The TREAT-NMD DMD Global Database: Analysis of More than 7,000 Duchenne Muscular Dystrophy Mutations


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Analyzing the type and frequency of patient-specific mutations that give rise to Duchenne muscular dystrophy (DMD) is an invaluable tool for diagnostics, basic scientific research, trial planning, and improved clinical care. Locus-specific databases allow for the collection, organization, storage, and analysis of genetic variants of disease. Here, we describe the development and analysis of the TREAT-NMD DMD Global database (http://umd.be/TREAT_DMD/). We analyzed genetic data for 7,149 DMD mutations held within the database. A total of 5,682 large mutations were observed (80% of total mutations), of which 4,894 (86%) were deletions (1 exon or larger) and 784 (14%) were duplications (1 exon or larger). There were 1,445 small mutations (smaller than 1 exon, 20% of all mutations), of which 358 (25%) were small deletions and 132 (9%) small insertions and 199 (14%) affected the splice site. Point mutations totalled 756 (52% of small mutations) with 726 (50%) nonsense mutations and 30 (2%) missense mutations. Finally, 22 (0.3%) mid-intronic mutations were observed. In addition, mutations were identified within the database that would potentially benefit from novel genetic therapies for DMD including stop codon read-through therapies (10% of total mutations) and exon skipping therapy (80% of deletions and 55% of total mutations).


KEY WORDS: DMD; Duchenne muscular dystrophy; TREAT-NMD; rare disease registries

Introduction

Duchenne muscular dystrophy (DMD) is a severe, X-linked, progressive neuromuscular disease caused by mutations in the DMD gene (DMD; MIM #310200) [Hoffman et al., 1988]. Mutations in this gene give rise to two forms of muscular dystrophy depending on whether the translational reading frame is lost or maintained: severe DMD, due to out of frame mutations leading to loss of protein function, or a milder form of muscular dystrophy known as Becker muscular dystrophy (BMD; MIM #300376), caused by a reduction in the amount and/or size of dystrophin protein due to frame maintaining mutations [Koenig et al., 1989]. The DMD gene is the largest known gene in humans, spanning 2.3 Mb of genomic DNA. The coding sequence spans 11 Kb and is made up of 79 exons [Ahn and Kunkel, 1993]. Many different types of mutation have been described for DMD including large deletions and duplications, point mutations, and small rearrangements.

DMD has a prevalence of 21.2/100,000 school aged boys [Mah et al., 2014]. Current care recommendations (specifically, the use of corticosteroids, cardiac medications, and assisted ventilation) improve outcomes and quality of life but do not modify the underlying progression of the disease [Sejerson and Bushby, 2009; Hoffman et al., 2012]. Potential treatment strategies center primarily on targeted mitigation of the causative genetic mutation. One example of a genetic-based potential therapy is nonsense stop codon read-through therapy [Howard et al., 2000; Wagner et al., 2001; Hirawat et al., 2007; Welch et al., 2007]. These treatments include aminoglycosides and ataluren (previously PTC124), and work by selectively inducing ribosomal read-through of premature stop codons but not normal stop codons. Specific nonsense mutations exist in DMD patients leading to premature stop codons (TGA, TAG, and TAA) and would potentially benefit from this therapy. Translarna recently obtained conditional marketing authorization from the European Medicine Agency for use in ambulant Duchenne patients over 5 years of age, and as such is the first drug to be approved for DMD.

A further example is the exon skipping approach. Exon skipping aims to moderate disease progression by taking advantage of the knowledge that internally deleted dystrophins (seen in BMD) can be partially functional [Béroud et al., 2007; Aartsma-Rus et al., 2009; van Ommen and Aartsma-Rus, 2013]. Significant research has been undertaken in the field of exon skipping to restore the open reading frame of dystrophin transcripts resulting in the production of partly functional dystrophin protein [van Ommen et al., 2008; Aartsma-Rus et al., 2009]. Exon skipping is achieved by the use of antisense oligonucleotides (AONs) that specifically bind to and hide exons from the splicing machinery, leading to an in-frame mRNA without this exon and giving rise to internally deleted dystrophin proteins as seen in BMD patients [Takeshima et al., 2001; Aartsma-Rus et al., 2003, 2004; Surono et al., 2004; McClure et al., 2006; Arechavala-Gomez et al., 2007; Gurvich et al., 2008]. Since DMD has a relatively high rate of new mutations (one in three mutations is new), most patients have unique mutations [Aartsma-Rus et al., 2006; Tuffery-Giraud et al., 2009]. However, approximately 60%–65% of all DMD patients carry a deletion of one or more exons, with a tendency to cluster between exons 45 and 55 [Aartsma-Rus et al., 2006; Tuffery-Giraud et al., 2009]. Furthermore, while the location of the breakpoints in introns will differ for patients with a deletion of exon 48–50, these deletions will give rise to identical transcripts. Therefore, the skipping of certain exons would be applied to relatively large numbers of patients.

Understanding the type and frequency of patient-specific mutations that give rise to DMD-associated phenotypes is an invaluable tool for genetic diagnosis, basic scientific research, and improved clinical care, potentially leading to new treatments for the disease. Currently, the TREAT-NMD DMD Global database contains over 7,000 (7,149 as of November 2013) mutations (http://umd.be/TREAT_DMD/). Locus-specific databases (LSDBs) allow for the collection, organization, storage, and analysis of genetic variants of disease. LSDBs collect all published and unpublished mutations for a specific gene along with complete clinical and phenotypic information. Additional confidence exists in these data sets due in part to the role of experts or “curators.” Curators validate the data held within the database and significantly reduce error rates [Béroud et al., 2005; Cotton et al., 2008]. In the case of LSDBs for DMD, a number of databases exist including the Leiden muscular dystrophy pages (http://www.dmd.nl/) in the Netherlands [Aartsma-Rus et al., 2006], and the UMD-DMD (http://www.umd.be/DMD/) in France [Cotton et al., 2008]. We here report a new global mutation database for DMD, and outline how this can be used for genetic analysis and development of genetic therapies.

Methods

A new global database for DMD (TREAT-NMD DMD Global database) based on the French UMD-DMD system has been developed with TREAT-NMD collaboration. TREAT-NMD was initially established as an EU-funded “network of excellence” with the remit of “reshaping the research environment” in the neuromuscular field ([http://www.treat-nmd.eu/], 2013; Bushby et al., 2009). Standardized mutation (DMD mutations) specific data based on TREAT-NMD mandatory and highly encouraged items from the national TREAT-NMD DMD registries [Bladen et al., 2013] were
transferred to the global DMD database via a secure File Transfer Protocol transfer in November 2013 in order to provide a single cohort of genetic and clinical variants (Fig. 1). Analysis of DMD genetic mutations was then carried out for the 7,149 patient data sets held within the TREAT-NMD DMD Global database. HGVS (Human Genome Variation Society) nomenclature was used throughout (http://www.hgvs.org/mutnomen/).

**Table 1. Type and Frequency of Mutations Held within the TREAT-NMD DMD Global Database**

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Percentage of total mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large mutations</td>
<td>5,682</td>
<td>79%</td>
</tr>
<tr>
<td>Large deletions (≥ 1 exon)</td>
<td>4,894</td>
<td>68%</td>
</tr>
<tr>
<td>Large duplications (≥ 1 exon)</td>
<td>784</td>
<td>11%</td>
</tr>
<tr>
<td>Small mutations</td>
<td>1,445</td>
<td>20%</td>
</tr>
<tr>
<td>Small deletions (&lt;1 exon)</td>
<td>358</td>
<td>5%</td>
</tr>
<tr>
<td>Small insertions (&lt;1 exon)</td>
<td>132</td>
<td>2%</td>
</tr>
<tr>
<td>Splice sites (&lt;10 bp from exon)</td>
<td>199</td>
<td>3%</td>
</tr>
<tr>
<td>Point mutations</td>
<td>756</td>
<td>11%</td>
</tr>
<tr>
<td>Nonsense</td>
<td>726</td>
<td>10%</td>
</tr>
<tr>
<td>Missense</td>
<td>30</td>
<td>0.4%</td>
</tr>
<tr>
<td>Mid-intronic mutations</td>
<td>22</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

**Results**

The TREAT-NMD DMD Global database currently contains 7,149 DMD mutations. There were 5,684 large mutations (80%), of which 4,894 (86%) were deletions (1 exon or larger) and 784 (14%) were duplications (1 exon or larger) (Table 1). There were 1,445 small mutations (20% of all mutations), of which 358 (25%) were deletions (smaller than 1 exon) and 132 (9%) were duplications (smaller than one exon); 199 (14%) splice site mutations were recorded. Point mutations totalled 756 (10% of all mutations, 52% of small mutations) with 726 nonsense mutations (10% of all mutations, 50% of small mutations) and three missense mutations (<1% of all mutations, 2% of small mutations). Finally, 22 (less than 1% of all mutations, 0.3% of small mutations) mid-intronic mutations were observed (Table 1).

**Large Mutations**

**Large deletions**

Four thousand eight hundred ninety four large deletions were reported and accounted for 68% of total mutations. Figure 2a highlights the ten most commonly reported (observed more than 100 times) large deletions within the database. The most common large deletion was a deletion of exon 45, which was recorded 316 times in the database (4% of deletions). Distribution of large deletions was nonrandom with the majority of large deletions (80%) covering either the distal region mutation hot spot of the dystrophin gene (exons 45–55) or the proximal region (exons 2–20) (Fig. 3).

**Large duplications**

Seven hundred eighty four large duplications were reported and accounted for 11% of total mutations. Figure 2b shows the eight most commonly reported large duplications (observed more than...
Figure 2. Most commonly reported large mutations. Most commonly reported large deletions (recorded 100 times or more) (A) and large duplications (recorded ten times or more) (B) in the TREAT-NMD DMD Global database.

Single exon deletions and duplications

The five most frequent single exon deletions recorded in the database (all reported more than 100 times) were deletion of exon 45 (4%), 51 (3%), 44 (3%), 52 (3%), and 50 (2%). Single exon duplications occurred less frequently than single exon deletions. Duplication of exon 2 was the most frequent and was reported 50 times, while the second most frequent single exon duplication was duplication of exon 17 and was reported 11 times in the database.

Small Mutations

The database contained 1,445 small lesions and included deletions (smaller than 1 exon; 355, 25%), duplications (smaller than one exon; 132, 9%), 199 (14%) splice site mutations and 756 (52%) point mutations, 726 (50%) nonsense mutations, 30 (2%) missense mutations, and 22 (0.3%) mid-intronic mutations (Table 1). Small deletions and mutations ranged in size from two nucleotides (occurring 85 times) to 111 nucleotides (occurring twice).

Nonsense mutations

Nonsense mutations represented 50% of the small mutations in the database and 10% of total mutations. Transition mutational events (70%) were more common than transversions (30%), with the C-to-T substitution being the most frequent (90%).

Potential DMD therapies

Nonsense stop codon read-through therapy has obtained conditional marketing authorization [Howard et al., 2000; Wagner et al., 2001; Hirawat et al., 2007; Welch et al., 2007]. This treatment selectively induces ribosomal read-through of premature stop codons but not normal stop codons. Mutations were identified...
within the database that would potentially benefit from this therapy. These included 317 mutations (4% of overall mutations) with a premature TGA stop codon, 215 (3%) with a TAG stop codon, and 194 (3%) with a TAA stop codon.

Exon skipping technology takes advantage of the fact that internally deleted dystrophins, often seen in BMD, can be partially functional. Mutations were identified within the database that would potentially benefit from exon skipping therapy. The top ten exon skips that would be applicable to the largest group of patients were skipping of exon 51 (14% of total mutations/21% of deletions), 53 (10%/15%), 45 (7%/13%), 44 (7%/11%), 43 (7%/11%), 46 (5%/7%), 50 (4%/6%), 52 (4%/5%), 55 (3%/4%), and 8 (2%/3%), respectively, as shown in Table 2. It is important to point out that the applicability of exon skipping of certain exons reduces once AONs targeting other exons have been developed. For example, the reading frame of exon 52 deletions can be restored by skipping exon 51 or by skipping exon 53. However, once an AON for exon 51 has been developed and approved for clinical use, the additional applicability of exon 53 skipping is then lower than the a priori applicability, since it now only applies to 8% of mutations rather than 10%, because the exon 52 deletion has already been rescued by exon 51 skipping. The top 10 of exon skips and their added applicability (i.e., taking this adjustment into account) is shown in Table 2.

### CpG sites

Substitutions involving a CpG dinucleotide accounted for 31% (233/756) of point mutations within the database. The CpG dinucleotide has been shown to undergo oxidative deamination of 5-methyl cytosine resulting in a mutational “hot spot” and mutation rates an order of magnitude higher than normally expected [Akalin et al., 1994; Krawczak et al., 1998; Flanigan et al., 2009].

### Geography and DMD mutations

Regardless of geographical location (determined by continent), large deletions were by far the most commonly observed (64% in Oceania to 88% in Africa) mutation followed by large duplications (5% in Africa to 12% in Europe). The number of small mutations was generally more variable (7% in Africa to 22% in Oceania) but this variability is likely explained by the fact that not all countries routinely assay for point mutations and other small lesions and indeed numbers of patients were significantly smaller, for example, in Africa compared to Europe (Fig. 4).

### Table 2. Overview of DMD Exons

<table>
<thead>
<tr>
<th>Exon</th>
<th>Mutation (%)</th>
<th>Deletion (%)</th>
<th>Adjusted³ Mutation (%)</th>
<th>Deletion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 51</td>
<td>14.0</td>
<td>20.5</td>
<td>Exon 51 14.0</td>
<td>20.5</td>
</tr>
<tr>
<td>Exon 53</td>
<td>10.1</td>
<td>14.7</td>
<td>Exon 45 9.0</td>
<td>13.1</td>
</tr>
<tr>
<td>Exon 45</td>
<td>9.0</td>
<td>13.1</td>
<td>Exon 53 8.1</td>
<td>11.8</td>
</tr>
<tr>
<td>Exon 44</td>
<td>7.1</td>
<td>11.1</td>
<td>Exon 44 7.6</td>
<td>11.1</td>
</tr>
<tr>
<td>Exon 43</td>
<td>7.5</td>
<td>11.0</td>
<td>Exon 50 3.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Exon 46</td>
<td>4.6</td>
<td>6.7</td>
<td>Exon 43 3.1</td>
<td>4.5</td>
</tr>
<tr>
<td>Exon 50</td>
<td>3.8</td>
<td>5.6</td>
<td>Exon 8 2.00</td>
<td>2.9</td>
</tr>
<tr>
<td>Exon 52</td>
<td>3.6</td>
<td>5.3</td>
<td>Exon 55 1.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Exon 55</td>
<td>2.7</td>
<td>3.9</td>
<td>Exon 52 0.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Exon 8</td>
<td>2.0</td>
<td>2.9</td>
<td>Exon 11 0.9</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*Overview of exons for which single exon skipping would be applicable to the largest groups of patients.

†Adjusted overview of applicability of single exon skipping.

### Discussion

#### Databases

Resources existed for DMD prior to the creation of the TREAT-NMD DMD Global database, the Leiden muscular dystrophy pages (http://www.dmd.nl/) in the Netherlands [Aartsma-Rus et al., 2006], and the UMD-DMD (http://www.umd.be/DMD/) in France [Cotton et al., 2008]. For both the previously existing databases, bias of recorded mutations has been an inherent problem due in part to the method used to determine the mutation. Historically, detection of deletions and duplications was easier than detection of point mutations and other small rearrangements leading to an overrepresentation of such mutations in the literature and indeed a possible underrepresentation of point mutations and other small rearrangements. However, this bias is becoming less of an issue due to current diagnostic techniques that are widely available [Prior and Bridgeman, 2005; Flanigan et al., 2009]. Also, while initially, the most commonly occurring mutations were recorded; now there is potentially a bias toward only novel mutations being recorded in the Leiden database. In addition to this, the UMD-DMD database is specific to France and could potentially include a bias for mutations observed with higher or lower frequencies only in France. The new TREAT-NMD DMD Global database houses what we believe to be the single largest cohort of verified DMD mutations in the world and was established to collect and compare and molecular mutations found within this patient group. Mutational analysis of the database illustrates the allelic heterogeneity of the DMD gene. Indeed, one-third of all DMD mutations occur de novo [Laing, 1993].

#### Analysis and Comparisons

Analysis of the TREAT-NMD DMD Global database revealed that large deletions were the most prevalent genetic mutation recorded and accounted for 68% of the total mutations analyzed, deletion of exon 45 being the single most common large deletion (reported 316 times). These results are similar to both the French UMD database [Tuffery-Giraud et al., 2009] with 62% of the mutations being large deletions and the Leiden database [Aartsma-Rus et al., 2006], where 72% of the mutations are large deletions. In the Leiden database and the TREAT-NMD DMD Global databases, deletion of exon 45 was the most common deletion, making up 4% of the mutations in the TREAT-NMD DMD Global database and 2% of the Leiden database. Large duplications accounted for 11% of mutations in the TREAT-NMD DMD Global database compared to 13% in the French UMD database and 8% in the Leiden database. The most commonly occurring large duplication was duplication of exon 2 in all three databases. Small rearrangements accounted for 20% of the TREAT-NMD DMD Global database that was similar to the French UMD database (26%) and the Leiden database (20%). Point mutations and nonsense mutation were the most prevalent small rearrangements with nonsense mutations accounting for 50% of the small rearrangements in the TREAT-NMD DMD Global database, compared to 40% in the French UMD database and 50% in the Leiden database. Large deletions and duplications follow a nonrandom distribution with 78% of them including either the proximal or distal mutation hot spots [Koenig et al., 1989; Prior and Bridgeman, 2005; Aartsma-Rus et al., 2006].

#### Reading Frame Rule

The majority of the reported (DMD) mutations in the TREAT-NMD DMD Global database resulted in frame-shift mutations.
Figure 3. Distribution of the most common large deletions and duplications on the DMD gene.

Figure 4. Geography and DMD mutations. Distribution of DMD mutation types stratified by continent.
(93%). Mutations not following the reading-frame rule in the TREAT-NMD DMD Global database accounted for 7% of total mutations compared with 4% in the UMD-DMD database and 9% in the Leiden database.

**Potential DMD Therapies**

Several potential novel DMD therapies exist and are focused on the mitigation of the underlying genetic defect. The two most promising examples are nonsense read-through and exon skipping. Mutations were identified within the database that would potentially benefit from this stop codon read-through therapy (10% of mutations). Exon skipping mutations were identified within the database that would potentially benefit from exon skipping therapy (55% of total mutations and 80% of deletions).

Understanding the type and frequency of patient-specific mutations that give rise to DMD-associated phenotypes will potentially lead to personalized (targeted/precision) therapies. DMD essentially serves as a paradigm for this type of treatment and ultimately could lead the way to similar approaches in other rare diseases and indeed in more common disorders.

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**References**


