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Pathogenic? Expanding the Spectrum of *DMD* Variants

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I. Introduction

Duchenne and Becker muscular dystrophies (DMD/BMD) are caused by pathogenic variants in the *DMD* gene. Deletions and duplications of *DMD* account for ~80% of pathogenic variants, making copy number analysis the first tier for DMD/BMD testing. Though *DMD* copy number variation (CNV) analysis is often performed via MLPA or targeted array CGH, chromosomal microarray analysis (CMA) also detects intragenic, partial, and whole-gene gains and losses of *DMD*. In some cases, CMA is ordered for patients with a diagnosis or family history of DMD/BMD, but most of the time *DMD* variants are incidental findings in our laboratory.

II. Methods

Microarray analysis was performed with the CytoScan HD microarray and CNVs were evaluated using Chromosome Analysis Suite (ChAS) 3.1 software. From 2013-2018 we reported positive *DMD* copy number results for 165 probands: 59 prenatal and 106 postnatal. We reviewed the clinical indications for testing, the deleted and duplicated exons, and the predicted reading frame changes to the NM_004006.2 transcript. Parental testing was recommended and family members were tested in some cases.

III. Results

Figure 1. Types of *DMD* deletions and duplications in 165 probands referred for microarray analysis

Figure 2. Genomic location of deletions (red), duplications (blue), and triplications (magenta).

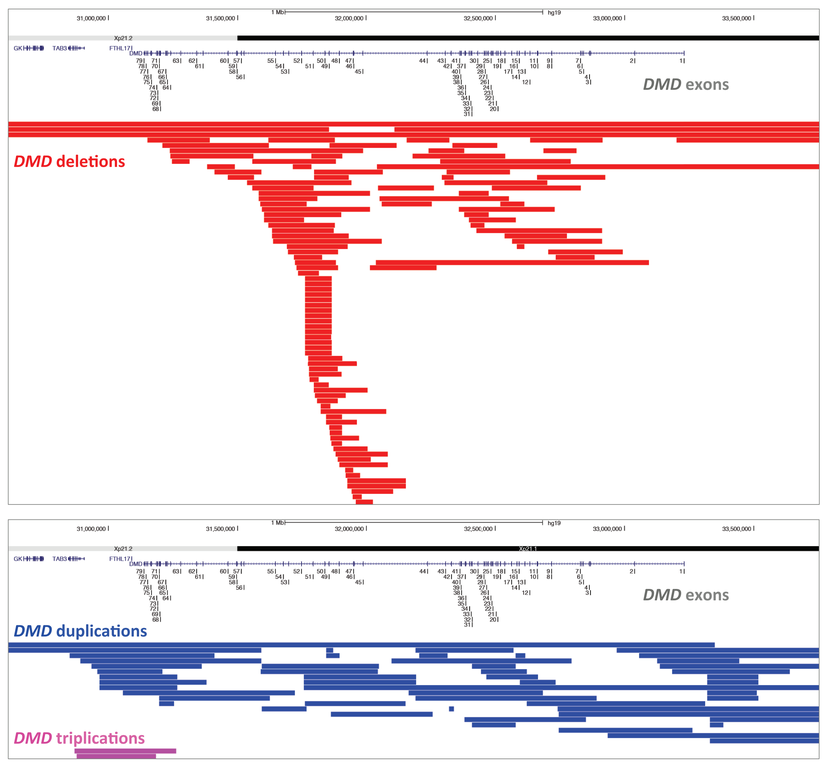

Table 1. Deletions and duplications from 18 males with DMD/BMD diagnosis provided to LabCorp

CNV	Exons	Frame Prediction	Age	Inheritance	Indication
del	14-19	out-of-frame	7	Unknown	Muscle disorder, ataxic gait
del	21-41	in-frame	2	Unknown	Muscle disorder
del	26-37	in-frame	45	Unknown	Becker diagnosis
del	26-41	in-frame	21	Unknown	Becker diagnosis
del	44	out-of-frame	3	Unknown	Gower sign, CPK levels ~3,200
del	44	out-of-frame	9	Unknown	Muscular dystrophy
del	45-47	in-frame	50	Unknown	Muscle wasting and atrophy
del	45-48	in-frame	3	Unknown	CPK level 13,673
del	45-48	in-frame	3	Maternal	Duchenne diagnosis
del	45-55	in-frame	6	Maternal	Muscular dystrophy
del	45-64	out-of-frame	10	Unknown	Very high CPK levels
del	48-49	in-frame	13	Unknown	Muscular dystrophy
del	49-50	out-of-frame	8	Maternal	Gower sign, CPK level 21,000+
del	51	out-of-frame	4	Unknown	Gower sign
del	52	out-of-frame	3	Unknown	Duchenne diagnosis
dup	8-13	out-of-frame	7	Unknown	Muscular dystrophy
dup	13-29	in-frame	10	Unknown	Muscular dystrophy
dup	56-70	out-of-frame	15	Unknown	Muscular dystrophy

Table 2. Deletions and duplications in adult males with a *DMD* incidental finding

CNV	Exons	Frame Prediction	Age	Indication
del	29-33	in-frame	38	Family history of 22q CNV
del	45-47	in-frame	Unk	Maternal grandfather of male fetus with *DMD* variant
del	45-50	out-of-frame	33	Father of female fetus with *DMD* variant
del	48-51	in-frame	44	Father of female fetus with *DMD* variant
del	48-53	in-frame	60	Maternal grandfather of male fetus with *DMD* variant
del	49-51	in-frame	74	Myelodysplastic syndrome
del	49-51	in-frame	29	Father of female with *DMD* variant
del	49-51	in-frame	26	Father of female with *DMD* variant
del	49-51	in-frame	32	Father of female fetus with *DMD* variant
dup	NM_000109 exon 1	partial	31	Family history of ID
dup	NM_000109 exon 1	partial	76	Maternal grandfather of female fetus with *DMD* variant
dup	1	partial	65	Maternal grandfather of male fetus with *DMD* variant
dup	1-2	partial	38	Father of female fetus with *DMD* variant
dup	1-7	partial	35	Maternal uncle of male with *DMD* variant
dup	45-51	in-frame	38	Father of female POC with *DMD* variant
dup	48-49	in-frame	35	Father of female POC with *DMD* variant
dup	52-55	in-frame	70	Maternal grandfather of female fetus with *DMD* variant

IV. Conclusions

Of the 65 male probands with positive postnatal results, only 18 provided a diagnosis of muscular dystrophy. They ranged in age from 3 to 50 years old and did not report other affected males in their families. Notably, all of the affected males had intragenic deletions or duplications; none were partial duplications. The paucity of males with muscular dystrophy could be due to 1) lack of clinical information provided at the time of testing, 2) a *DMD* variant detected in a young boy before muscular dystrophy onset, or 3) mild/absent muscular dystrophy in an adult. *DMD* variants are even more likely to be incidental findings in prenatal testing. Indeed, only 13 of 59 prenatal cases had a previously identified *DMD* variant in the family; nine of these were carrier screen results in the mother.

The most common CNV was deletion of exons 49-51 (n=16), which it is predicted to be in frame and has been described in males with DMD/BMD. However, we found this deletion in males ranging in age from newborn to 74 without a muscular dystrophy diagnosis. The exon 49-51 deletion was inherited from four fathers and four mothers. Familial follow up studies are important for CNV interpretation, especially for prenatal and asymptomatic cases. Of the 69 probands with parental studies, ten *de novo*, 51 maternal, and eight paternal CNVs were observed. Interestingly, five of the maternally inherited CNVs were also found in the maternal grandfathers (ages 60-76) and one was found in a maternal uncle.

These data suggest that some *DMD* CNVs have a mild or even benign effect. Though pathogenic *DMD* variants are well described in the literature, information regarding normal variation in *DMD* is lacking. As more laboratories offer *DMD* testing through carrier screening, interpretation of *DMD* variants in unaffected individuals becomes more and more important. Despite our lack of detailed clinical information, this large study provides a resource for other clinical laboratories interpreting *DMD* variants.

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