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A novel duplication involving *PRDM13* in a Turkish family supports its role in North Carolina macular dystrophy (NCMD/MCDR1)

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Purpose: To clinically and molecularly investigate a new family with North Carolina macular dystrophy (NCMD) from Turkey, a previously unreported geographic origin for this phenotype.
Methods: Clinical ophthalmic examinations, including fundus imaging and spectral domain-optical coherence tomography (SD-OCT), were performed on eight members of a two-generation non-consanguineous family from southern Turkey. Whole genome sequencing (WGS) was performed on two affected subjects, followed by variant filtering and copy number variant (CNV) analysis. Junction PCR and Sanger sequencing were used to confirm and characterize the duplication involving *PRDM13* at the nucleotide level. The underlying mechanism was assessed with in silico analyses.
Results: The proband presented with lifelong bilateral vision impairment and displayed large grade 3 coloboma-like central macular lesions. Five of her six children showed similar macular malformations, consistent with autosomal dominant NCMD. The severity grades in the six affected individuals from two generations are not evenly distributed. CNV analysis of WGS data of the two affected family members, followed by junction PCR and Sanger sequencing, revealed a novel 56.2 kb tandem duplication involving *PRDM13* (chr6:99560265–99616492dup, hg38) at the *MCDR1* locus. This duplication cosegregates with the NCMD phenotype in the five affected children. No other (likely) pathogenic variants in known inherited retinal disease genes were found in the WGS data. Bioinformatics analyses of the breakpoints suggest a replicative-based repair mechanism underlying the duplication.
Conclusions: We report a novel tandem duplication involving the *PRDM13* gene in a family with NCMD from a previously unreported geographic region. The duplication size is the smallest that has been reported thus far and may correlate with the particular phenotype.

North Carolina macular dystrophy (NCMD/MCDR1) is an autosomal dominant, completely penetrant, congenital, non-progressive macular malformation first reported in a large family in North Carolina as described by Lefler, Wadsworth, and Sidbury 50 years ago, and later by Small 30 years ago [1-3]. The disease was named after the location of the founder effect, in the western part of North Carolina [4]. Although rare, NCMD has been found worldwide in more than 50 families in the United States, Europe, Central America, Australia, New Zealand, South Korea, and China [3,5-21]. Therefore, North Carolina macular dystrophy is a misnomer.

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One of the most striking clinical features of NCMD is the typical intrafamilial phenotypic variability and the relatively good vision despite severe-appearing macular malformations in some patients. It is important to mention that affected individuals have a particular grade of NCMD at birth and do not progress; therefore, individuals do not progress from grade 1 to grade 2, or from grade 2 to grade 3, contrary to previous descriptions [20-22]. There can be some vision decline later in life secondary to the development of choroidal neovascularization. However, patients who develop choroidal neovascular membranes (CNVMs) are the only ones who experience progressive moderate to severe vision loss and usually only in one eye [23]. CNVMs typically occur along the temporal edge of the coloboma where they do not affect the vision. When CNVMs occur in grade 2 or along the nasal edge of the grade 3 coloboma, in NCMD patients, anti-VEGF injections have been beneficial [23].

Phenocopies of this disease include drusen of age-related macular degeneration, Stargardt macular dystrophy, Best macular dystrophy, torpedo maculopathy, and toxoplasmosis [24-26]. Since 1990, Small et al. hypothesized that the causative gene(s) for NCMD are involved in embryonic macular development based on congenital and non-progressive clinical features. This would help explain why vision is relatively good considering the severe-appearing lesions present in some cases [11-20]. The electroretinogram (ERG) and electrooculogram (EOG) are typically normal, as is the color vision test. As expected, multifocal ERG recordings reveal significant amplitude reductions in the central retina in severely affected subjects only [27].

Small et al.'s genetic linkage analysis of this single family revealed a locus on chromosome 6q16 (MCDR1/NCMD; OMIM 136,550) [26-29]. Subsequent linkage analysis of additional families yielded a logarithm of the odds (LOD) score greater than 40 [28-31]. Targeted genomic sequencing of the 880 kb linked region eventually identified three noncoding single nucleotide variants (SNVs) 12 kb from the nearest gene, located in a DNase I hypersensitivity site [14]. These SNVs potentially alter regulation of expression of the neighboring gene encoding the PR/SET domain-containing zinc finger protein 13 (PRDM13; OMIM 616,741) [14]. Ellingford et al. later confirmed one of the SNVs in a small independent family with NCMD in the United Kingdom [32].

In addition, a duplication of 123 kb was found in the MCDR1 locus in a Mayan Belizean family, involving the same upstream DNase I hypersensitivity site and the *PRDM13* gene [14]. Bowne et al. subsequently and independently found a distinct large duplication involving the DNase I site and *PRDM13* [33]. Another unique duplication in the same genomic region was found by Manes et al. in a family from northern Italy [34]. *PRDM13* is expressed in the fetal retina and dorsal spinal columns and is not expressed in adult tissues [35]. The duplication in families with NCMD and overexpression experiments in *Drosophila* suggest that the malformation of the macula, including drusen, is due to overexpression of *PRDM13* [14,33-35].

Rosenberg and colleagues had previously mapped a Danish family with the NCMD phenotype to a second locus on chromosome 5 (5p21, MCDR3), showing genetic heterogeneity [12]. Using this positional information, a large duplication involving another DNase I site and the *IRX1* (OMIM 606197; Gene ID: 79192) gene was found by Small et al. [14]. Subsequently, Cipriani et al. reported in several European families with NCMD, two different overlapping smaller tandem duplications located in a noncoding region 791 kb downstream of the *IRX1* gene, involving the same DNase I site [36].

In 1996, a large genomic region overlapping MCDR1 was mapped in a single family, with nystagmus and severe congenital developmental anomaly/coloboma of the maculae, representing progressive bifocal retinochoroidal atrophy (PBRCA) [37,38]. Recently, Silva et al. found two distinct noncoding SNVs located in another DNase I site 7.8 kb upstream of *PRDM13*. This was found in three small unrelated families with congenital macular dystrophies, varying from NCMD to the more severe PBRCA [39]. Recently, another unique noncoding SNV within the same DNase I site as the original family with NCMD, upstream of *PRDM13* was reported. However, this was found in a small genetically isolated Georgian Jewish family with probable NCMD but also with diagnostic inconsistencies and molecular confounding factors with a *CFH* (OMIM 134370; Gene ID: 3075) duplication in some [40]. This discovery must be corroborated before any definitive conclusions can be made. We report a novel 56.2 kb tandem duplication at the MCDR1 chromosome 6 site involving the *PRDM13* gene in a family with NCMD from Turkey.

METHODS

Clinical assessment: Fundus photos were obtained using a Zeiss Visucam NM/FA (Glendale, AZ). Spectral domain-optical coherence tomography (SD-OCT) was performed using a Zeiss Cirrus HD-OCT (Dublin, CA). Blood or saliva or both was collected from consenting family members. Institutional Review Board (IRB) approval was obtained (# 94–07–241–21). Blood was drawn through a venipuncture procedure onto a sterile lavender tube and stored in a 2-8 ºC fridge. Genomic DNA was isolated from whole blood utilizing the Qiagen (Germantown, MD) extraction method.

Genetic assessment: DNA was extracted using standard methods and banked with pseudonymous identifiers. For targeted testing of the known pathogenic variants (SNVs) implicated in NCMD (Table 1), PCR (3 min 95 °C, 15 sec 95 °C, 10 sec 55 °C, 1 min 60 °C-repeat cycle 30 times then 1 min 72 °C, 10 min 4 °C) and Sanger sequencing was performed. Whole genome sequencing (WGS) was performed using standard protocols (NovaSeq 6000, Illumina, San Diego, CA), on DNA from two affected individuals (I:2 and II:7; pedigree represented in Figure 1) [41]. In short, after sample quality control (QC), sequencing libraries were prepared using the NEBNext® DNA Library Prep Kit (New England Biolabs, Ipswich, MA) according to the manufacturer's recommendations. Libraries were then sequenced using paired-end 2×125 bp format at >30X (Illumina). After

adaptor and quality trimming, QC FASTQ files were used in alignment with Burrows-Wheeler Aligner (BWA) to the reference human genome (hg38) [41-44]. Final BAM files were obtained at this stage. At the John P. Hussman Institute for Human Genomics, Pindel analysis was performed on the final BAM files using default settings to detect large structural variants (SVs) [41-46]. To exclude the presence of pathogenic variants in the genes known to be associated with inherited retinal diseases, we analyzed the RetNet panel on the WGS data of the two affected family members (I:2 and II:7). Therefore, BWA was used for alignment to the reference human genome (hg38), and Alamut Batch was used for annotation of variants located in RetNet genes. Filters were applied based on population frequency (<0.02) and coding effect, and the remaining variants were eventually filtered based on associated phenotype, so that only those variants associated with a macular phenotype remained.

To confirm the presence of the identified duplication in the MCDR1 locus, primers were designed to amplify across the breakpoints identified in the WGS data (forward primer 5′-AGT CAC CCA AGG GTC TGG AT-3′ and reverse primer 5′-CCA TGA CAT CTT TCC CAA CTG-3′). Subsequent Sanger sequencing was performed to assess exact breakpoints. The breakpoint regions were analyzed using multiple sequence alignment (ClustalW) and RepeatMasker (UCSC Genome Browser), respectively.

RESULTS

Clinical study: Clinical ophthalmic examinations were performed on eight members of a two-generation family (Figure 1), originating from Urfa in southeastern Turkey. There is no history of migration from the affected mother's side of the family from elsewhere. There is no reported consanguinity between the proband (I:2) and her partner (I:1). A summary of the clinical status, gender, age at examination, and visual acuity of the examined family members is provided in Table 2.

Table 1. Known genetic defects in the *PRDM13* and *IRX1* regions found in NCMD and possibly related diseases.

Variant Number	Type of Variant	Chromosomal Position (hg19)	Chromosomal Position (hg38)	Nucleotide Change	Phenotype	Reference
MCDR1 locus (*PRDM13*), chromosome 6q16						
V1	SNV	chr6:100040906	chr6:99593030	G>T	NCMD	Small 2016 [13]
V2	SNV	chr6:100040987	chr6:99593111	G>C	NCMD	Small 2016 [13]
V3	SNV	chr6:100041040	chr6:99593164	C>T	NCMD	Small 2016 [13]
V4	Tandem DUP	chr6:100020205–100143306	chr6:99572329–99695430	123,101 bp DUP	NCMD	Small 2016 [13]
V6	Tandem DUP	chr6:99996226–100065137	chr6:99548350–99617261	69,912 bp DUP	NCMD	Bowne 2016 [33]
V7	Tandem DUP	chr6:99984309–100082698	chr6:99536433–99634822	98,389 bp DUP	NCMD	Manes 2017 [34]
V10	SNV	chr6:100046804	chr6:99598907	T>C	PBCRA	Silva 2019 [38]
V11	SNV	chr6:100046783	chr6:99598928	A>C	NCMD PBCRA	Silva 2019 [38]
V12	SNV	chr6:100040974	chr6:99593098	A>C	Possible NCMD	Namburi 2020 [39]
V13	Tandem DUP	chr6:100008141–100064368	chr6:99560265–99616492	56,228 bp DUP	NCMD	This report
MCDR3 locus (*IRX1*), chromosome 5p21						
V5	Tandem DUP	chr5:3587901–4486027	chr5:3587787–4485914	898,126 bp DUP	NCMD	Small 2016 [13]
V8	Tandem DUP	chr5:4391377–4436535	chr5:4391264–4436422	45,158 bp DUP	NCMD	Cipriani 2017 [35]
V9	Tandem DUP	chr5:4396927–4440442	chr5:4396814–4440329	43,515 bp DUP	NCMD	Cipriani 2017 [35]

Abbreviations used: bp: base pair, chr: chromosome, DUP: duplication, SNV: single nucleotide variation. A: adenine, C: cytosine, G: guanine; T: thymine. NCMD: North Carolina Macular Dystrophy. PBCRA: progressive bifocal chorioretinal atrophy.

Table 2. Clinical characteristics of the individuals of Turkish family 780.

Family members	Gender	Macular dystrophy (bilateral)	Age of examination (year)	Visual acuity (Snellen) (OD/OS)
I:1	M	Unaffected	38	1.0/1.0
I:2	F	Affected	34	0.2/0.2
II:1	M	Unaffected	13	1.0/1.0
II:2	M	Affected	12	0.2/0.2
II:4	M	Affected	11	0.5/0.5
II:5	M	Affected	9	0.2/0.3
II:6	F	Affected	7	0.2/0.2
II:7	M	Affected	4	0.8/0.8

Abbreviations used: M: male; F: female. OD: right eye. OS: left eye.

The proband (I:2) is a 34-year-old woman presenting with lifelong bilateral vision impairment. Snellen visual acuity was 20/100 for the right eye (OD) and 20/100 for the left eye (OS). The anterior segments and the intraocular pressure were normal. Fundus assessment and SD-OCT showed symmetric macular coloboma-like excavations. Both optic discs had a normal aspect. Overall, the clinical features were consistent with NCMD grade 3 (Figure 2).

The six living children were subsequently examined. Five (II:2, II:4, II:5, II:6, and II:7) were found to have similar coloboma-like macular malformations consistent with NCMD grade 3, and a variable degree of decreased visual acuity ranging from 20/100 to 20/25 (Table 2). Their father I:1 was examined and found to be clinically unaffected.

Genetic study: The proband (I:2) underwent testing of known pathogenic variants previously reported in NCMD. This revealed no known pathogenic SNVs. CNV analysis of WGS data of affected family members I:2 and II:7 showed a 56.2 kb tandem duplication encompassing PRDM13 (chr6:99560265–99616492dup, hg38) at the MCDR1 locus on chromosome 6. Sequencing across the breakpoint showed the duplication in all affected family members, confirming cosegregation of the duplication with the disease (Figure 3). The duplication is novel and not present in any of the public variant databases. The breakpoint regions were analyzed for the degree of microhomology and for the presence of repetitive elements, showing 3-bp microhomology. Because of the absence of extensive homology and of repetitive elements, it was concluded that the nonrecurrent duplication may be

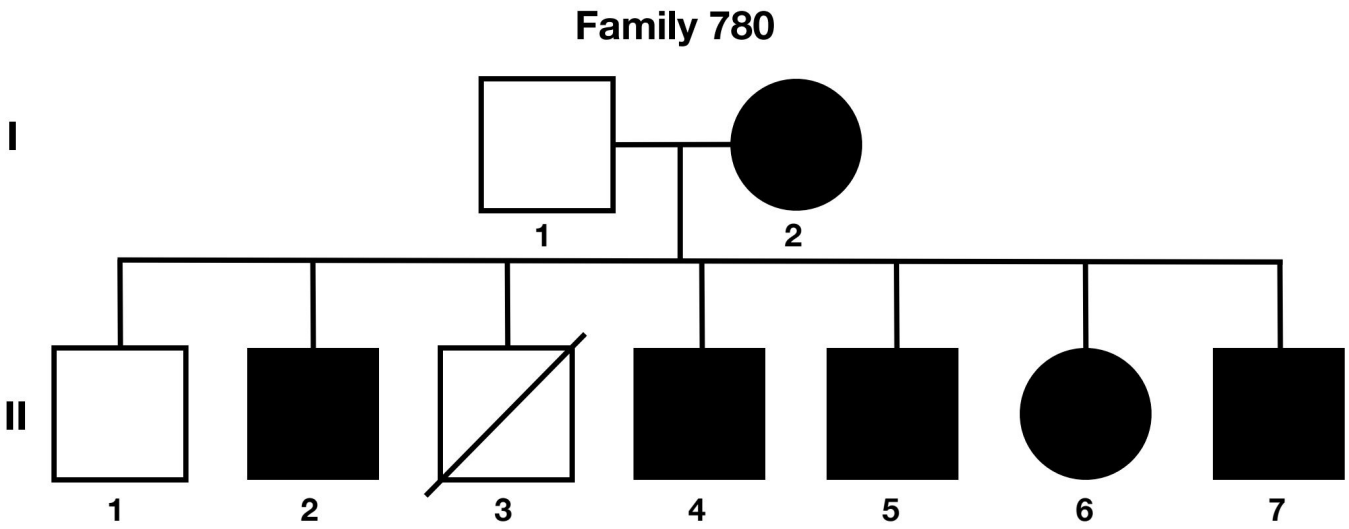

Figure 1. Pedigree of family 780. Two-generation pedigree with affected individuals represented by black filled symbols.

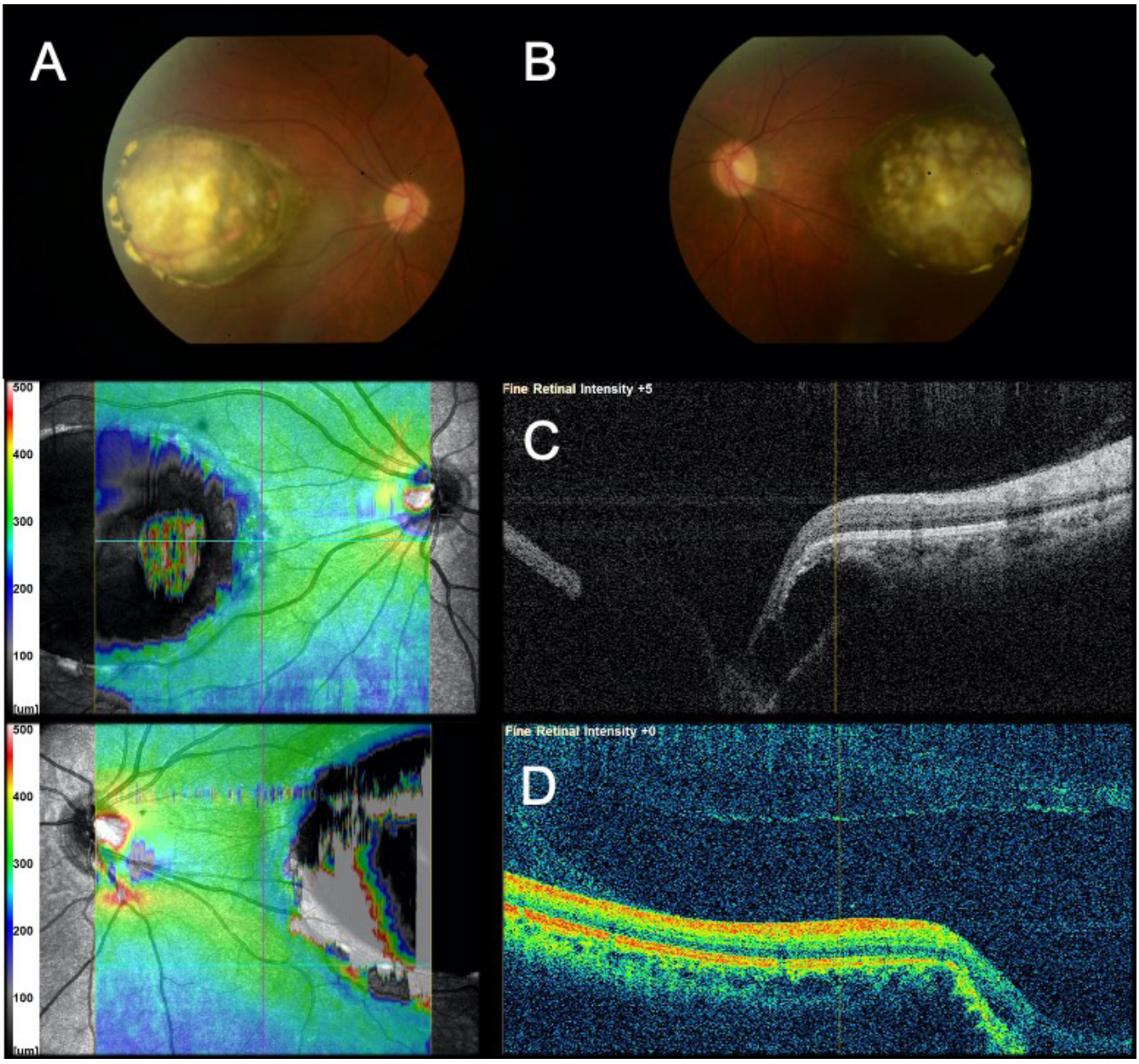

Figure 2. Fundus photo and SD-OCT of the proband (I:2). Fundus picture of the right (**A**) and left (**B**) eyes, showing normal optic discs and symmetric macular coloboma-like excavations, consistent with North Carolina macular dystrophy (NCMD) grade 3. Spectral domain-optical coherence tomography (SD-OCT) of the right eye (**C**) and of the left eye (**D**) illustrate a macular coloboma-like lesion with an absence of the RPE and intrachoroidal fluid representing a lacuna.

caused either by nonhomologous end-joining or by a replicative-based repair mechanism. The presence of the 3-bp microhomology (Figure 3) at the junction of the duplication and the absence of an information scar, typical of NHEJ, favors the latter hypothesis. These replicative-based repair mechanisms include fork stalling and template switching (FoSTeS), microhomology-mediated break-induced replication (MMBIR), and serial replication slippage (SRS) [47]. Finally, RetNet analysis of the available WGS data from the two affected family members (I:2 and II:7) did not reveal any other (likely) pathogenic variants that could explain the retinal phenotype in this family.

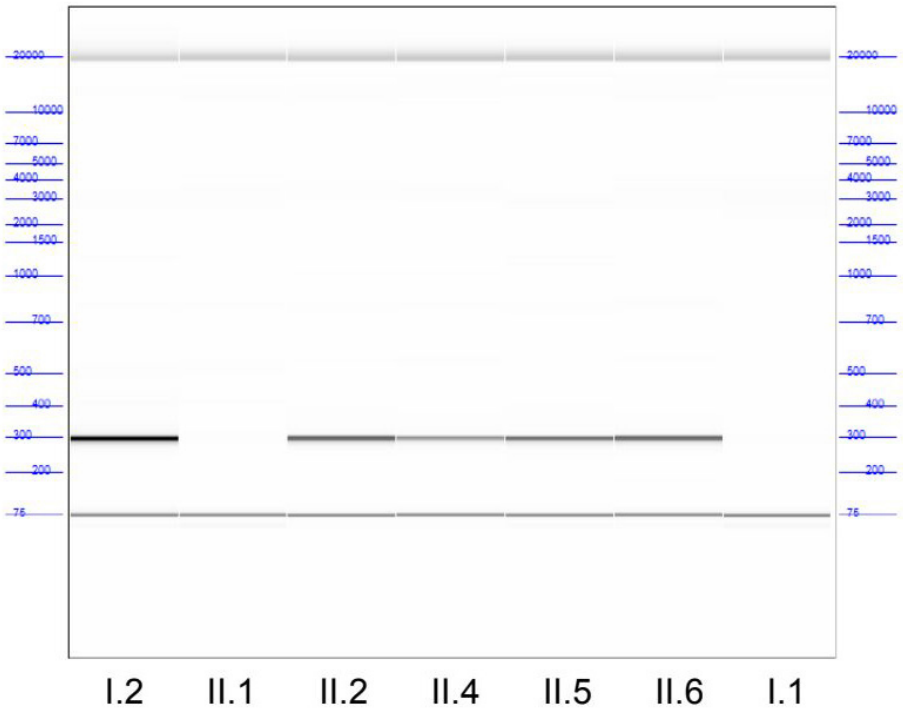

Figure 3. Breakpoint junction PCR results for seven tested individuals of family 780. The expected junction PCR fragment size is 279 bp. All affected individuals in this family were positive for the new 56.2 kb tandem duplication thus demonstrating segregation.

DISCUSSION

We clinically and genetically examined a two-generation Turkish family with NCMD that originates from a previously unreported geographic region for NCMD. As many families with NCMD are found outside North Carolina, the name of the disease is misleading. Most families with NCMD examined to date show considerable intrafamilial variable expressivity. Clinically, the family with NCMD in this report is unique because of the lack of variable expressivity. All of the six affected individuals in this family have severe large grade 3 coloboma-like lesions, while it would be expected that at least some family members would have one of the milder forms of NCMD. We cannot exclude unexamined branches of this family displaying milder phenotypes of NCMD, and an ascertainment bias favoring finding the more severe and symptomatic subjects.

Insight into the underlying genetic basis and a comparison with other pathogenic variants of the *PRDM13* region in NCMD and possibly related diseases such as PBRCA can help to explain this apparently unique clinical spectrum in this family. The identified 56.2 kb tandem duplication (Figure 4 and Figure 5) in this Turkish family is novel and smaller than the three previously reported duplications [14,33,34]. It adds to a total number of ten distinct pathogenic variants of the *PRDM13* region found in patients with NCMD and PBRCA. Six are unique noncoding SNVs located in two distinct DNase I sites, and four are unique tandem duplications overlapping the originally reported DNase I site and the *PRDM13* gene [14,33,34]. Thus far, a common feature of these variants, SNVs and SVs, is that they all involve DNase I sites. Interestingly, this is also the case for the three overlapping duplications of the *IRX1* region (MCDR3 locus) [14,36].

It can be hypothesized that the more severe grade phenotype observed in this family is caused by stronger dysregulation of *PRDM13* and its regulatory element caused by the smaller duplication, early in embryonic development of the macula. Disease severity may depend on spatiotemporal expression of *PRDM13* during development rather than the *PRDM13* dosage. This hypothesis is supported by the fact that *PRDM13* is not expressed in the adult retina [35].

Moreover, it is known that SVs, such as duplications, affect not only gene dosage but also gene regulation. They can change the copy number of regulatory elements or alter the 3D genome by disrupting higher-order chromatin organization, such as topologically associating domains (TADs) [48]. The impact of SVs on the 3D genome and on

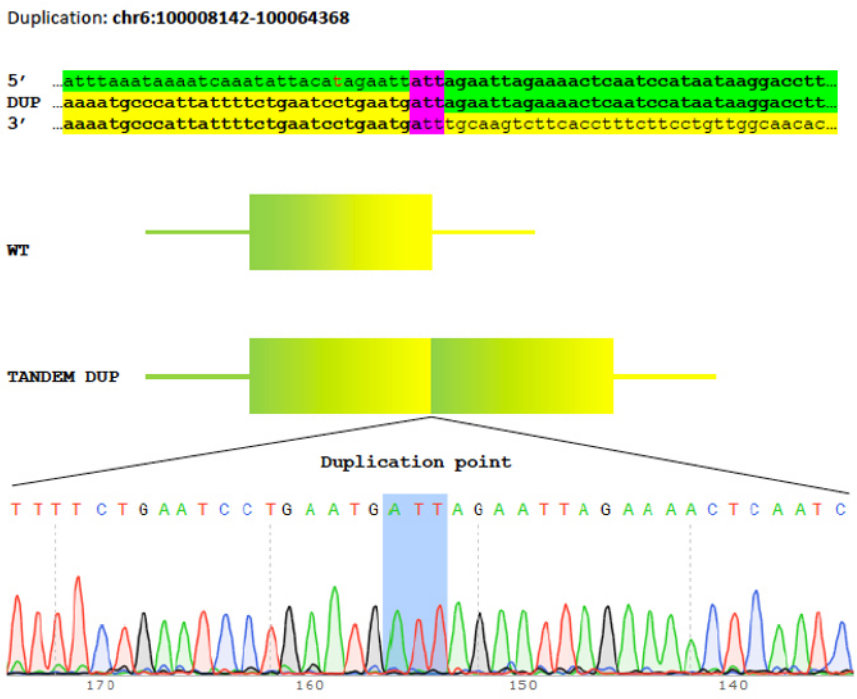

Figure 4. Visualization of the breakpoint of the new 56.2 kb tandem duplication found in family 780. Top: The 3-bp microhomology is represented in pink. Bottom: Sanger electropherogram spanning the duplication breakpoint.

gene expression regulation has to be considered when interpreting the consequences of these variant types [48]. Potential pathomechanisms resulting from an SV, such as the formation of neo-TADs, can become apparent with high-throughput chromosome conformation capture (Hi-C) generated from cultured patient cells in comparison with a wild-type reference Hi-C map [48,49]. Although Hi-C can help interpret the possible pathogenic effects of the SVs in individuals with developmental diseases such as NCMD, it is difficult to have access to patient-derived material in the relevant spatiotemporal window (developmental macula in the case of NCMD). Specifically, we did not have access to patient-derived cells that could be reprogrammed into induced pluripotent stem cells (iPSCs) and differentiated to retinal organoids.

In general, an increasing number of coding and noncoding SVs have been shown to underlie inherited retinal

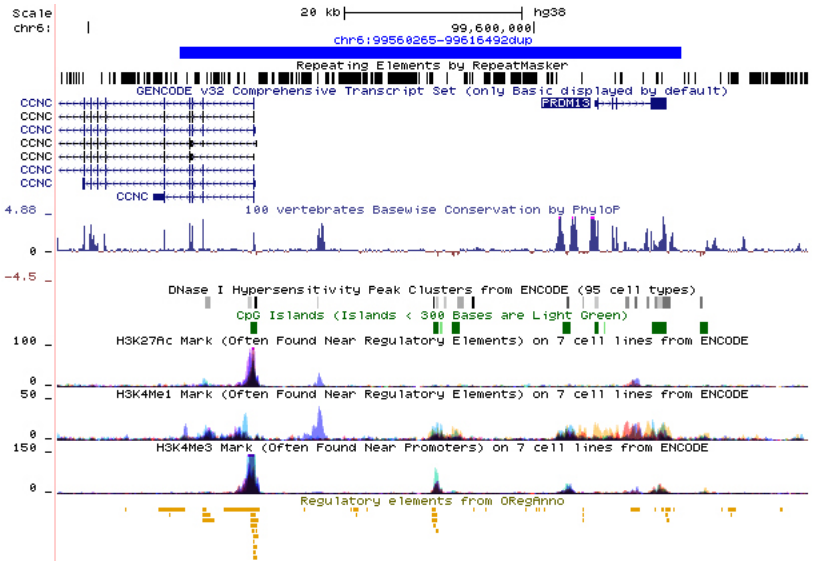

Figure 5. UCSC tracks for the identified duplication. The duplication is represented by the blue bar. It overlaps with several DNase I sites (in gray) and multiple candidate *cis*-regulatory elements (NCBI functional elements and ORegAnno).

diseases (IRDs) [50-55]. From reported noncoding SNVs, the majority have an effect on splicing. Only a handful of noncoding *cis*-regulatory variants have been identified in IRDs, however [51]. NCMD can be considered a model for noncoding regulatory SNVs and SVs in IRDs. Future studies in patient-derived cells may help elucidate the underlying mechanisms of this *cis*-regulatory disease.

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