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Prevalence and Characteristics of Chinese Patients With Duchenne and Becker Muscular Dystrophy: A Territory Wide Collaborative Study in Hong Kong

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Abstract

The aim of this collaborative study on Duchenne muscular dystrophy and Becker muscular dystrophy is to determine the prevalence and to develop data on such patients as a prelude to the development of registry in Hong Kong. Information on clinical and molecular findings, and patient care, was systematically collected in 2011 and 2012 from all Pediatric Neurology Units in Hong Kong. Ninety patients with dystrophinopathy were identified, and 83% has Duchenne muscular dystrophy. The overall prevalence of dystrophinopathy in Hong Kong in 2010 is 1.03 per 10 000 males aged 0 to 24 years. Among the Duchenne group, we observed a higher percentage (40.6%) of point mutations with a lower percentage (45.3%) of exon deletions in our patients when compared with overseas studies. Although we observed similar percentage of Duchenne group received scoliosis surgery, ventilation support, and cardiac treatment when compared with other countries, the percentage (25%) of steroid use is lower.

Keywords

Duchenne muscular dystrophy, dystrophinopathy, prevalence, Becker muscular dystrophy, neuromuscular disorder, Duchenne muscular dystrophy gene mutation

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Duchenne muscular dystrophy and Becker muscular dystrophy are both dystrophinopathy due to mutations of the Duchenne muscular dystrophy gene on the X-chromosome and predominantly affect male. The Duchenne muscular dystrophy gene mutations could result in complete loss of dystrophin protein that lead to the severe condition called Duchenne muscular dystrophy, or there is only partial decrease in dystrophin protein that lead to Becker muscular dystrophy the milder form. Dystrophinopathy, including both Duchenne muscular dystrophy and Becker muscular dystrophy, is the commonest neuromuscular disorder in children. It is characterized by progressive muscle weakness and muscle degeneration as the child grows. The rate of deterioration is much faster in the Duchenne muscular dystrophy when compared to the milder Becker muscular dystrophy. From the previous natural history studies, the boys with Duchenne muscular dystrophy lost ambulation between 6 and 11 years old, developed respiratory and cardiac complications in the teenage years, and died in the late 10s or early 20s.[1-3] Boys with Becker muscular dystrophy, on the other hand, have a later age of onset and a more variable clinical weakness with a slower progression. Most of them keep walking on entering adulthood.

Since the discovery of Duchenne muscular dystrophy gene in 1986 by Monaco et al[4] and the dystrophin protein in 1987 by Hoffman et al,[5] there were numerous researchers trying to replace the deleted dystrophin in patient muscles and to identify possible molecular therapies for Duchenne muscular dystrophy/Becker muscular dystrophy. These include direct gene repair at DNA level, exon skipping, or stop codon read through at messenger RNA level, and even utrophin upregulation as the compensatory strategies. Some of these approaches are only applicable to mutations caused by specific exon deletion; others are targeted at mutations due to small rearrangement.[6]

The current study served as an initial step to gather the mandatory data set including demographic information, clinical, and molecular findings, as well as their intervention and care, for this group of patients, and served as a prelude to the development of registry that allow the future coordination of possible clinical trial readiness.

In Hong Kong, all the children diagnosed to have dystrophinopathy will be under the care of pediatrics neurologists who are also the main coordinators for the multidisciplinary care for this group of children following the standard of care guideline. Once the diagnosis was confirmed, besides regular follow-up by the neurology team, the affected child also had regular assessments by the cardiology and the respiratory teams. Regular cardiac assessment by cardiologist included echocardiogram arranged at once every 1 to 2 years before the age of 10 years, and once every year after the age of 10 years old onwards. For the respiratory monitoring, regular nocturnal oxygen saturation study at yearly interval was arranged when the child lost ambulation. If scoliosis was suspected, orthopedic follow-up and regular spine X-ray evaluation would be arranged.

Materials and methods

This is a collaborative study jointly participated by all the 10 Neurology units of the Pediatrics departments in all regional hospitals under the Hospital Authority (HA) of Hong Kong. This extensive collaboration allows us to capture almost all the affected patients with Duchenne muscular dystrophy under the age of 18 years old in Hong Kong. Patients with confirmed diagnosis of either Duchenne muscular dystrophy or Becker muscular dystrophy and had been regularly follow-up by the Pediatrics Neurology teams between June 2006 and December 2010 were included. The diagnosis of dystrophinopathy was based on either genetic mutations and/or abnormal expression of dystrophin immunohistochemical stainings in muscle biopsy. In Duchenne muscular dystrophy, the dystrophin immunolabeling was essentially absent while in Becker muscular dystrophy, it was present but reduced. In some patients older than 12 years old, the diagnosis could also be confirmed by the clinical course. Patients with Duchenne muscular dystrophy lost ambulation on or before 12 years old, while those who continued to walk after the age of 12 years without steroid treatment were classified as having Becker muscular dystrophy.

Clinical data, including date of birth, clinical diagnosis, genetic findings, performance of muscle biopsy, age at loss of ambulation, and history of cardiomyopathy, scoliosis, and feeding problems, were systematically collected between June 2011 and June 2012. Information on the oral steroid use, ventilator care, scoliosis surgery, and gastrostomy were also obtained. This study was approved by Institutional Review Board of all the participating hospitals.

Results

Prevalence

As of December 2010, 90 individuals with dystrophinopathy were identified. Two age-specific prevalence of dystrophinopathy among males were calculated. For those male in the age-group of 0 to 14, the prevalence is 1.14 per 10 000 males, and for those in the age-group of 15 to 24 years, the prevalence is 0.85 per 10 000 males. The overall prevalence of dystrophinopathy in Hong Kong in 2010 is 1.03 per 10 000 males aged 0 to 24 years.

Age Range

Among the whole group, Seventy-five patients (83%) have Duchenne muscular dystrophy and 15 patients (17%) have Becker muscular dystrophy. Most of the patients were between 6 and 25 years old. The age range for patients with Duchenne muscular dystrophy was 0.58 to 34.55 years with 48 (64%) patients were above 12 years old. For those patients identified to have Becker muscular dystrophy, their age ranged from 9.54 to 24.88 years (Figure 1).

Diagnosis

For the diagnostic confirmation, among the 75 patients with Duchenne muscular dystrophy, 85.3% of patients had genetic study and 65% of patients had muscle biopsy. Around half (54.7%) of this group had both genetic study and muscle biopsy done, while 33% had only genetic testing and 12% had only muscle biopsy performed. For the 15 patients identified having Becker muscular dystrophy, similar percentage of patients had muscle biopsy (80%) and genetic study (73%). Again around

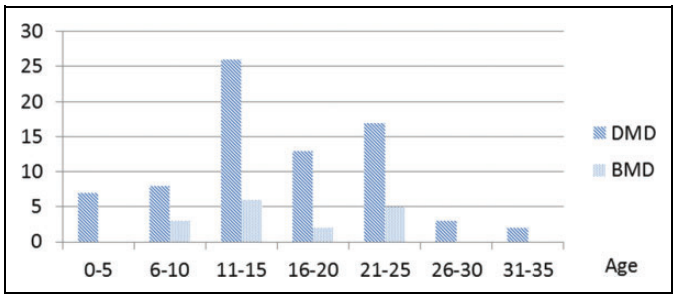

Figure 1. Number of patients with Duchenne muscular dystrophy and Becker muscular dystrophy at different age range in years.

Table 1. Total Number and Percentages of Patients With Duchenne Muscular Dystrophy and Becker Muscular Dystrophy Undergoing the Diagnostic Procedures and the Different Interventions.

	Patients With Duchenne Muscular Dystrophy No. of Cases (75)	(%)	Patients With Becker Muscular Dystrophy No. of Cases (15)	(%)
Age <15	37	(49)	9	(53)
Age >15	38	(51)	7	(47)
Muscle biopsy done	49	(65)	12	(80)
Genetic mutation study	64	(85)	11	(73)
Steroid treatment	19	(25)	2	(14)
Scoliosis surgery	14	(19)	0	(0)
Cardiac treatment	23	(31)	1	(7)
Noninvasive ventilation	19	(25)	1	(7)
Gastrostomy	2	(3)	0	(0)

half of the group (53.3%) had both genetic study and muscle biopsy, with 26.7% had only genetic study, and 13.3% had only muscle biopsy (Table 1).

Clinical Presentation and Interventions

In all, 21 patients had been started on oral steroid (prednisolone), with 19 patients from the Duchenne muscular dystrophy group but 2 from the Becker muscular dystrophy group (Table 1). The steroid used was oral prednisolone given daily. The mean steroid starting age ($\pm$1 standard deviation [SD]) was 8.45 $\pm$ 2.0 years, with the age ranged from 4.3 to 12.3 years (Figure 2). For the 12 patients who had stopped steroid, the mean ($\pm$1 SD) steroid stopping age was 10.67 $\pm$ 1.89 years, with the age ranged from 8 to 13.3 years (Figure 2). The mean duration of steroid use was only 2.1 years. The most common reasons for stopping steroid was loss of ambulation, obesity, and behavioral problems. Only one-fifth of the patients who had been started on steroid continued the treatment after loss of ambulation. The mean age ($\pm$1 SD) of loss of ambulation was 10.7 $\pm$ 1.5 years for those who had not been on steroid and was similar to those who had been on steroid (10.6 $\pm$ 1.3 years).

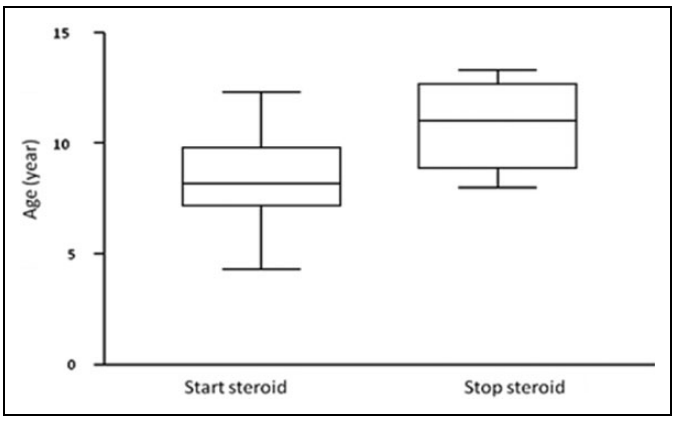

Figure 2. Box and whiskers for steroid starting age (n = 21) and steroid stopping age (n = 12) in years.

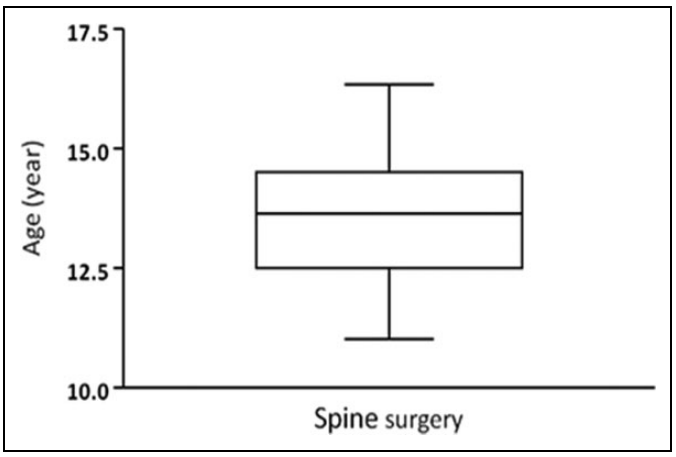

Figure 3. Box and whiskers for the age of scoliosis surgery (n = 14) in years.

Most children with Duchenne muscular dystrophy developed scoliosis in their early 10s. Of the 60 patients with DMD aged after 11 years old, a quarter of this group (14 patients) had undergone posterior spinal fusion. The mean age ($\pm$1 SD) for the scoliosis surgery was 13.6 $\pm$ 1.4 years, with the earliest age for surgery at 12 and the latest at 15.1 years (Figure 3).

Among the 60 patients who were either at or older than 11 years old in the Duchenne muscular dystrophy group, one-third of the group (19 patients) required noninvasive ventilation with the mean starting age ($\pm$1 SD) at 17.4 $\pm$ 5.0 years with the age ranged from 13.1 to 23.4 years (Figure 4). Twenty-three patients (two-third of the group) had echocardiographic evidence of cardiomyopathy and were started on cardiac medications. The mean age $\pm$1 SD for starting cardiac medication was 18.2 $\pm$ 3.6 years (Figure 5). The first-line treatment was angiotensin-converting enzyme inhibitors including enalapril, captopril, perindopril, and ramipril. β-Blockers, diuretics, and digoxin were the add-on treatment if progressive heart failure developed. Only 2 patients had undergone gastrostomy, with one

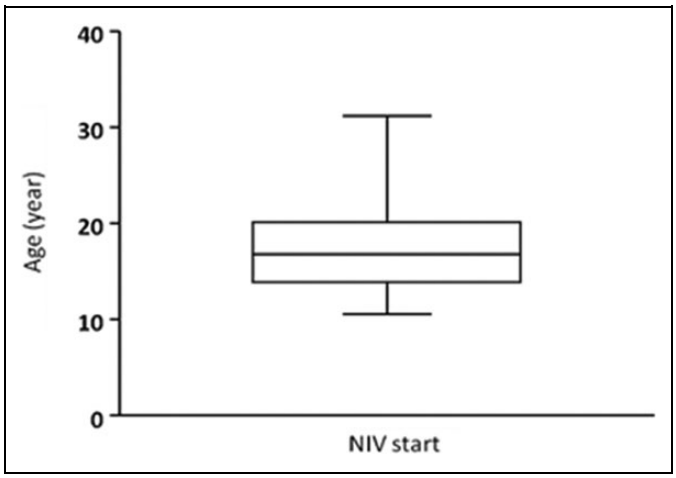

Figure 4. Box and whiskers for noninvasive ventilation (NIV) starting age (n = 20) in years.

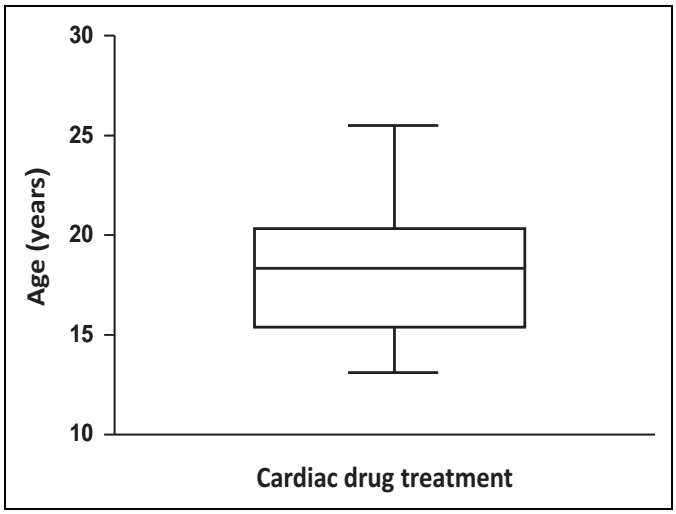

Figure 5. Box and whiskers for cardiac drug starting age (n = 24) in years.

at the age of 22.1 years and the other at 26.6 years (Table 1). Four patients died during the followed up period, with 1 patient at the age of 15.1 years and 3 patients in their 20s (23.1 years, 23.5 years, and 26 years).

Among the 15 patients with Becker muscular dystrophy, most enjoyed stable health with only 1 patient had cardiomyopathy and 1 required noninvasive ventilation due to obstructive sleep apnea syndrome. Two patients were put on oral steroid.

Mutation Analysis

In Hong Kong, the genetic study for dystrophinopathy was carried out by the Clinical Genetic Service under the Hong Kong Department of Health. In the Clinical Genetic Service, multiplex polymerase chain reaction was used at the early years. With modification of the test, exon duplications could be detected. Since 2004, multiplex ligation-dependent probe amplification that could detect both exon deletions and duplications with whole gene coverage was used, and small rearrangements or point mutations were identified either by direct Sanger sequencing of the entire coding region or by initial mutation screening with denaturing high-performance liquid chromatography followed by Sanger sequencing. If those patients suspected to have Duchenne muscular dystrophy and had initial negative findings on multiplex ligation-dependent probe amplification, further testing with direct sequencing would be arrange to confirm the diagnosis.

Table 2. Mutation Analysis Result of the Whole Group in Patients With Duchenne Muscular Dystrophy and Becker Muscular Dystrophy.

	Overall		
Distribution of Mutation	No. of Cases	% of Cases	95% Confidence Interval
Exon deletion	37	49.3	37.6-61.1
Exon duplication	7	9.3	3.8-18.3
Point mutation/ small rearrangement	28	37.3	26.4-49.3
No mutation found	3	4.1	0.8-11.3
Total	75	100	

Table 3. Mutation Analysis Result Comparison Between Patients With Duchenne Muscular Dystrophy and Becker Muscular Dystrophy.[a]

	Duchenne Muscular Dystrophy		Becker Muscular Dystrophy	
Distribution of Mutation	No. of Cases	% of Cases (95% CI)	No. of Cases	% of Cases (95% CI)
Exon deletion	29	45.3 (33.7-57.4)	8	72.7 (43.4-90.3)
Exon duplication	6	9.4 (4.4-18.9)	1	9.1 (1.6-37.8)
Point mutation/ small rearrangement	26	40.6 (29.5-52.9)	2	18.2 (5.1-47.7)
No mutation found	3	4.7 (1.6-12.9)	0	0
Total	64	100	11	100

[a]Some of the value is zero and to make the analysis possible, 0.5 was added to each value for calculation.
Note. CI: confidence interval.

Seventy-five patients of the whole group had undergone mutation analysis. Most mutations were caused by large exon deletions (49.3%), followed by point mutations (37.3%) and large exon duplication (9.4%). For the point mutations, these include the small deletions or insertions, single-base changes, and splicing mutations. Three patients did not have any mutation identified. A higher percentage (40.6%) of point mutation was observed in patients with Duchenne muscular dystrophy (Tables 2 and 3).

Among the Duchenne muscular dystrophy group with identified mutations, 12 mutations had not been reported previously. For the 26 patients identified to have point mutations, most had nonsense mutations (61.5%), with others

Table 4. Point mutations or small rearrangements for DMD and BMD patients (Reference sequence: NM_004006.2).

DMD Point Mutation	
Exon 6/c.453T>A, Tyr151*	Exon 34/c.4729C>T, Arg1577*
Exon 12/c.1375G>T, Glu459*[a]	Exon 41/c.5800del7+c.5845_5846ins14[a]
Exon 13/c.1594C>T, Gln532*	Exon 44/c.6385_6388delAAGA[a]
Exon 16/c.1873C>T, Gln625*	Exon 53/c.7755G>A, Tyr2585*
Exon 16/c.1843C>T, Glu615*	Exon 53/c.7798_7799insCA, Arg2600Thrfs*15[a]
Exon 17/c.2086del13, Val696Lysfs*29	Exon 56/c.8224C>T, Glu2742*[a]
Exon 20/c.2601delAA, Gln869Valfs*5	Exon 58/c.8608C>T, Arg2870*
Exon 23/c.2968C>T, Gln990*	Exon 59/c.8745G>A, Trp2915*
Exon 26/c.3556G>T, Glu1186*	Exon 61/c.9156_9157insT
Exon 30/c.4099C>T, Gln1367*	Exon 62/c.9204_9207delCAAA
Exon 32/c.4375C>T, Arg1459*	IVS36-9G>A
Exon 32/c.4499C>A, Ser1500*[a]	IVS45-1G>T[a]
Exon 33/c.4570A>T, Lys1524*	IVS70+1G>A
BMD Point Mutation	
Exon 18/c.2169-1_2169GG>TT[a]	Exon 25/c.3432+1G>A, skip exon 25[b]

Abbreviations: DMD, Duchenne Muscular Dystrophy; BMD, Becker Muscular Dystrophy.
[a]Mutations that have not been reported in the literature.
[b]In-frame mutation by prediction.

Table 5. Exon Deletion for Patients With Duchenne Muscular Dystrophy and Becker Muscular Dystrophy.

	5′ Hot Spot (Exons 3-19)	3′ Hot Spot (Exons 42-60)	Spanning From 5′ to 3′ Hot Spots	Other
Duchenne muscular dystrophy	Del 2-17 (2) Del 3[a] Del 5-7 Del 7 Del 8-9 Del 10-19[b]	Del 43 Del 44 Del 45 (2) Del 45-50 (2) Del 46-47 Del 46-48 (2) Del 46-49 Del 46-51 Del 48-50 (3) Del 49-52 Del 50 Del 53 Del 55-60 Del 56-57[a,b]	Del 3-43 Del 12-43[a]	Del 63-79
	(n = 7)	(n = 19)	(n = 2)	(n = 1)
Becker muscular dystrophy	Del 3[a] Del 3-5 (3)[a] Del 3-6	Del 45-53[a] Del 49-52 Del 52-53[a]		
	(n = 5)	(n = 3)		

Abbreviations: n, number of patient for each subgroup; ( ), number of patients with the same deletion.
[a]In-frame mutation by prediction.
[b]Mutations that have not been reported in the literature.

had indel mutations (27%) and splice site mutations (11.5%) (Figure 6). For the 29 patients identified to have exon deletions, most were in the 3′ hot spot (58%) with less were in the 5′ hot spot (27.6%) and outside hot spots region. Only 6 patients had exon duplications with mutations involved all regions. Among the 36 patients with exon deletions/duplications, 5 patients have out-of-phase in-frame mutation by prediction (Tables 2-6).

Table 6. Exon Duplication for Patients With Duchenne Muscular Dystrophy and Becker Muscular Dystrophy.

	5′ Hot Spot (Exons 3-19)	3′ Hot Spot (Exons 42-60)	Others
Duchenne muscular dystrophy	Dup 2 Dup 3-44[a] Dup 17-19	Dup 44-45[a,b] Dup 45 Dup 56-70[b]	Dup 22-23[b]
	(n = 3)	(n = 3)	
Becker muscular dystrophy	Dup 3-12[a]		
	(n = 1)		

Abbreviation: n, number of patient for each subgroup.
[a]In-frame mutation by prediction.
[b]Mutations that have not been reported in the literature.

For the Becker muscular dystrophy group, among the identified mutations, 1 mutation had not been reported in previous literatures. Of the 11 patients, 8 had exon deletions with 63.5% occurred at 5′ hot spot and the rest at the 3′ hot spot. Only 1 patient had duplication. Most mutations are in-frame by prediction except 3. The point mutations identified were only associated with splice site mutation. (Tables 2-6) (Figure 6).

Discussion

Prevalence

A previous study had confirmed that dystrophinopathy was the most common neuromuscular disease in Hong Kong.[7] From the current study, the overall local prevalence of dystrophinopathy in 2010 is 1.0 per 10 000 males aged 0 to 24 years. Two age-specific prevalence of dystrophinopathy among males were calculated. For those male in the age-group of 0 to 14, the prevalence is 1.14 per 10 000 males, and for those of the age-group of 15 to 24 years, the prevalence is 0.85 per 10 000 males. The number was calculated using the Hong Kong population statistics of male aged 0 to 24 years in the mid-2010 (Hong Kong Special Administrative Region, Census and

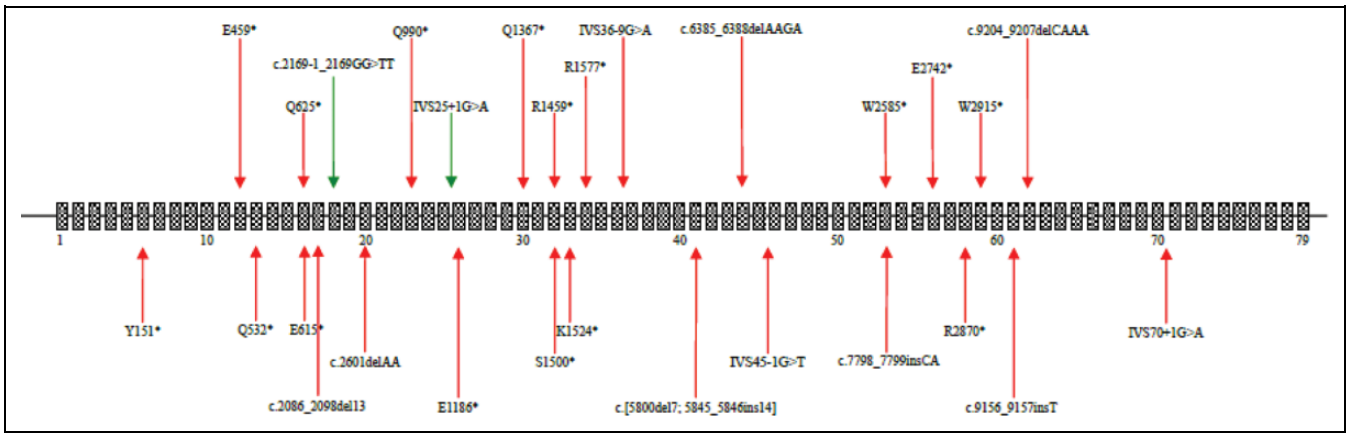

Figure 6. Schematic diagram illustrating the distribution of the small mutations. Vertical rectangles represent different exons of the Duchenne muscular dystrophy gene. Arrows in red = Duchenne muscular dystrophy; arrows in green = Becker muscular dystrophy.

Statistics Department Web site: www.censtatd.gov.hk). When compared with the population-based prevalence of dystrophinopathy of 1.3 to 1.8 per 10 000 males aged 5 to 24 years in 2007 of 4 States of United States,[8] our prevalence rate is slightly lower but comparable.

Genetic Mutation

The overall percentage of exon deletions (49.3%, 95% confidence interval 37.6%-61.1%) of our whole group of patients is lower than the figures of 60% to 70% generally found in the previous overseas studies,[9-13] though this is statistically significant only in the Duchenne muscular dystrophy group in which only 45.3% (95% confidence interval 33.7%-57.4%) of patients have exon deletions. On the contrary, there is a significantly higher percentage of point mutations or small rearrangements up to 40.6% (95% confidence interval 29.5%-52.9%) in our Duchenne muscular dystrophy group, in contrast to the lower percentage of 10.4% reported in the US population-based study,[9] 15% in the Czech Republic and Slovakia registry,[10] 20% in the comprehensive Leiden DMD mutation database,[11] 24.5% in the Japanese national registry,[12] and 26% in the French UMD- Duchenne muscular dystrophy multicenter database.[13] The 9.3% exon duplication in our overall Duchenne muscular dystrophy and Becker muscular dystrophy groups is similar to the reported 6% to 13% in other studies.[9-13] As these percentage figures have influence on one another, we cannot draw conclusion yet whether the lower percentage of exon deletions is secondary to a genuinely higher percentage of point mutations or small rearrangements, and vice versa. A similar findings were also noted in an earlier study.[14] Out-of-phase mutations were noted in both the Duchenne and Becker groups. For those identified mutations with exon deletion/duplication, 13.9% of the Duchenne group had in-frame deletion by prediction, and 27.3% of the Becker group had out-of-frame mutation by prediction.

Steroid Therapy

In this study, only 25.3% of the patients in the Duchenne group were treated with steroid. This is lower when compared to 41% in Japan[12] and 61% in the international DuchenneConnect Registry from America.[15] The mean steroid starting age in our group was 8 years. Comparing our findings of steroid starting age with those reported in the British study at 6.4 years,[16] and the standard of care recommendation between 4 and 6 years,[17] our patients had a later steroid starting age. With the introduction of steroid at late ambulatory stage, the motor beneficial effect on ambulation is limited. It is understandable why most children only continued steroid for a short period of time as most of them stopped steroid when they lost ambulation. This important finding had been shared among local health professionals in 2012 to increase the awareness of the steroid treatment for Duchenne muscular dystrophy. For the past 2 years, more children with Duchenne muscular dystrophy have been started on steroid and at an earlier age between 4 and 6 years. Ongoing education to parents, pediatricians, and other medical specialists on the evidence-based long-term benefits of steroid and to continue such treatment even during the nonambulatory stage is necessary. Use of steroid among Becker muscular dystrophy remains controversial.

Interventions Required

When compared the treatment of our patients having Duchenne muscular dystrophy with those of the Japanese registry,[12] we found a similar percentage of patients required cardiac medical treatment (31% in Hong Kong vs 29.5% in Japan) and noninvasive ventilator support (25% in Hong Kong vs 22% in Japan). In Japan, most ventilated patients (80%) were on noninvasive ventilation with 20% using invasive ventilation, while in Hong Kong, all patients were on noninvasive ventilation. For the scoliosis surgery, Hong Kong has a much higher percentage of patients undergone this treatment (23% in Hong Kong vs 3.9% in Japan). This can be explained by the presence of a centralized orthopedic spine service for whole Hong Kong providing timely posterior spinal surgery for this group of patients before critical respiratory deterioration has occurred. Another possible explanation could be due to the fact that a higher percentage of the Japanese patients were using steroid, so the scoliosis progression could be milder and hence a smaller number of patients required such surgery.

Swallowing and feeding problems leading to underweight are common in Duchenne muscular dystrophy in early adulthood. This could be due to degeneration of smooth muscle in the gastrointestinal tract due to dystrophin deficiency leading to gastrointestinal symptoms. Gastrostomy has been recommended in the Standard of Care guideline.[17,18] Of the 21 patients with Duchenne muscular dystrophy more than 20 years old in our study, only 2 had undergone gastrostomy in their 20s by 2012. In Japan, Mizuno et al[19] reported their experience of 77 patients with Duchenne muscular dystrophy who had undergone gastrostomy between 2007 and 2009. The median age for gastrostomy was 26 years (range 13-47 years). The introduction of gastrostomy feeding resulted in amelioration of malnutrition, swallowing difficulty, and respiratory status; most complications were tolerable with respiratory failure and peritonitis as the 2 main concerns.[19] In France, between 1997 and 2007, 25 patients with Duchenne muscular dystrophy had gastrostomy at the median age of 23 years (range 11-28 years). Improved weight-for-age ratio from 69% to 87% was noted when the patients were followed up at 2 years. Complications occurred in 84% of patients but were all well tolerated.[20] Earlier sharing of our findings with local pediatricians had raised awareness on the need of gastrostomy feeding and a coordinated centralized surgical service to allow such group of patients to benefit from this intervention timely with low risk of complications. Since then more patients with DMD and other severe neuromuscular disorders had undergone gastrostomy in our locality.

Need of Patient Registry

Currently a number of phase 2 and phase 3 clinical trials on potential treatments for Duchenne muscular dystrophy/Becker muscular dystrophy are actively ongoing around the world. Among the many different clinical drug trials, some are targeted on genetic therapy. These include the antisense oligonucleotides using exon 51-targeting phosphorodiamidate morpholino oligomers[21] for those who had specific exon deletions that can benefit from exon 51 skipping, and the research drug to induce ribosomal read through of the premature termination mutation due to small rearrangement or point mutation.[22,23] As different potential therapeutic drugs target at different patient cohorts of specific mutations and clinical profiles, setting up of national registry will facilitate more rapid identification and selection of suitable candidates for such purpose. Although Duchenne muscular dystrophy/Becker muscular dystrophy national registries have been set up in over 30 countries, a global registry for Duchenne Muscular Dystrophy has also been established.[24] This first territory wide study in Hong Kong on this group of patients provides clear evidence that such registry could be set up involving all participating centers in Hong Kong. Maintenance of such registry required the support from local health authority, the clinical teams, and the patient support group.

Study Limitation

There are a few limitations in the current study. Although Hospital Authority (HA) in Hong Kong is taking care of over 90% of our local population, the coverage is not 100%. Some of the patients especially those with milder Becker muscular dystrophy presentation could remain undiagnosed until they reached adulthood or only had their follow-up in the private hospitals instead of HA hospitals. Also in a few HA hospitals, when patients with Duchenne muscular dystrophy had their age reached 18 years or over, they were transferred to the adult services to continue the medical care, so this group of patients could have been missed out in this study as we were collecting data only from the pediatric neurology departments, but this number is expected to be small. Therefore, the local prevalence calculated from this study is a reasonable good estimate of the situation in Hong Kong with a possibility of only slight underestimation. With a study design of retrospective review, some of the collected information including the age at diagnosis and the definition of cardiomyopathy among different centers were incomplete, so further analysis on these aspects is not possible.

Conclusion

This first territory wide study for individuals with dystrophinopathy in Hong Kong suggests a slightly lower but comparable prevalence with the Western countries. Compared with other studies, we have a higher percentage of point mutations and a lower percentage of exon deletions in the Duchenne muscular dystrophy group. The findings in this study are unique and reliable as we were able to capture almost all the patients with Duchenne muscular dystrophy under the age of 18 years in Hong Kong to be included in this study, and the genetic study is performed in a centralized accredited genetic diagnostic service. The study also provides valuable information on some aspects of the natural history of our patients and the multispecialty interventions they were receiving, which could potentially allow us to develop more robust clinical management strategies for this group of patients. This study serves as a prelude to the development of registry with the objective of establishment of an ongoing Duchenne muscular dystrophy–Becker muscular dystrophy registry and allows possible future coordination for clinical trial readiness and better multidisciplinary care.

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Author Contributions

Dr. Sophelia HS Chan conceptualized and designed the whole study, coordinated and supervised data collection from all hospitals, collected data from her own hospital, analyzed collected data from the all the Paediatric Neurology teams of all the participating hospitals, drafted and

revised the manuscript, and approved the final manuscript as submitted. Dr. Ivan MF Lo supported the genetic analysis, curation and presentation of the molecular data, critical review of the manuscript and approval of the final manuscript as submitted. Dr. Sharon WW Cherk, Dr. WW Cheng, Dr. Eva LW Fung conceptualized and designed the whole study, coordinated and supervised data collection of several Paediatric Neurology teams, collected data from their own hospital, critically reviewed the manuscript and approved the final manuscript as submitted. Dr. WL Yeung, Dr. Mary Ngan, Dr. WC Lee, Dr. L Kwong, Dr. SN Wong, Dr. CK Ma, Dr SM Tai, Dr. Grace SF Ng, Dr. SP Wu collected data from their own hospital, and approved the final manuscript as submitted. Prof. Virginia CN Wong critically reviewed the manuscript, and approved the final manuscript as submitted.

Declaration of Conflicting Interests

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Ethical Approval

Ethical approval had been obtained by all the participating Paediatric Neurology teams of all the involved hospitals from the Institutional Review Boards (IRB) under Hospital Authority/ University of Hong Kong/ Chinese University.

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