Genotype-related respiratory progression in Duchenne muscular dystrophy: a multicenter international study

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Genotype-related respiratory progression in Duchenne muscular dystrophy—A multicenter international study

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Abstract

Introduction/Aims: Mutations amenable to skipping of specific exons have been associated with different motor progression in Duchenne muscular dystrophy (DMD). Less is known about their association with long-term respiratory function. In this study we investigated the features of respiratory progression in four DMD genotypes relevant in ongoing exon-skipping therapeutic strategies.

Methods: This was a retrospective longitudinal study including DMD children followed by the UK NorthStar Network and international AFM Network centers (May 2003 to October 2020). We included boys amenable to skip exons 44, 45, 51, or 53, who were older than 5 years of age and ambulant at first recorded visit.

Abbreviations: AFM, Association Française contre les Myopathies; AON, antisense oligonucleotide; CS, corticosteroids; DMD, Duchenne muscular dystrophy; FVC%, forced vital capacity percent predicted; FVC, absolute forced vital capacity; LoA, loss of ambulation; NIV, noninvasive ventilation.

† Deceased.

Subjects who were corticosteroid-naive or enrolled in interventional clinical trials were excluded. The progression of respiratory function (absolute forced vital capacity [FVC] and calculated as percent predicted [FVC%]) was compared across the four subgroups (skip44, skip45, skip51, skip53).

Results: We included 142 boys in the study. Mean (standard deviation) age at first visit was 8.6 (2.5) years. Median follow-up was 3 (range, 0.3-8.3) years. In skip45 and skip51, FVC% declined linearly from the first recorded visit. From the age of 9 years, FVC% declined linearly in all genotypes. Skip44 had the slowest (2.7%/year) and skip51 the fastest (5.9%/year) annual FVC% decline. The absolute FVC increased progressively in skip44, skip45, and skip51. In skip53, FVC started declining from 14 years of age.

Discussion: The progression of respiratory dysfunction follows different patterns for specific genotype categories. This information is valuable for prognosis and for the evaluation of exon-skipping therapies.

KEYWORDS

Duchenne muscular dystrophy, exon skipping, forced vital capacity, genotype, respiratory function

1 | INTRODUCTION

Progressive respiratory impairment occurs invariably in boys affected by Duchenne muscular dystrophy (DMD) and represents one of the main causes of patient mortality.[1] Corticosteroids (CS), used as standard treatment,[2,3] have prolonged life expectancy and reduced respiratory complications in DMD.[4,5] In addition, new therapeutic options for DMD have emerged of which exon skipping is a promising one.

Exon skipping is aimed to restore the reading frame of the dystrophin transcript through the use of antisense oligonucleotides (AONs). AONs induce skipping of the target exon by binding to a specific sequence in the dystrophin pre–messenger RNA. This skip restores the reading frame of the deleted RNA messenger and enables the production of a partially functional dystrophin protein associated with a milder, Becker muscular dystrophy–like, phenotype.[6] Four of the molecules used for skipping of exon 51 (eteplirsen), exon 53 (golodirsen and vitolarsen), and exon 45 (casimersen) demonstrated efficacy in restoring dystrophin production.[7] They have been approved in the United States by the US Food and Drug Administration, and currently eteplirsen is administered in Europe under a managed access program. An open-label study showed that DMD subjects treated with eteplirsen had a delayed respiratory progression when compared with natural history[8] and to mutation-matched controls.[9] Other antisense oligonucleotides are currently being evaluated in larger confirmatory studies (NCT04129294, NCT03532542, NCT02667483, NCT03218995, NCT02500381, NCT02081625). The availability of such targeted treatments has prompted the identification of a specific pattern of progression associated with each genotype.[10-14]

The studies available so far have primarily focused on subjects' motor function.[13-15] They showed that mutations amenable to skip exon 44 are associated with a slower motor decline, whereas subjects amenable to skip exon 51 and exon 53 have a faster motor decline.[15,16]

The data available for the genotype-associated progression of respiratory function in DMD is very scant and heterogeneous. The assessment of respiratory function via spirometry is challenging, particularly in children, as it is dependent upon motivation and the assessor. This can in part contribute to the existing lack of consistency in the evaluation of respiratory function in small cohorts of DMD patients. In addition, recent case reports suggest that, even within the same genotype, heterogeneity in respiratory progression may exist and needs to be considered in the evaluation of emerging therapies.[17-20]

In a recent study by our group, we observed that boys with skip44 (n = 20) had a slower decline of forced vital capacity (FVC) expressed as a percent predicted value (FVC%) over 5 years compared with boys carrying other genotypes. We did not find an association between skip53 (n = 23) and a faster FVC% decline.[4] A recent study in an international DMD cohort suggested that mutations downstream from exon 44 were associated with lower FVC% than proximal mutations. Skip53 (n = 37) was associated with the lowest mean FVC% value.[21]

The pattern of long-term respiratory decline associated with these four specific genotypes is currently unknown. We hypothesized that specific DMD genotypes, defined as mutations of the *DMD* gene amenable to the skip of one targeted exon, are associated with different patterns of long-term respiratory progression. We compared the long-term respiratory progression of subjects carrying *DMD* mutations amenable to the skip of exons 44, 45, 51, and 53, respectively. The main aim of the study was to identify whether the maximum value of FVC% and FVC and their yearly decline differed among different genotypes.

2 | METHODS

2.1 | Study design

This was a retrospective study of pediatric DMD subjects (aged >5 years and <18 years) followed by UK centers within the UK NorthStar Network and by international centers of the Association Française contre les Myopathies (AFM) Network (NCT02780492) from May 2003 to October 2020. The Ethics Committee and Institutional Review Board of the UK approved the UK NorthStar Network for data collection and the conduct of research studies within the network. Ethics approval of natural history studies in DMD within the AFM Network was obtained from the ethics review board of each center partner: Paris (Institute of Myology); London (NIHR Great Ormond Street Biomedical Research Centre); Newcastle (John Walton Muscular Dystrophy Research Center); Nijmegen (Radboud University Medical Center); and Leiden (Leiden University Medical Center).

We included subjects whose parents consented to either the UK NorthStar Network or AFM Network database. We included DMD boys carrying *DMD* mutations amenable to the skip of one of the four exons (exon 44, 45, 51, and 53). Subjects with a single deletion of exon 52 were included in the subgroup of those amenable to skipping of exons 51 and 53.[15] We analyzed the data of subjects with at least two visits including lung function tests.

We excluded subjects enrolled in interventional clinical trials or already under treatment with exon-skipping strategies. We also excluded subjects nonambulant at first recorded visit and subjects who were CS-naive. Subjects displaying clinical symptoms of respiratory infection at the time of assessment and subjects with less than two lung function results were also excluded.

2.2 | Subjects' characteristics and genotyping information

All information was retrospectively collected from medical records. The first visit after 5 years of age for which respiratory assessment was recorded for each patient was defined as baseline. Clinical visits were carried out every 6 months from 5 years of age onward. Height was assessed while standing for ambulant subjects or from arm span in nonambulant subjects. Ambulatory status was recorded at each visit. Loss of ambulation (LoA) was defined as the inability to walk 10 meters independently. All boys enrolled were on regular CS treatment. For each boy, the CS regimen was recorded as the majority treatment, defined as the CS regimen administered for over 60% of the recorded follow-up.

Data on *DMD* gene mutations were collected and subjects were grouped in four genotypes based on amenability to skip exons 44, 45, 51, or 53 (called skip44, skip45, skip51, and skip53 hereafter). Table S1 (see Supporting Information) includes all mutations amenable to skipping of each of the four exons.

2.3 | Respiratory status

Pulmonary function data were collected retrospectively from a shared platform of the electronic medical record. Spirometry was performed in a seated position according to ERS/ATS guidelines.[22] The best of three reliable attempts conducted by trained respiratory physiologists was recorded. Absolute FVC (in liters) was collected and FVC% was calculated according to GLI reference data.[23] The long-term progression of respiratory function (FVC% and absolute FVC) was outlined for each genotype and compared with the other subgroups.[13-15] For each genotype, the need for noninvasive ventilation (NIV) and the age at establishment as well as the number of chest infections and the need for a cough assist device were reported when available.

TABLE 1 Study population

	Exon 44 (n = 35)	Exon 45 (n = 37)	Exon 51 (n = 46)	Exon 53 (n = 29)
Measurement (n)	130	139	197	127
Median (range) follow-up, years	2.9 (0.5-6.7)	2.5 (0.3-8.0)	3.5 (0.4-8.3)	3.4 (0.5-8.3)
Mean age (SD) first visit[a], years	8.4 (2.7)	8.1 (2.5)	9.6 (2.6)	8.3 (2.4)
Mean age (SD) last visit, years	11.2 (3.1)	11.1 (3.4)	13.1 (2.9)	11.7 (3.2)
Ambulant last visit, n (%)	27/34[b] (79%)	26 (70%)	25 (54%)	18/28[b] (64%)
Median age (IQR) at LoA, years	16.8 (11.9-16.8)	14.1 (11.7-15.9)	13.4(11.7-16.6)	13.6 (11.4-15.8)
Mean age (SD) at starting CS, years	6.9 (2.4)	5.8 (1.4)	5.8 (1.9)	5.7 (1.4)
Majority CS regimen (>60% treatment)				
Daily	18	24	30	20
Intermittent	15	11	12	5
Unknown	2	2	4	4

Abbreviations: CS, corticosteroids; FVC%, forced vital capacity percent predicted; FVC, absolute forced vital capacity; LoA, loss of ambulation; SD, standard deviation.

[a]Mean age (SD) at the first recorded visit with lung function test available.

[b]Ambulatory status was missing for one patient at latest visit.

TABLE 2 Details of respiratory progression across DMD genotypes

	Exon 44 (n = 35)	Exon 45 (n = 37)	Exon 51 (n = 46)	Exon 53 (n = 29)
Mean (SD) FVC% first visit	81.7 (21.3)	90.5 (16.1)	89.3 (18.6)	83.3 (22.6)
Estimated age at peak, years	8.7	NA	NA	8.5
Estimated max FVC% (95% CI) at peak	89.8 (83.5-96.1)	NA	NA	89.4 (81.1-97.8)
Estimated max FVC% at age 9 years	89.8 (83.6-96.0)	86.8 (81.6-92.1)	92.8 (87.2-98.4)	89.0 (80.8-97.2)
Estimated yearly decline in FVC% after age 9 years (95% CI)	−2.7 (−4.5 to −1.0), $P < .01$	−3.4 (−5.1 to −1.8), $P < .01$	−5.9 (−7.1 to −4.8), $P < .01$	−4.5 (−6.1 to −3.0), $P < .01$
Mean FVC (SD) first visit, L	1.4 (0.5)	1.4 (0.4)	1.6 (0.5)	1.3 (0.5)
Estimated increase in FVC after age 9 years, mL	49 (−2 to 79), $P = .06$	11 (−16 to 39), $P = .43$	25 (−6 to 55), $P = .11$	NA

Abbreviations: CI, confidence interval; FVC%, forced vital capacity percent predicted; FVC, absolute forced vital capacity; NA, not applicable.

2.4 | Statistical analysis

Population characteristics are presented as mean (standard deviation [SD]), median (range or interquartile range [IQR]) for skewed data, and frequency (percent) for categorical data.

For FVC%, we described the longitudinal trajectories and estimated the mean annual change using mixed effects regression models, accounting for the repeated design of the longitudinal measurements and age at baseline. For each genotype we considered the decline of FVC% after its estimated maximum value and after the age of 9 years, the age of deflection of FVC% to linear decline in DMD boys, as demonstrated in previous studies.[4,21] The results are presented as estimates with their confidence intervals (CIs) in view of the wide variability. We compared rates of decline in a separate set of models according to subjects' amenability to exon 44, 45, 51, and 53 skipping, using appropriate interaction terms. Results are presented as mean annual change, or difference in mean annual change between subgroups, with 95% CIs. All analyses were conducted in Stata version 15 (StataCorp, College Station, TX) with $P < .05$ considered significant.

3 | RESULTS

3.1 | Study population

The study population included 142 DMD boys, 125 from the UK NorthStar Network and 17 from the international AFM Network. Mean age (SD) at the first recorded visit with lung function test available was 8.6 (2.5) years. Thirty-five subjects had skip44 mutations, 37 had skip45, 46 had skip51, and 29 had skip53. Five subjects had mutations amenable for skip of either exon 51 or 53. Study population characteristics are summarized in Table 1.

Table S2 (see Supporting Information) includes all mutations for all subjects in the study, grouped per genotype.

3.2 | Progression of respiratory function across genotypes

Data on FVC% and absolute FVC at first visit and their progression corrected for age for each genotype are shown in Table 2.

In skip45 and skip51, FVC% declined linearly from the age of 5 years (ie, the first recorded visit), whereas, in skip44 and skip53, the estimated maximum FVC% was reached at the age of 8.7 and 8.5 years, respectively.

From the age of 9 years, FVC% showed a linear decline in all four genotypes. Skip44 had the slowest annual decline, whereas skip51 had the fastest FVC% decline. The patterns of FVC% progression in the four genotypes are shown in Figure 1.

When assessing absolute FVC, we also observed a different progression according to genotype. In skip44, skip45, and skip51, absolute FVC increased steadily up to the age of 18 years. However, while in skip44 and skip51 we observed a small yet regular increase in absolute FVC, skip45 tended to stabilize after 12 years of age. Skip53 had a plateau phase between 10 and 14 years, followed by a decline, but there was no significant difference in FVC trajectory across genotypes (Figure 2).

Information on NIV requirement at latest follow-up was available for 111 patients, among whom only 5 required NIV: 4 skip51 (median age, 15.2 years; IQR, 13-16.1 years) and 1 skip45 (age, 14.8 years).

Information on the requirement of a cough assist device at latest follow-up was available for 83 patients. Only three patients, all skip51, required a cough assist device at a median age of 14.2 (IQR, 10.4-14.4) years. Two of these patients were already on NIV.

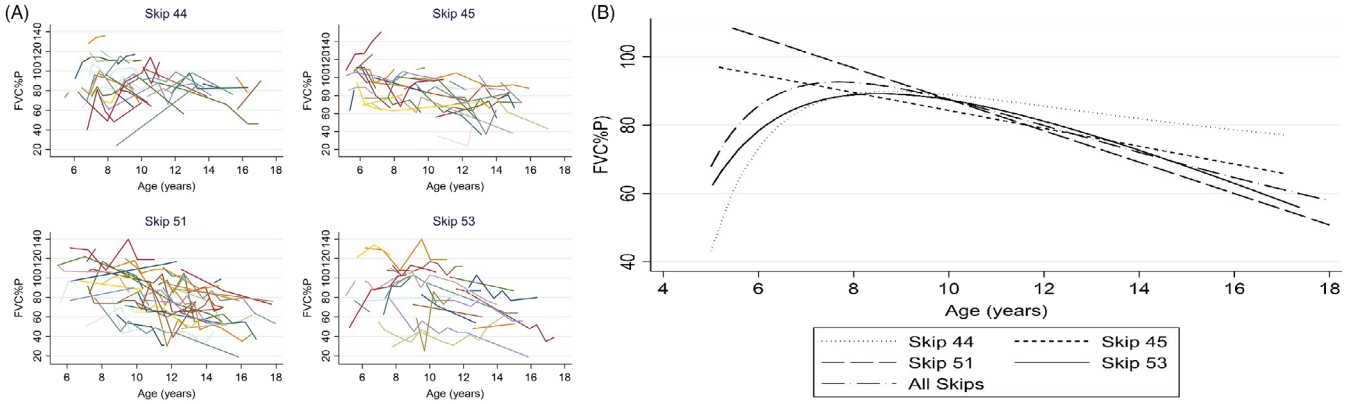

FIGURE 1 Long-term progression of forced vital capacity percent predicted (FVC%) in subjects amenable to skipping of exons 44 (n = 35), 45 (n = 37), 51 (n = 46), and 53 (n = 29), according to genotypes. A, Spaghetti plot showing FVC% trajectory for individual subjects in each genotype. B, FVC% model fitted for each genotype and for the whole study population

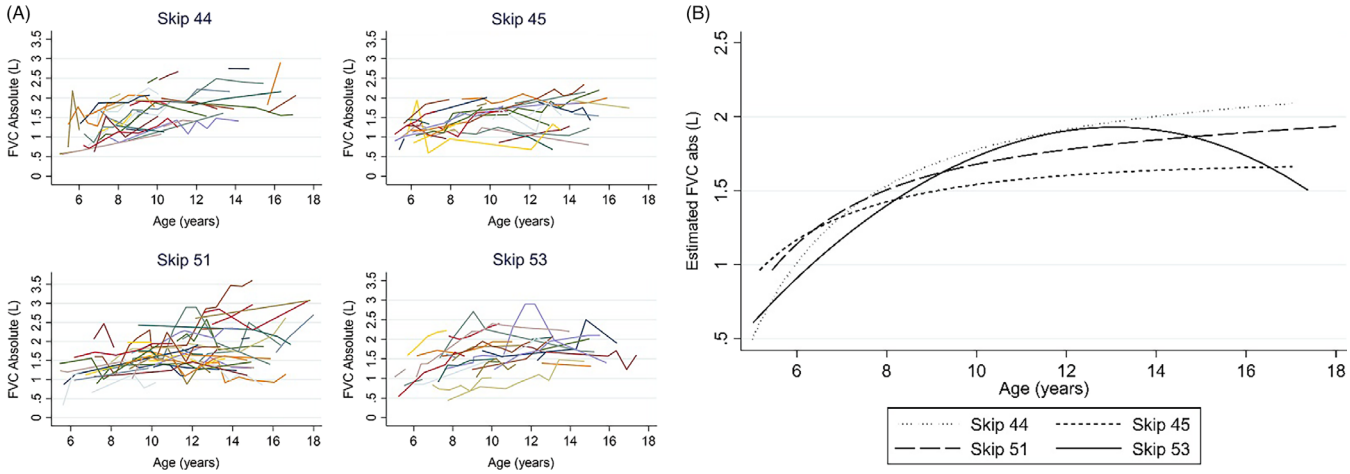

FIGURE 2 Long-term progression of absolute forced vital capacity (FVC) in subjects amenable to skipping of exons 44 (n = 35), 45 (n = 37), 51 (n = 46), and 53 (n = 29), according to genotypes. A, Spaghetti plot showing FVC trajectory for individual subjects in each genotype. B, FVC model fitted for each genotype and for the whole study population

Data on recurrent respiratory infections requiring hospitalization were available for 63 patients. Of these patients, only three, all skip51, had chest infections, with a median age of 13 years (IQR, 10.9-14.2 years). One patient was already on overnight NIV and two were started on a cough assist device as result of the infection.

4 | DISCUSSION

Our work on an international and homogeneous DMD cohort (subjects were all ambulant at first visit and on CS treatment) confirms that specific DMD genotypes are associated with specific patterns of respiratory progression of peak pulmonary function, age at peak, and its subsequent decline.

First, the maximum FVC% value and age at peak differed across genotypes due to several factors. Boys amenable to skipping exon 45 and exon 51 had an almost linear decline of FVC%. Subjects amenable to skipping exon 44 and exon 53 had an increase in estimated FVC% from 5 to 8.7 and 8.5 years of age, respectively, followed by a progressive decline. These findings on the latter two genotypes are in line with previous reports of motor progression. As observed for respiratory function, skip44 is characterized by an improvement in motor function (6-minute walk test) in the first years of life before a decline.[15] Skip53 peaked at a later age and reached a lower FVC% peak in terms of value. Boys with mutations downstream from exon 44 have progressively worse motor function, which has been linked to cumulative loss of dystrophin isoforms.[24] As such, skip53 has been described to have a later peak in motor achievements (NorthStar Ambulatory Assessment and 10-minute walk test).[15] The loss of isoforms downstream from exon 44 is also linked to a higher prevalence of cognitive impairment.[25] Thus, a later and lower FVC% peak in skip53 could also be linked to incomplete or delayed full compliance with performance of lung function tests. Skip53 patients reach peak FVC% late due to delayed maturation and cognitive impairment.

They also have a fast decline of respiratory function after the peak, likely due to the contribution of their more severe motor progression. Skip53 in our cohort lost ambulation earlier than the other subgroups. Loss of ambulation is known to play a major causative role in FVC% decline.[26]

Second, when comparing the rate of annual FVC% decline after 9 years of age, when FVC% declined linearly in all genotypes, we found the most remarkable differences. Unsurprisingly, skip44 had the slowest FVC% progression of 2.7% per year. Skip51 had the fastest decline in FVC% of 5.9% per year, and skip53 had an FVC% decline of 4.5% per year.

Previous studies have shown contrasting results for absolute FVC. McDonald et al[5] described a progressive increase of FVC up to 18 years of age in 397 boys with DMD. Mayer et al[27] reported an FVC increase up to 10 years of age in 60 boys with DMD aged 5 to 24 years, followed by stabilization from 10 to 18 years and then a subsequent decline. Our pediatric cohort included only boys younger than 18 years of age. Although the overall long-term progression of absolute FVC was not statistically different across the four genotypes, we observed some differential trends. A steady increase seemed consistent with the trajectory of subjects amenable to skipping exons 44, 45, and 51, whereas this was not observed in subjects amenable to skipping exon 53. In the latter, absolute FVC increased steadily until 10 years of age and then started declining after 14 years of age.

The main limitations of this study are its retrospective design across multiple centers and the wide variability in the number of measurements between patients. Forty-one patients had two or three assessments available, and seven patients had more than ten assessments. The differences found in the respiratory progression across the four genotypes are based on aggregate data and are dependent on the statistical model used. Subjects in the skip51 group were older at baseline, resulting in a slightly longer follow-up. We have, however, collected long-term respiratory data (average of over 3 years) and included only assessments conducted by highly skilled operators in tertiary international sites with a certified expertise in DMD care.

This work contributes further information in defining the genotype-associated respiratory variability within DMD and developing a better understanding of this disease. These findings will serve as a benchmark for comparisons of long-term respiratory progression in subjects treated with targeted exon-skipping or other therapies. Further prospective studies, with larger cohorts, are needed to confirm our suggestion of a respiratory genotype-phenotype correlation in DMD. We postulated that the age at peak is influenced by cognitive impairment and by a learning factor in reliably performing lung function as well as motor and cardiac function tests. Hence, future correlations between motor, cardiac, and respiratory function, which are inevitably interconnected, must consider subjects' genotypes and the recognized association with intellectual impairment.[25]

In conclusion, we have identified distinct genotype-related patterns of respiratory progression in DMD boys. These data are valuable for prognosis and for evaluation of long-term exon-skipping treatment effects.

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CONFLICT OF INTEREST

E.H.N. reports consultancies for BioMarin, Summit, and Wave Therapeutics for which reimbursements were received by the LUMC. I.d.G. received consulting and education fees from PTC Therapeutics, Santhera, and Biomarin/Prosensa. J.-Y.H. has received consulting fees from Biogen, Sarepta, and Minoryx. L.S. has received consulting fees from Roche, Biogen, Avexis, Cytokinetics, Sarepta, Biomarin, Santhera, Servier, Biophytis, and Dynacure, and he is currently coordinating natural history studies funded by Valerion, Dynacure, and Roche. V.S. received speaker honoraria from Sanofi Genzyme and has served on advisory boards for Audentes Therapeutics, Biogen, AveXis, Pharmaceuticals, Pfizer, Roche, Sanofi Genzyme, Sarepta Therapeutics, Summit Therapeutics, and Wave Therapeutics. V.R. is co-founder of EVP, CMO of DiNAQOR, and served as a consultant for Solid Biosciences and Antisense Therapeutics. F.M. has received grants from Sarepta, Wave Therapeutics, and PTC, and personal fees from Avexis, Roche, Pfizer, Dyne Therapeutics, and Sarepta (outside the submitted work). F.T., D.R., K.M., M.C., P.M., A.S., S.R., R.Q., M.R., C.W., E.C., F.A., S.D.L., and A.M. declare no potential conflicts of interest.

ETHICAL PUBLICATION STATEMENT

The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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APPENDIX

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