Title: North Carolina Macular Dystrophy: 30-50-year follow-up of the original family

Authors: Kent W. Small, MD$^{1,2}$; Fadi Shaya$^{1,2}$; Jessica Avetisjan$^{1,2}$; Nitin Udar, PhD$^1$; Robert Wiggins, MD$^3$

Affiliations:
1. Molecular Insight Research Foundation, Los Angeles, CA, United States.
2. Macula & Retina Institute, Glendale and Los Angeles, CA, United States.
Financial Disclosures

Patent Pending US 2018/0117091 (KWS)
Kent W. Small, M.D.

SOLO PRIVATE PRACTICE (RETINA)
Molecular Insight Research Foundation
Cedar-Sinai Regenerative Medicine Institute
Los Angeles, CA
Glendale, CA
Summary

- 25 subjects re-examined
- From original NCMD family (family 765)
- The point mutation CHR6: 99593030 (Hg38) in a non-coding region of a DNASE1 hypersensitivity binding site on chromosome 6 (MCDR1) in all affected subjects
- One of the features of NCMD is the lack of progression in an individual
- Most NCMD patients have stable vision and fundus findings up to 50 years follow-up
- The ones who lost vision did so with NCMD grade 2 disease
  - developed choroidal neovascularization
- Only patients with grade 2 NCMD seem to be at risk for further / progressive vision loss
- With anti-VEGFs now available, some of these patients may benefit from these treatments
Introduction

• The clinical phenotype of NCMD is
  • highly variable
  • remains poorly appreciated and understood
• One feature of NCMD is the lack of progression
• Original Lefler, Wadsworth and Sidbury Syndrome
• named it “dominant progressive foveal dystrophy” 1971
autosomal dominant
congenital
completely penetrant
non-progressive (except CNVMs)
macular malformation
Marked variable expressivity,
drusen,
confluent drusen,
fibrosis,
coloboma – like lesion
NCMD is worldwide

- NCMD has been found worldwide in
- over 50 families by one investigator (KWS)
- Families have been reported in the
- United States,
- Europe, (eastern and western)
- Central America (Belize)
- Australia
- New Zealand
- Korea
- China

“North Carolina macular dystrophy” is a gross misnomer
Phenocopies of NCMD

- AMD (drusen)
- Torpedo maculopathy
- Congenital Toxoplasmosis
- Fovea plana
Initial publication of mutations 11 families
Methods

• 25 affected subjects of the original NCMD pedigree
• recently re-examined by KS in an office setting
• Evaluation on all affected subjects included:
  • Standard Snellen visual acuity
  • Slit lamp examination, 90 D and 20 D fundus examinations
  • Fundus photography (OPTOS California; Marlborough, MA)
  • SD-OCT (Zeiss Cirrus 5000; Oberkochen, Germany)
• findings were compared with the original data collected by KS in 1988 and images from 1971 by Lefler (HL) et al.
• SD-OCT was not available original ascertainment of the family in 1988
• Blood was collected for DNA extraction and analysis
• IRB approval and signed consent was obtained on all participating subjects
Results

• The 25 subjects examined were part of the original NCMD family (family 765)

• The point mutation CHR6: 99593030 G>C (Hg38) was found

• in a non-coding region of a DNASE1 hypersensitivity binding site on chromosome 6 MCDR1 in all affected subjects

• 8 were affected children of those originally examined
RESULTS

• 17 subjects (34 eyes) had been examined 30-50 years previously
• 6 previously examined by Lefler 50 years ago and fundus photos published in 1971
• Out of those 17 subjects (34 eyes):
  • 4 (11%) eyes showed worsening of vision
  • with fundus photos showing evidence of fibrosis from CNVM
  • Some have surrounding atrophy: resolved subretinal fluid
  • 1 unexplained improvement in VA
Patient 2 at 29 years old
NCMD grade 3
VA: 20/40 OD

Patient 2 at 60 years old NCMD grade 3
VA: 20/40 OD
Patient 2 at 29 years old
NCMD grade 3
VA: 20/80 OS

60 years old NCMD grade 3
20/100 OS
Patient 5 at 16 years old NCMD grade 3
VA: 20/40 OS

36 years old NCMD grade 3
VA: 20/40 OS

67 years old NCMD grade 3
Va 20/60 OS
Patient 5 at 67 years old
NCMD grade 3
VA: 20/200 OD, 20/60 OS
Patient 7 at 21 years old
NCMD grade 3
VA: 20/30 OD, 20/200 OS

IMPROVED:
55 years old
NCMD grade 3
VA: 20/40 OD, 20/50 OS
Patient 11 at 29 years old
NCMD grade 3
VA: 20/30 OU

70 years old
NCMD grade 3
VA: 20/70 OU

40 years old
NCMD grade 3
VA: 20/30 OU
Patient 11 at 70 years old
NCMD grade 3
VA: 20/70 OU
Patient 12 at 3 years old
NCMD Grade 2
VA: 20/30 OS

14 years old
NCMD grade 2
VA: 20/200 OS

51 years old
NCMD grade 2
VA: 20/250 OS
Patient 12 at 51 years old
NCMD grade 2
VA: 20/70 OD, 20/250 OS
Visual Acuity Changes in the Original NCMD Family 765 (30-50 years later)

<table>
<thead>
<tr>
<th>Name</th>
<th>Current Age</th>
<th>Previous VA OD</th>
<th>Previous VA OS</th>
<th>Current VA OD</th>
<th>Current VA OS</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>20/30</td>
<td>20/50</td>
<td>20/50</td>
<td>20/80-1</td>
<td>STABLE</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>20/40</td>
<td>20/80</td>
<td>20/40-2</td>
<td>20/100-1</td>
<td>STABLE</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
<td>20/20+1</td>
<td>20/15-1</td>
<td>STABLE</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>20/40</td>
<td>6/200</td>
<td>20/20</td>
<td>20/200</td>
<td>STABLE</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>20/100</td>
<td>20/40</td>
<td>20/200</td>
<td>20/60-2</td>
<td>STABLE</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>20/25+2</td>
<td>20/30</td>
<td>20/40-2</td>
<td>20/150-2</td>
<td>OS WORSE</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>20/30</td>
<td>20/200</td>
<td>20/40</td>
<td>20/50</td>
<td>OS IMPROVED</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>NA</td>
<td>NA</td>
<td>20/80-1</td>
<td>20/60-1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>39</td>
<td>NA</td>
<td>NA</td>
<td>20/20</td>
<td>20/20</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>13</td>
<td>NA</td>
<td>NA</td>
<td>20/40-2</td>
<td>20/30+2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>70</td>
<td>20/30</td>
<td>20/30</td>
<td>20/70-2</td>
<td>20/70</td>
<td>STABLE</td>
</tr>
<tr>
<td>12</td>
<td>51</td>
<td>HM</td>
<td>20/50</td>
<td>20/70</td>
<td>20/250</td>
<td>OD IMPROVED</td>
</tr>
<tr>
<td>13</td>
<td>25</td>
<td>NA</td>
<td>NA</td>
<td>20/30</td>
<td>20/20-2</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>45</td>
<td>2060+2</td>
<td>20/70-1</td>
<td>20/150-1</td>
<td>20/250</td>
<td>STABLE</td>
</tr>
<tr>
<td>15</td>
<td>49</td>
<td>20/30</td>
<td>20/70</td>
<td>20/100-2</td>
<td>20/150</td>
<td>WORSE OU</td>
</tr>
<tr>
<td>16</td>
<td>16</td>
<td>NA</td>
<td>NA</td>
<td>20/20-2</td>
<td>20/20-2</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>81</td>
<td>20/20-3</td>
<td>20/20-3</td>
<td>20/20-2</td>
<td>20/25</td>
<td>STABLE</td>
</tr>
<tr>
<td>18</td>
<td>83</td>
<td>20/40</td>
<td>20/30</td>
<td>CF @ FACE</td>
<td>20/40</td>
<td>OD WORSE</td>
</tr>
<tr>
<td>19</td>
<td>45</td>
<td>20/25</td>
<td>20/40</td>
<td>HM</td>
<td>20/40</td>
<td>OD WORSE</td>
</tr>
<tr>
<td>20</td>
<td>23</td>
<td>NA</td>
<td>NA</td>
<td>20/30-1</td>
<td>20/30-1</td>
<td>STABLE</td>
</tr>
<tr>
<td>21</td>
<td>40</td>
<td>20/20</td>
<td>20/25</td>
<td>20/15-2</td>
<td>20/40-2</td>
<td>STABLE</td>
</tr>
<tr>
<td>22</td>
<td>15</td>
<td>NA</td>
<td>NA</td>
<td>20/40</td>
<td>20/30-2</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>64</td>
<td>20/200</td>
<td>20/40</td>
<td>20/100-2</td>
<td>20/50-1</td>
<td>STABLE</td>
</tr>
<tr>
<td>24</td>
<td>11</td>
<td>NA</td>
<td>NA</td>
<td>20/25+1</td>
<td>20/15-1</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

• Most NCMD patients have stable vision and fundus findings throughout their lives even up to 50 years follow-up.
• The ones who lost vision did so with NCMD grade 2, rarely grade 3
  • developed choroidal neovascularization
  • More common than previously recognized
• anti-VEGFs may benefit these patients
Acknowledgements

• Funded in part by Molecular Insight Research Foundation and Foundation for Fighting Blindness Grant #: BR-GE-1216-0715-CSH