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Neurol Genet
2016;2:e103; doi: 10.1212/
NXG.000000000000103

OUTDATED RISK ASSESSMENT IN A FAMILY WITH DUCHENNE DYSTROPHY: IMPLICATIONS FOR DUTY TO REASSESS

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Carrier risk assessment for Duchenne muscular dystrophy (DMD) is necessary to counsel women at risks of developing cardiomyopathy and having a child with DMD. Comprehensive molecular testing for dystrophin gene mutations has only been available since 2003¹; women counseled earlier have outdated risk assessments. We present a 5-generation family in whom results of familial mutation testing for DMD newly identified 10 obligate carriers and 28 women at risk to be carriers for DMD.

Case descriptions. The proband presented to us at 5 years of age for evaluation of weakness and motor developmental delay. His examination revealed low muscle tone with calf atrophy; strength was 4/5 in the Medical Research Council scale in his deltoids and hip flexors. He had a lordotic gait with inability to run and a positive Gower maneuver. A 5-generation pedigree was obtained (figure). Individual III-10, the proband's grandmother, provided the history and identified V-1 as a patient at our center, who had been diagnosed with DMD. V-1 is the proband's third cousin through a lineage comprising women. Individuals III-1, III-18, and IV-7 were noted to have died at ages 21, 22, and 19, respectively, of DMD. At the time the family history was obtained, II-9 and III-10 reported that they were not carriers of DMD. III-10 and her sister, III-11, were tested in the 1980s and were told that they were "low carriers" for DMD, while III-3 was told that she was a "high carrier" for DMD; similar risk categorization has been used in the literature² and may reflect the genetic counseling they were provided. This assessment led III-3 to decide not to have more children.

Review of V-1's records confirmed that he had a novel *DMD* splice site mutation, c.8669-2A>T, which is predicted to disrupt the exon 59 splice acceptor site. Creatine kinase (CK) level of the proband was elevated at 21,837 IU/L, and genetic testing confirmed the same splice site mutation identified for V-1. The dystrophinopathy

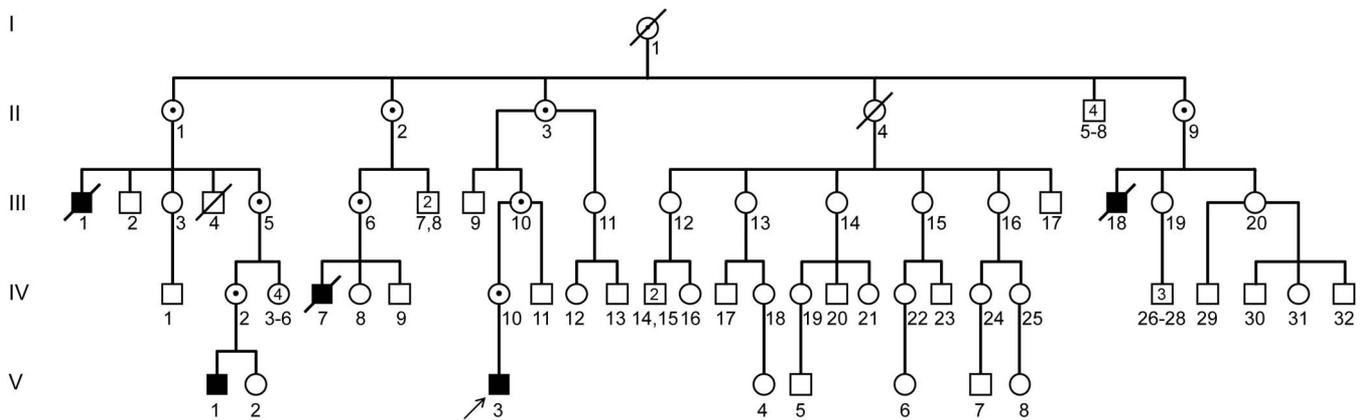
phenotype, early onset, and ages of death indicated that the splice site mutation c.8669-2A>T was causative for DMD. Seven new diagnoses of obligate carriers, including III-10, were identified via the lineage of women that connected the proband and V-1, extending back to the patients' common great-great-grandmother. Three additional obligate carriers, including II-9, were identified based on the pattern of affected males. Twenty-eight other women in the family were identified as at risk to be carriers, including III-11.

Discussion. Our objective was to highlight the importance of reassessing individuals who received their initial DMD risk assessment prior to 2003. Women who know that they are carriers for DMD use this information to make choices about future pregnancies or continuing current pregnancies.² Carriers require early, lifelong cardiac screening because of increased risk to develop cardiomyopathy.³ With the exception of women who can be assigned an obligate carrier status based on affected family members, direct molecular testing for the familial mutation is the only way to determine an individual's carrier status.

Understanding the historical timeline of DMD testing is helpful in identifying those who need reassessments. From 1960 through 1980, risk assessments were made using a combination of pedigree analysis, serum CK, and muscle biopsy.⁴ While these frequently identified carriers with a low false-positive rate, confirmation of negative carrier status was not possible because not all demonstrated abnormalities. Molecular analysis for DMD began in the 1980s with haplotype analysis, using restriction fragment length polymorphisms linked to the disease locus.⁵ However, this method could not predict disease/carrier status with certainty because of the chance for meiotic recombination. Following complete cloning of the complementary DNA for DMD in 1987, direct tests for common deletions became available.⁶ Dystrophin sequencing, which was required to detect the splice site mutation in our family, became clinically available in 2003.¹ Thus, careful probing can reveal whether the first diagnosis in the family took place before the availability of the testing method specific to the familial mutation, as with our family.

See editorial

Figure Family pedigree



The proband is indicated by an arrow. Shaded individuals are those affected by Duchenne muscular dystrophy. Obligate carrier status for Duchenne is denoted by a dot within the individual's symbol. Within the text, individuals are identified by their roman numeral generation number followed by the number of individuals; reading from left to right, this identifies their location within the generation. These numbers are inclusive of the total number of individuals in grouped sibships, which are denoted by an individual symbol containing a number.

Outdated risk assessments are not unique to neurologic genetic disorders; given advances in genetic testing technology over the last decade alone, patients with previously negative risk assessments may benefit from periodic reassessment to meet contemporary standards. As summarized in a recent review of 61 articles on the topic of “Duty to Reassess,” most patients favor being recontacted; physicians favor recontacting in principle, but note practical barriers such as lack of infrastructure to track former patients and their tests.⁷ We recommend that healthcare professionals confirm the timing and method of genetic diagnoses, specifically for DMD families reporting negative carrier risk assessments from prior to 2003.

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Author contributions: Ms. Bogue: clinical data acquisition, analysis and interpretation of genetic data, and manuscript preparation. Dr. Ramchandren: clinical data acquisition and interpretation and manuscript revision.

Study funding: Dr. Ramchandren is funded by the NIH (National Institute of Neurological Disorders and Stroke K23-NS072279).

Disclosure: Dr. Bogue reports no disclosures. Dr. Ramchandren has received research support from NIH. Go to Neurology.org/ng for full disclosure forms. The Article Processing Charge was paid by the authors.

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Received June 20, 2016. Accepted in final form August 3, 2016.

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Neurol Genet 2016;2;
DOI 10.1212/NXG.0000000000000103

This information is current as of October 5, 2016

Neurol Genet is an official journal of the American Academy of Neurology. Published since April 2015, it is an open-access, online-only, continuous publication journal. Copyright © 2016 American Academy of Neurology. All rights reserved. Online ISSN: 2376-7839.



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