorp PM, Neklason DW, Jorde LB, Quinlan AR, Eberle MA, Eichler EE. Human de novo mutation rates from a four-generation pedigree reference. Nature 2025; 643:427-36. [PMID: 40269156].

51. Seplyarskiy VB, Sunyaev S. The origin of human mutation in light of genomic data. Nat Rev Genet 2021; 22:672-86. [PMID: 34163020].

52. Veltman JA, Brunner HG. De novo mutations in human genetic disease. Nat Rev Genet 2012; 13:565-75. [PMID: 22805709].

Articles are provided courtesy of Emory University and The Abraham J. & Phyllis Katz Foundation. The print version of this article was created on 25 September 2026. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.