

Case report: North Carolina macular dystrophy misdiagnosed as congenital ocular toxoplasmosis

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Purpose: This report discusses a case of North Carolina macular dystrophy (NCMD) in a 7-year-old boy initially diagnosed as congenital toxoplasmosis. Genetic testing was performed on the child and his family after the suspicion of NCMD was raised by the treating ophthalmologist. This case report highlights the similarities between congenital toxoplasmosis and NCMD.

Methods: DNA was collected from the family with consent and underwent comparative genomic hybridization and Sanger sequencing.

Results: Genetic testing identified a previously reported single base substitution (chromosome 6: 99,593,111 (G>C) NC_000006.11(GRCh38):g.100040987G>C), which confirms a diagnosis of NCMD.

Conclusions: We believe this is the first confirmed case of NCMD in Australia. This case highlights the similarities between NCMD and more commonly recognized conditions, such as ocular toxoplasmosis, and raises the question; How many other cases are misdiagnosed as ocular toxoplasmosis?

North Carolina macular dystrophy (NCMD) is an inherited autosomal dominant disease causing non-progressive macular impairment with congenital or infantile onset [1–3]. NCMD was first discovered in a large family in North Carolina, but has since been identified in literature from countries including the United States, Belize, England, Germany, and France [3]. The pathophysiology of NCMD remains poorly understood. Linkage studies in 1992 by Small et al. identified 6q13-q21 as the most likely region to harbor the causative gene [4], and was designated as *MCDRI* (Gene ID: DHS6S1, OMIM 616842; Phenotype OMIM 136550) by the Human Genome Organization. Later, genetic heterogeneity was found by Rosenberg et al. in a Danish family that mapped to chromosome 5 [5]. This was designated *MCDR3* (Phenotype OMIM 608850). In 2016, Small et al. [6] found three point mutations (V1, V2, and V3) in nine different families in a non-coding region of a DNASE1 hypersensitivity binding site at 6q16.2, and a single large duplication involving this region, as well as the retinal transcription factor *PRDM13* (Phenotype OMIM 616741). Additionally, his team found a large duplication causing the disease of *MCDR3* on chromosome 5 [6]. Others subsequently confirmed Small et al.'s findings with additional overlapping duplications of the chromosome 6 (*MCDRI*) and chromosome 5 (*MCDR3*) locations [7,8]. We report a case of NCMD,

which, to our knowledge, is the first genetically confirmed case published in scientific literature of NCMD in Australia.

METHODS

DNA was extracted from lymphocytes, and array comparative genomic hybridization analysis (Illumina Infinium CytoSNP-850K BeadChip, San Diego, CA) was performed to look for copy number variants, with manual analysis of *MCDRI* and *MCDR3*. Whole blood was collected from the patient in an Ethylenediaminetetraacetic acid (EDTA) tube and DNA extracted using a standard automated method (QIAsymphony® AS instrument, Qiagen, Hombrechtikon, Switzerland) as recommended by the manufacturer. Sanger sequencing of the *PRDM13* gene and the NCMD mutation hotspot 13 kb was performed by Molecular Vision Laboratory (Hillsboro, OR). Informed written consent was obtained from the family for genetic testing and for publication purpose. [6].

The research was conducted in accordance with the Declaration of Helsinki, and local institutional ethical requirements were met. The research, which adhered to ethical principles of medical research involving human subjects, was conducted in accordance with the Declaration of Helsinki, and local institutional ethical requirements were met.

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RESULTS

A 4-year-old boy failed his preschool vision screening, and was referred to an ophthalmologist. His best corrected visual acuity (BCVA) was 6/24 in the right eye and 6/12 in the left eye. He had a variable angle right exotropia and normal anterior segments in both eyes. Fundoscopic examination reported central bilateral excavated geographic atrophy six to seven disc diameters with surrounding submacular fibrosis. These circular lesions had some peripheral hyperpigmentation with raised fibrotic edges (Figure 1A,B). He was subsequently seen in the Ocular Genetics clinic at the Women's and Children's Hospital [4].

Family history revealed the father also had bilateral macular scarring, with a provisional diagnosis of congenital toxoplasmosis. He had been diagnosed when he was an infant, and had not progressed. On assessment of the boy's father, his BCVA in the right eye was 6/6 and in the left eye was 6/60. Fundoscopic examination revealed in the right eye a half disc diameter area of RPE atrophy involving the central macula, with scattered, fine drusen in the background retina (Figure 1C). In the left eye, a macular scar of approximately one disc diameter was noted with surrounding multiple fine

drusen in the macular area of the posterior pole (Figure 1D). The boy's mother and younger brother had normal ocular examinations. The family were Australian with a mixture of German and English heritage. During array comparative genomic hybridization, no copy number variants were identified, and Sanger sequencing identified a previously reported single base substitution (chromosome 6: 99,593,111 (G>C) NC_000006.11(GRCh38); g. 100040987G>C). The father was also shown to have this mutation, but it was not present in the unaffected sibling, confirming that the mode of inheritance is autosomal dominant.

DISCUSSION

The mutation reported was previously reported by Small et al. [6] as "V2", which was in the French and German families he studied. This is not the "V1" mutation of the original NCMD family of Lefler, Wadsworth, and Sidbury [2], although V1 and V2 are within 100 bp of each other in a non-coding region in the same DNASE1 binding site. The "V2" mutation has been more commonly reported in England and Europe, and this Australian family may likely share a common founder [8].

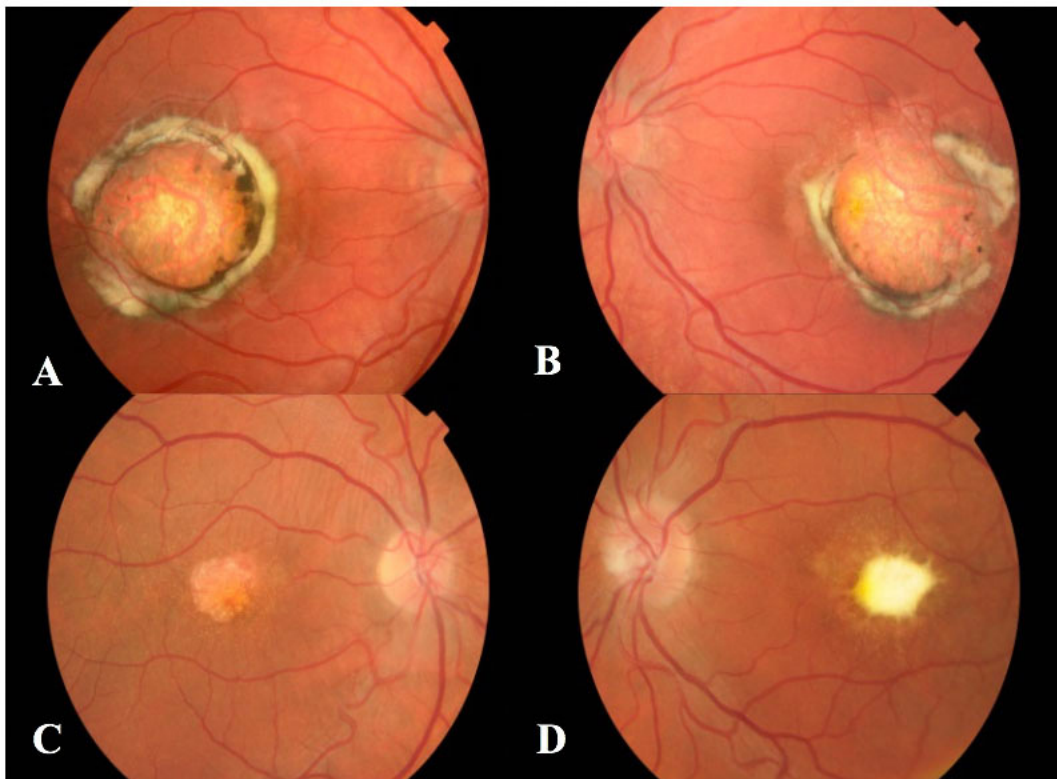


Figure 1. Fundus photos. A: Patient RE. B: Patient LE. C: Father RE. D: Father LE. RE= Fundus photos of right eye. LE= Fundus photos of left eye.

The phenotypic features of NCMD are highly variable even within a family [1-3]. NCMD features range from small drusen-like parafoveal deposits to large coloboma-like lesions in the central macula, which are seen in almost one third of affected individuals [1-3]. The disease generally involves stable lifelong impaired central vision, with the exception of those individuals with choroidal neovascularization [1-3].

Conversely, congenital toxoplasmosis most commonly presents with chorioretinal scars, although more prevalent in the periphery. In this family, a father and son were eventually found to be affected, which cast serious doubt on the previous diagnosis of congenital toxoplasmosis as no transplacental transmission could have occurred. This also highlights the importance of examining as many family members as possible, and the usefulness of this examination in making the correct diagnosis.

Conclusion: We are not the first to misdiagnose a patient with NCMD as having congenital toxoplasmosis. During the ascertainment of the original NCMD family, Small found that many of the family members had been misdiagnosed by their local ophthalmologists as having congenital toxoplasmosis [9] (K. Small, personal communication). Telander and Small listed toxoplasmosis in the differential diagnosis of NCMD [3]. Therefore, when an isolated individual presents with stable vision and what appears to be bilateral congenital toxoplasmosis, it would be advisable to examine other family members and consider genetic testing. Due to the similar appearance of these pathologies, and resultant visual acuities, NCMD should be considered for a differential diagnosis for congenital toxoplasmosis.

In conclusion, we believe this is the first confirmed case of NCMD in Australia, published in a scientific journal. This case highlights the similarities between NCMD and more commonly recognized conditions, such as ocular toxoplasmosis, and suggests that NCMD may be underdiagnosed in the general population or mistaken for conditions such as ocular toxoplasmosis [3].

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