

The mechanics behind gait problems in patients with Dravet Syndrome

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Reference

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Abstract

Background

Dravet Syndrome (DS) is a developmental and epileptic encephalopathy starting in infancy and characterised by treatment resistant epilepsy with cognitive impairment and progressive motor dysfunction. Walking becomes markedly impaired with age, but the mechanical nature of gait problems remains unclear.

Research question

What are the kinetic strategies characterised in gait of patients with DS?

Methods

This case-control study compared 41 patients with DS aged 5.2 to 26.1 years (19 female, 22 male) to 41 typically developing (TD) peers. Three dimensional gait analysis (VICON) was performed to obtain spatiotemporal parameters, kinematics and kinetics during barefoot, level walking at self-selected walking velocity. The sagittal plane support moment was analysed using Statistical Parametric Mapping (SPM). Three DS subgroups were identified based on differences in kinetic strategies characterised by the net internal knee joint moments and trunk lean. Kinematic and kinetic time profiles of the subgroups were compared to the TD group (SPM *t*-test). Clinical characteristics from physical examination and parental anamnesis were compared between DS (sub)groups using non-parametric tests (Kruskal-Wallis, Wilcoxon rank-sum, Fisher's exact).

Results

Support moments in stance were significantly increased in the DS group compared to TD and strongly related to minimum knee flexion in midstance. Persistent internal knee extension moments during stance were detected in a subgroup of 27% of the patients. A second subgroup of 34% showed forward trunk lean and attained internal knee flexion moments. The remaining 39% had neutral or backward trunk lean with internal knee flexion moments. Subgroups differed significantly in age and functional mobility.

Significance

Inefficient kinetic patterns suggested that increased muscle effort was needed to control lower limb stability. Three distinct kinetic strategies that underly kinematic deviations were identified. Clinical evaluation of gait should pay attention to knee angles, trunk lean and support moments.

Keywords

Dravet Syndrome, Severe Myoclonic epilepsy of infancy (SMEI), kinematics, kinetics, support moment, trunk lean

Highlights

- This is the first study to document kinetics of gait in patients with Dravet Syndrome
- Lower limb support moments were increased in patients with Dravet Syndrome
- Three subgroups were characterised by sagittal knee moment and trunk lean
- Crouch gait and skeletal malalignments were detected
- Kinetics and trunk lean revealed distinct strategies behind kinematic deviations.

Introduction

Dravet Syndrome (DS) is a developmental and epileptic encephalopathy characterized by drug resistant infantile onset seizures with cognitive and progressive motor impairments [1,2]. It is primarily caused by mutations in the neuronal sodium voltage-gated channel type 1 alpha subunit encoding gene (*SCN1A*) [3]. The sodium channel interneuronopathy induces intractable epileptic seizures and a variety of comorbidities [4]. Around adolescence, walking problems become evident, making many of the patients lean on others or use a wheelchair for longer distances [5]. Literature on gait deviations in patients with DS is still scarce and mainly observational [6]. Quantitative analysis of gait in this population is only recently reported [7]. Crouch gait is often described in about half of the population, next to a variety of other deviations [6,7]. Crouch gait is defined by excessive knee flexion in stance and was originally described in populations with cerebral palsy, where it is caused by a

complex of muscle weakness, spasticity and contractures [8,9]. However, these symptoms are rarely seen in patients with DS [6,10], hence the nature of their gait problems remains unclear.

Studying biomechanics provides insight in how the central nervous system controls movements. The central nervous system can select many combinations of muscle forces to yield the same moment around a joint. Moreover, many combinations of hip, knee and ankle moments can result in the same knee angle. Therefore, when deviations in joint angles (kinematics) are observed, analysis of muscle and soft tissue forces that cause these motions (kinetics) is necessary to understand the neuromuscular control behind gait abnormalities [11].

To obtain an indicator of lower limb control during gait [12,13], Winter (1980) proposed to combine the three major lower limb moments into one single measure: the ‘support moment’ (M_S), defined as the algebraic sum of the net internal extension moments at hip, knee and ankle [12]. The magnitude of the M_S depends on the ground reaction force (GRF) and the knee flexion angle and can be interpreted as the total internal extension moment that is generated to prevent collapse of the stance limb [13]. Relatively higher M_S may thus suggest that extensor muscles are inducing larger moments and more muscular effort is needed to stabilise the limb.

To maintain stability of the stance limb in normal gait, ankle plantar flexors are active in midstance to slow down the forward momentum and align the GRF anterior to the knee. An internal hip and knee flexion moment produced by soft tissue forces is attained during single leg stance. This way, less muscle activity is required, which optimizes the energy expenditure [14]. When a person fails to align the GRF in front of the knee, persistent internal knee extension moments occur, greatly increasing energy demands [14]. Forward trunk lean influences the direction of the GRF and is often observed as a compensatory strategy to reduce this internal extension moment [15].

The observed gait deviations in patients with DS, especially wide based and crouch gait, may reflect a lack of stance limb stability [7], probably caused by underlying neuromuscular control disturbance [4,16,17]. Recently, Di Marco et al. (2019) reported gait kinematics of patients with DS [7], but to our knowledge, no studies on gait kinetics in DS have been published yet. Therefore, this study aims to characterise kinetic strategies employed by patients with DS to support the lower limb during stance phase of gait. First, analysis of the M_S may provide evidence of lower limb support abnormalities. Furthermore, distinguishing subgroups based on differences in kinetic strategies characterised by the net internal knee joint moments and trunk lean, may enhance understanding of the heterogeneity of gait deviations. Lastly, detecting differences in gait and clinical characteristics between these subgroups may highlight the functional impact of the observed kinetic strategies.

Methods

Study design and setting

This case-control study was part of a larger project registered at ClinicalTrials.gov (<https://clinicaltrials.gov/ct2/show/NCT03857451>) and approved by the ethics committees of the Antwerp and Leuven University Hospitals (Belgian Registration Number: B300201627079). Patient data collection was performed between May 2016 and February 2020 (most recent session selected per patient) at the Multidisciplinary Motor Centre Antwerp (M²OCEAN).

Participants

Volunteers with DS were recruited through the department of child neurology at the Antwerp University Hospital and the parent organization of the Netherlands and Flanders ‘Stichting Dravetsyndroom

Nederland/Vlaanderen'. All candidates with a clinical diagnosis with DS were included if *SCN1A* mutation was confirmed and they had a minimum age of five and maximum of 25 years at enrolment. Exclusion criteria were the occurrence of a severe epileptic seizure within 24 hours before assessment and comorbidities of neurological and/or orthopaedic disorders not related to DS (figure 1).

Data collection

Gait data

Body segment motion and ground reaction forces were captured and processed using a VICON system (Nexus v2.8.1, VICON, Oxford Metrics, Oxford, UK) with eight optoelectronic cameras (100 Hz), two optical cameras (50 fps, Basler AG, Ahrensburg, Germany) and four force plates (1000 Hz, low-pass filtered at 20 Hz, AMTI, Watertown, MA, US). Retroreflective markers were placed following the PlugInGait Lower Limb marker model [18]. All participants performed walking trials at self-selected walking velocity. Patients were only included when kinetic data were successfully collected. A control group, balanced for age, was selected from available databases of typically developing children and healthy adults without neurological or orthopaedic conditions, collected at M²OCEAN and the Clinical Motion Analysis Laboratory of the University Hospital Pellenberg, Leuven (CMAL-P), collected and processed with identical procedures. All gait analysis and physical examination data were collected by the same two researchers (L.W. and K.V., MSc physiotherapists)

Clinical characteristics

Via medical record screening and parental anamnesis, the following information was obtained: type of mutation, age of epilepsy onset, current epileptic severity and age of independent walking. The patients usual mobility was inquired using the Functional Mobility Scale (FMS) and by asking the maximum distance the patient was currently able to walk ('walking distance'). Note that we gave FMS score four when the patient usually held a person's hand [19]. Levels of intellectual disability (ID) were estimated as mild, moderate or severe, supported by cognitive test scores if available [20]. During physical examination, goniometric measures of joint range of motion (ROM), muscle length and skeletal alignment were obtained and compared to age-related norm values [21,22].

Data processing

Spatiotemporal parameters, lower limb joint kinematics and kinetics were calculated. Visual inspection of data quality and further processing was performed using custom made MATLAB® software (vR2018a, The Mathworks Inc, Natick, MA, US). Spatiotemporal and kinetic data were non-dimensionally normalized for leg length, body mass and gravitational acceleration [23,24]. For each instant of the gait cycle, sagittal plane M_s were calculated according to the formula by Hof (2000) [13].

$$M_s = \frac{M_H}{2} + M_K + \frac{M_A}{2}$$

with M_H , M_K , and M_A indicating the net internal moment (positive values for extension) around hip, knee and ankle respectively [13]. Per participant, all available trials of one randomly selected side (ranging from one to twelve trials) were averaged, because further analyses required single observations per subject.

Trunk lean was assessed by one researcher (L.W.) based on sagittal plane video images. The angle between vertical and the trunk axis (estimated trochanter major to acromion) was measured on a still frame taken at 'opposite toe-off' using Kinovea (v0.8.15, <http://www.kinovea.org>). Trunk lean was then categorized as 'neutral' (between vertical and 5° of forward or backward inclination), 'forward' or 'backward' [15,25].

Subgrouping

We constructed a decision making tree to identify subgroups within DS based on minimal sagittal knee moment in midstance (between 30% of stance phase and toe-off) and trunk lean. The *KMext subgroup* was defined by a persistent internal knee extension moment throughout stance, regardless of trunk position. The *KMflex-Tf subgroup* contained patients who attained an internal knee flexion moment in midstance in combination with forward trunk lean. The remaining patients formed the *KMflex-Tn/b subgroup*, characterized by an internal knee flexion moment in combination with a neutral or backward inclined trunk (figure 1).

Statistical analysis

Spatiotemporal parameters and clinical characteristics were analysed using non-parametric tests, since graphical inspection and formal tests (Kolmogorov-Smirnov) revealed that the assumption of normality was not fulfilled. Wilcoxon rank-sum tests (two-tailed $\alpha=.05$) were used to compare age, BMI and non-dimensional spatiotemporal parameters between DS and TD. Fisher's exact tests (categorical data, including physical examination categorised as 'normal' or 'deviant') and Kruskal-Wallis tests (two-tailed, $\alpha=.05$) with post-hoc pairwise Wilcoxon rank-sum tests with Bonferroni correction (numerical data) were used to identify differences in clinical characteristics between subgroups. As Fisher's exact test is somewhat conservative [28], α -levels were set at 0.10 for this test.

Kinematic and kinetic time profiles were analysed using statistical parametric mapping (SPM) [26]. Prior to SPM analyses, time profiles were normalized to 50% stance and 50% swing phase, in order to eliminate influence of differences in stance phase duration. Test statistics (t -test or regression, see further) were calculated for each time node and expressed as SPM $\{t\}$ trajectories. A critical threshold was then defined that only 5% ($\alpha=0.05$) of identically smooth random curves were expected to exceed. Parts of the gait cycle where SPM $\{t\}$ trajectory crossed this threshold were identified as clusters with significant outcome, for which cluster-specific P -values were calculated based on the Random Field Theory [27]. Small clusters (<3% GC) were not considered clinically relevant and therefore not discussed. An SPM t -test was used to identify differences in M_S between DS and TD. SPM regression analyses explored association with walking velocity and minimum knee angle in midstance for DS and TD separately. After that, SPM t -tests were used to detect kinematic and kinetic deviations comparing each subgroup to the TD group. Bonferroni correction for multiple testing brought α to .017. All SPM analyses were performed using spm1d open source code (vM.0.4.5, <http://www.spm1d.org>) in MATLAB®. All other statistical analyses were executed in R (v4.0.0, R Foundation, Vienna, Austria)

Results

Participants

Out of 50 candidates, 41 patients aged 5.2 to 26.1 years (19 female, 22 male) were included in this study (individual characteristics: appendix, table A1). Five patients were not eligible and four others were not cooperative enough to collect kinetic data (figure 1). The control group of 41 TD individuals did not differ from the DS group for age and BMI. Participants with DS walked significantly slower with shorter and wider steps and longer relative stance time ($P<.05$; table 1).

Support moment

SPM t -test showed a significantly higher M_S ($P<.001$) in the DS group during most of stance phase (figure 2, left panel). Significant positive associations between M_S and walking velocity were identified in early stance ($P<.001$) only for the DS group. Significant positive associations ($P<.001$) with minimum knee flexion angle in

midstance were observed for the majority of stance for both groups (figure 2, middle panel). The absence of an association with walking velocity in midstance and the significant correlation with knee angle are illustrated for one time point (50% stance phase) in figure 2, right panel. Details of SPM analyses can be consulted in appendix figure A1.

Subgrouping

Three DS subgroups were identified using the decision making tree. The *KMext subgroup* included eleven patients (27%) of whom five walked with neutral trunk and six showed forward lean. The *KMflex-Tf subgroup* consisted of fourteen patients (34%). The *KMflex-Tn/b subgroup* of sixteen patients (39%) of whom seven had a neutral trunk position and nine a backward lean (figure 1).

Gait pattern

Comparison of kinematic and kinetic curves (internal moments) revealed significant differences for each subgroup compared to the TD group (figure 3).

In *KMext*, kinematics were characterized by significantly increased hip ($P<.001$) and knee ($P<.001$) flexion for most of the gait cycle, increased ankle dorsiflexion in mid- and terminal stance (MSt-TSt; $P<.001$), decreased ankle plantar flexion in initial swing (ISw; $P=.004$) and increased external foot progression ($P<.001$). The underlying M_S was significantly increased in loading response (LR; $P=.001$) and MSt-TSt ($P<.001$), resulting from decreased flexion moments at the hip in TSt ($P<.001$), increased knee extension moments in MSt-TSt ($P<.001$), ankle plantarflexion moments in LR ($P=.001$) and decreased plantarflexion moments around TSt ($P<.001$).

In *KMflex-Tf*, kinematics were characterized by increased anterior pelvic tilt ($P<.001$), hip ($P<.001$) and knee ($P<.001$) flexion over the entire gait cycle, with increased dorsiflexion in LR ($P=.004$) and MSt ($P=.016$) and decreased dorsiflexion in pre-swing (PSw) and ISw ($P<.001$) and increased external foot progression ($P<.001$). The M_S was significantly increased from LR to TSt ($P<.001$), resulting from increased hip extension moments in LR ($P=.014$) and MSt-TSt ($P<.001$), knee flexion moments in LR ($P=.017$) and TSt ($P<.001$) and plantarflexion moments in LR ($P<.001$) and decreased plantarflexion moment around TSt ($P<.001$). Furthermore, first ($P=.002$) and second ($P<.001$) peak hip abduction moment were decreased.

In *KMflex-Tn/b*, kinematics were characterized by increased hip flexion over stance and ISw ($P<.001$) and in terminal swing (TSw; $P=.016$) and knee flexion from initial contact to TSt ($P<.001$) and in TSw ($P=.011$) and increased external foot progression ($P<.001$). Ankle dorsiflexion was increased in LR ($P=.006$), MSt ($P=.004$), PSw ($P=.012$) and ISw ($P<.001$). Significantly increased M_S were found in LR ($P=.002$) and in MSt ($P<.001$), resulting from decreased hip flexion moments in TSt ($P<.001$), knee extension moments in LR ($P=.012$) and MSt-TSt ($P<.001$), and plantarflexion moments in TSt ($P=.001$). Furthermore, second peak hip abduction moment was decreased ($P<.001$).

In swing, significant differences in joint moments were also identified for each subgroup, but will not be discussed since they did not attribute to stance limb support. Additional graphs of coronal and transverse plane are reported in the appendix (figure A2). Details of SPM analyses can be consulted in the appendix, (figure A3).

Clinical characteristics

Subgroups differed significantly in age, walking distance and the FMS-500m scores. Post-hoc tests indicated that *KMext* contained older participants than *KMflex-Tf*, while patients in *KMflex-Tn/b* could walk longer distances and walked more independently (table 2). Abnormalities in ROM, muscle length and alignment were present in

the three subgroups, equally distributed. Most frequent deviations were plantar flexor tightness, external tibial torsion and planovalgus feet (table 3). No clear spasticity was detected.

Discussion

This study aimed to characterise kinetic strategies in gait of patients with DS by evaluating the M_S and defining subgroups based on internal knee extension moments and trunk lean. Increased M_S were observed and three main strategies were identified with characteristic kinematic and kinetic deviations.

The M_S equals force in the direction of the hip-ankle axis times knee eccentricity and is thus mainly determined by GRF magnitude and knee flexion angles [13]. Walking velocity is known to affect both factors and was significantly different between the DS and TD. The absence of an association in midstance, however, suggested that M_S abnormalities were not just walking velocity effects. Knee flexion angles on the other hand were significantly increased in the three subgroups and correlated with M_S . The increased M_S suggested that participants with DS require more muscular effort for stance limb support. Future studies on EMG activity should test this hypothesis. Three subgroups were distinguished based on strategies that could influence the knee eccentricity.

Although six patients in *KMext* walked with forward trunk lean, they all failed to align the GRF in front of the knee. The resulting kinematic pattern of flexion in hip, knee and ankle with a neutral pelvis position and persistent internal knee extension moment can be defined as ‘uncompensated crouch gait’ [9,29]. Persistent knee extension moments are expected to require extra muscle activity and thereby lead to higher energy costs that could impact functional mobility in this subgroup.

Even though *KMflex-Tf* also showed increased flexion in the three lower limb joints, the forward trunk lean strategy might reduce M_S . However, anterior pelvic tilt and hip flexion increased as a consequence and evoked increased internal hip extension moments, so the resulting M_S remained high compared to TD. The required increased hip extensor activity makes this pattern energetically inefficient. The trunk and pelvis position together with internal knee flexion moments can be classified as ‘compensated crouch gait’ [29]. It remains unclear whether trunk lean was purely a support strategy or reflected underlying trunk control deficits [15].

In contrast to the other subgroups, internal knee flexion moments were attained without forward trunk lean in *KMflex-Tn/b*. The observation of normal internal plantar flexion moments in early- and midstance suggested functional plantar flexion – knee extension couple. However, M_S were still increased compared to TD, combined with increased flexion angles in hip, knee and ankle. Nevertheless, all deviations remained close to normative values, indicating that gait in this subgroup was only mildly affected.

Our subgrouping process was based on kinetic strategies, and therefore did not follow the kinematic classification proposed by Di Marco et al. (2019) [7]. In that previous study, an ‘atypical crouch’ gait pattern was distinguished from a ‘straight’ pattern based on knee angle at initial contact. Their findings of anterior pelvic tilt, increased hip and knee flexion and external foot progression angles were confirmed in the present study. Furthermore, three main kinetic strategies were revealed that underly the observed deviations. These results imply that clinical evaluation of gait should pay attention to knee angles, trunk lean and M_S . When forward trunk leaning is observed, kinetic analysis can reveal whether this potential compensation for crouch gait was successful.

Lever arm dysfunction and weakness or impaired control of muscles were identified as possible causes of crouch gait in patients with cerebral palsy [14]. External tibial torsion and pes planovalgus were frequently observed in patients with DS, decreasing the lever arm of the foot, which may disrupt the plantar flexion-knee extension couple. However, these malalignments were equally distributed over the three subgroups and might not impose the kinetic strategies. Measuring muscle strength was too challenging owing to cognitive impairments.

Age differences revealed that compensated crouch gait was mostly observed in younger children, which might evolve to uncompensated crouch in adolescence. These findings are in line with previous research suggesting progressive deterioration of gait [5]. The progression of crouch gait as observed in cerebral palsy, involves the risk to develop hamstrings tightening with knee flexion contractures and loss of functional independency [30]. Functional mobility was indeed more limited in *KMext*. Hamstrings tightening was present in half of the participants, independent from their kinetic strategies, but flexion contractures at the knee joint were only observed in *KMext* (two patients). Longitudinal studies are needed to document the evolution and detect prognostic factors.

Other clinical characteristics did not differ significantly between subgroups. This may suggest that epileptic activity and cognitive development were not determinative for gait strategies. However, due to small numbers of participants per subgroup and heterogeneity within DS, associations might be hard to detect. Ideally, gait interventions prevent crouch gait development and help patients achieve an overall more efficient gait pattern with a favourable functional outcome. Further research on causal mechanisms behind mechanical deviations in DS could guide therapy.

The M_S is limited to the sagittal plane, where major kinetic strategies were situated. However, coronal and transverse plane deviations were also observed. Internal hip abduction moments contribute to stance limb support and were characterised by a decreased second peak, which might be explained by step width or lateral trunk motion. Cross-plane interactions could be the subject of future research.

Limitations

A first limitation of this study were cognitive and behavioural problems that challenged participants to comply with rigorous protocols of gait analysis. This has led to the exclusion of four participants. The sample was large and therefore strongly representative for a rare disorder. Nevertheless, it remains uncertain whether the included patients' gait was representative for patients with the most severe cognitive and behavioural problems. A second limitation was the large age range of the included patients. Assembling childhood, adolescent and young adult clinical presentation may have increased the heterogeneity of the sample, but also offered an opportunity to demonstrate the diversity in gait deviations from early to adult age. This study accounted for effects of height and weight differences by non-dimensional normalisation of spatiotemporal parameters and joint moments [23]. Furthermore, the use of video images to assess trunk lean was less objective and reliable than quantitative registration using trunk markers, which would be recommended for future instrumented gait analysis in this population [31].

Conclusion

An overall inefficient walking pattern was evident in patients with DS. Increased M_S suggested that more extensor muscle effort was required to maintain stance limb stability. Forward trunk lean was mostly employed by younger patients with various degrees of success to attain alignment of the ground reaction force that

facilitates knee extension. Closer-to-normal kinetic strategies were as well observed, with mild gait deviations and a favourable functional outcome.

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FIGURES AND TABLES

	DS (n = 41)	TD (n = 41)	P-value
	median (IQR)	median (IQR)	Wilcoxon
Demographics:			
Age (years)	11.4 (10.1)	12.0 (9.1)	0.98
Gender (f / m)	19 / 22	27 / 14	
BMI	17.0 (8.6)	17.1 (5.4)	0.68
Spatiotemporal parameters:			
Walking velocity (m/sec)	1.03 (0.37)	1.21 (0.20)	
Non-dimensional walking velocity	0.360 (0.136)	0.460 (0.082)	<0.001*
Cadence (steps/sec)	2.01 (0.45)	2.02 (0.33)	
Non-dimensional cadence	0.570 (0.091)	0.560 (0.048)	0.71
Step length (m)	0.49 (0.18)	0.55 (0.15)	
Non-dimensional step length	0.650 (0.166)	0.760 (0.155)	0.006*
Step width (m)	0.16 (0.06)	0.10 (0.04)	
Non-dimensional step width	0.220 (0.096)	0.130 (0.061)	<0.001*
Stance time (%GC)	60.4 (4.4)	59.3 (2.5)	0.02*

Table 1: Comparison of patient and control group. Median and interquartile range (IQR) with *P*-value of the Wilcoxon rank-sum test. *Significant at $\alpha = 0.05$; DS, Dravet Syndrome; TD, typically developing; f, female; m, male; BMI, Body Mass Index.

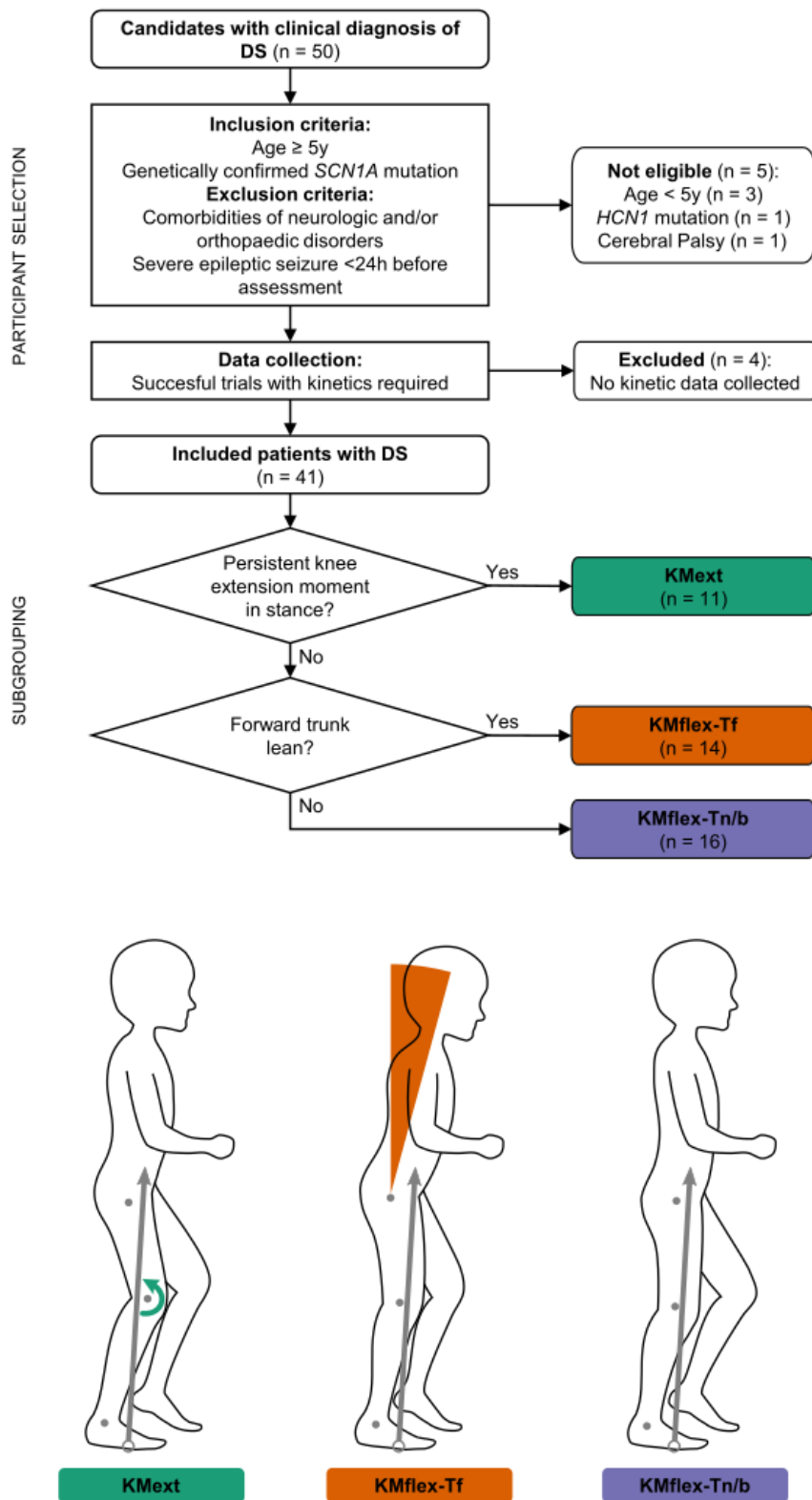


Figure 1: Illustrated flow chart of the participant selection and subgrouping process. Patients who fail to align the GRF (grey arrow) in front of the knee, show a persistent internal knee extension moment (green arrow). Forward trunk lean (>5°; orange angle) influences the direction of the GRF. DS, Dravet Syndrome; TD,

Typically Developing; KM, internal knee moment flexion (flex) or extension (ext); T, trunk lean forward (f)
neutral (n) or backward (b).

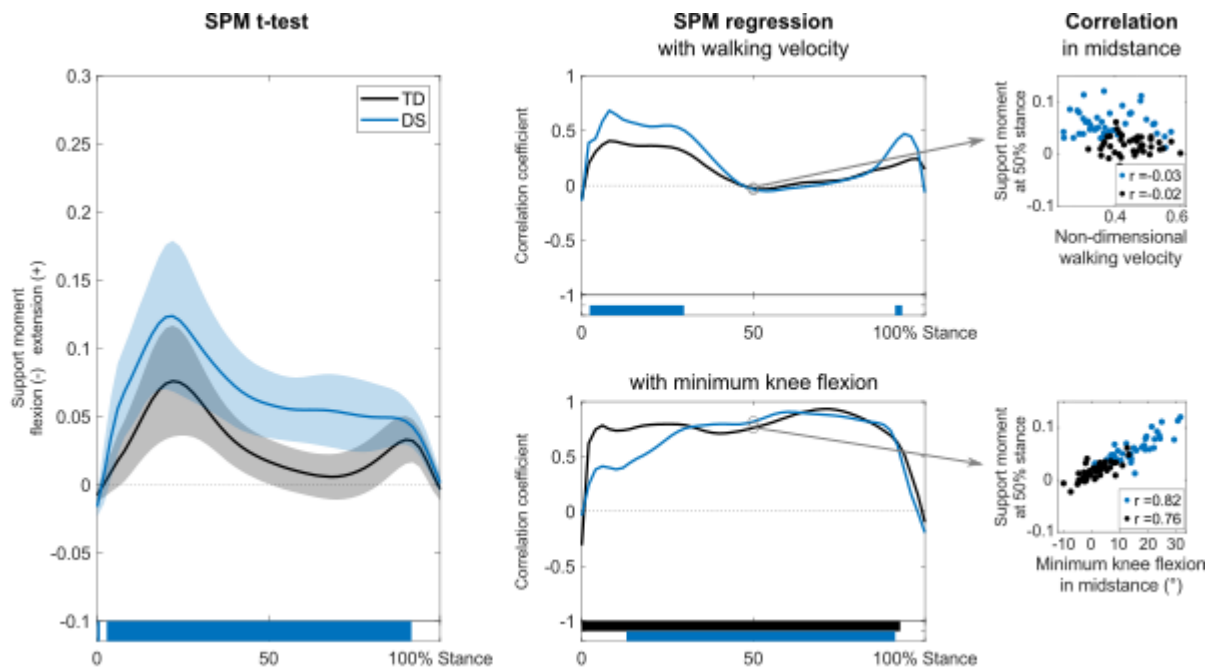


Figure 2: The support moment and its association with walking velocity and minimum knee flexion. Left: The non-dimensional support moment (averaged curve with 1SD region) was increased in patients with Dravet Syndrome (DS, blue) compared to typically developing participants (TD, black) Middle: Coefficients of the correlation between non-dimensional sagittal support moment and walking velocity (upper) and minimum knee flexion angle in midstance (lower). Right: In midstance, association with walking velocity was absent, but with minimum knee flexion was significant, as illustrated for 50% of stance phase. Horizontal bars represent clusters with significant differences (SPM *t*-test, left) or significant associations (SPM regression, middle).

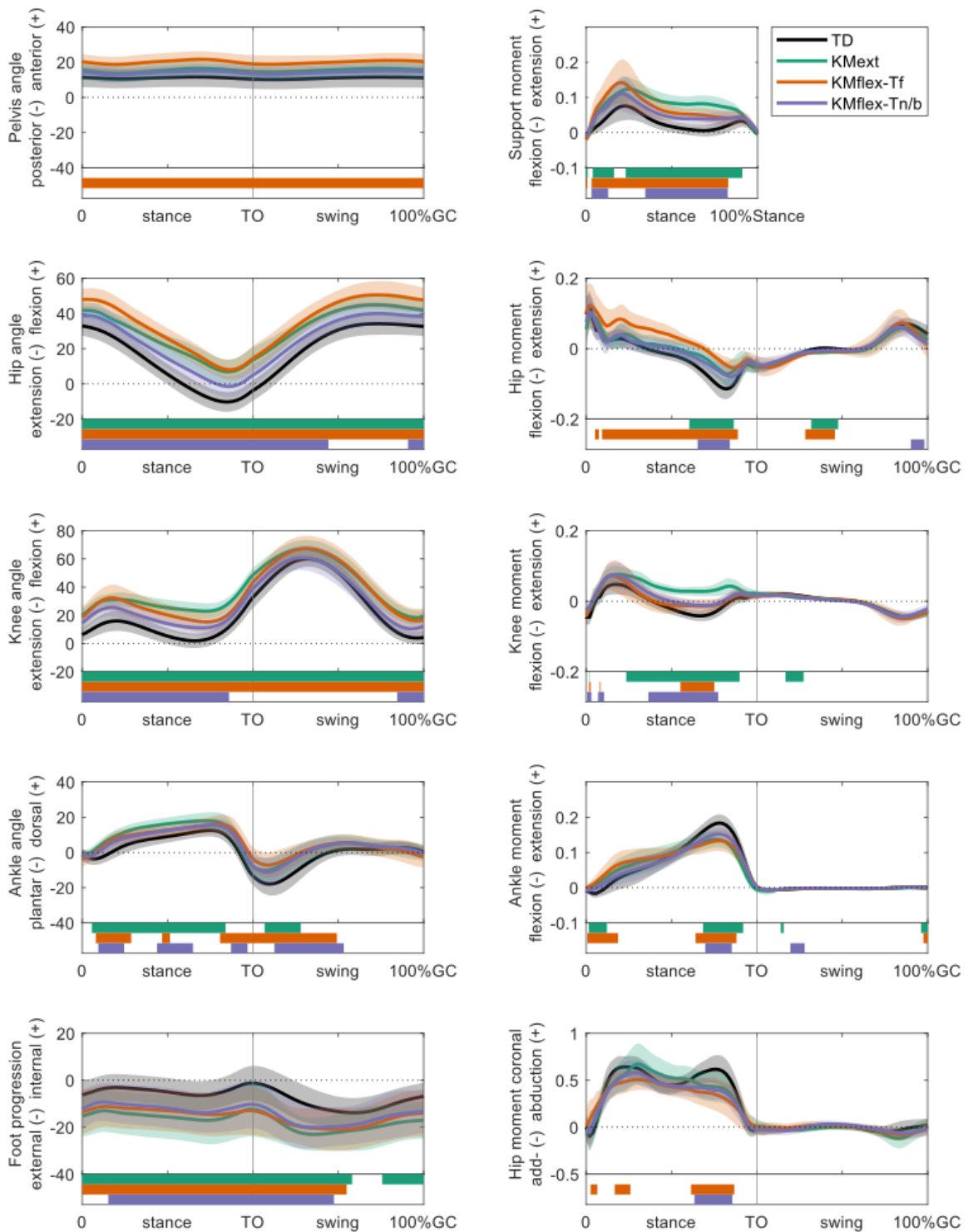


Figure 3: Comparison of kinematic and kinetic curves between Dravet Syndrome subgroups and typically developing (TD) controls. Group averaged curves and 1SD regions are plotted for joint angles ($^{\circ}$) and internal net joint moments (non-dimensional) in the sagittal plane, complemented with the foot progression angle (under, left) and hip moment in the coronal plane (under, right). Horizontal bars represent clusters with significant differences (SPM t -tests) comparing subgroups with the TD group. TO, toe off; GC, gait cycle.

	KMext (n = 11)	KMflex-Tf (n = 14)	KMflex-Tn/b (n = 16)	P-value		
	median (IQR) or n (%)	median (IQR) or n (%)	median (IQR) or n (%)	K-W	Fisher	Post-hoc
Age (years)	17.1 (5.5)	9.2 (6.9)	11.1 (8.9)	0.04		0.03^(a)
Gender (f / m)	5 / 6	7 / 7	7 / 9			
BMI	19.2 (11.0)	17.1 (4.5)	16.1 (5.7)	0.45		
Age of onset epilepsy (months)	5 (4)	5 (4)	5 (2)	0.80		
Current epileptic frequency					0.17	
Free (for >1 year)	1 (9%)	3 (21%)	6 (38%)			
Mild (yearly)	5 (45%)	5 (43%)	4 (25%)			
Moderate (monthly)	0 (0%)	3 (21%)	4 (25%)			
Severe (weekly)	5 (45%)	2 (14%)	2 (13%)			
Intellectual disability:					0.42	
Mild	3 (27%)	2 (14%)	6 (38%)			
Moderate	3 (27%)	6 (43%)	7 (44%)			
Severe	5 (45%)	6 (43%)	3 (19%)			
Age of independent walking (months)	18 (10)	18 (1)	16 (4)	0.18		
Walking velocity (m/sec)	1.08 (0.28)	1.04 (0.44)	1.00 (0.31)			
Non-dimensional walking velocity	0.366 (0.106)	0.382 (0.159)	0.358 (0.115)	0.77		
Walking distance					0.02	0.03^(b) 0.009^(c)
<1km	5 (45%)	8 (57%)	1 (7%)			
1km-3km	3 (27%)	2 (14%)	3 (20%)			
>3km	3 (27%)	4 (29%)	11 (73%)			
FMS-5m:						
Score 4	0 (0%)	1 (7%)	0 (0%)			
Score 5	10 (91%)	11 (79%)	10 (67%)			
Score 6	1 (9%)	2 (14%)	5 (33%)			
FMS-50m:						
Score 4	3 (27%)	6 (43%)	1 (7%)			
Score 5	7 (64%)	6 (43%)	10 (67%)			
Score 6	1 (9%)	2 (14%)	4 (27%)			
FMS-500m:					0.10	0.04^(c)
Score 1	5 (45%)	8 (57%)	2 (2%)			
Score 4	3 (27%)	1 (7%)	3 (23%)			
Score 5	2 (18%)	5 (36%)	7 (47%)			
Score 6	1 (9%)	0 (0%)	3 (20%)			

Table 2: Clinical characteristics of the three subgroups. Median and interquartile range (IQR) with *P*-value of the Kruskal-Wallis test (K-W) for numerical data. Count and percentage (%) with *P*-value of the Fisher's exact test (Fisher) for categorical data. Significantly different values are in bold, with $P \leq 0.05$ for Kruskal-Wallis and $P \leq 0.10$ for Fisher's exact test. *P*-values of post hoc tests were only reported when significant with ^(a)

between KMext and KMflex-Tf, ^(b) between KMext and KMflex-Tn/b, and ^(c) between KMflex-Tf and KMflex-Tn/b. FMS: Functional Mobility Scale. FMS values were missing for one participant in the KMflex-Tn/b group.

Test (method)	KMext (n = 11)	KMflex-Tf (n = 14)	KMflex-Tn/b (n = 16)
	median (IQR) or n (%)	median (IQR) or n (%)	median (IQR) or n (%)
Joint ROM and muscle length			
Hip extension, m psoas (Thomas test)			
Normal	7 (64%)	12 (86%)	12 (75%)
Limited	4 (36%)	2 (14%)	4 (25%)
Knee flexion, m rectus femoris (Duncan Ely)			
Normal	3 (27%)	10 (71%)	8 (50%)
Limited	8 (73%)	4 (29%)	8 (50%)
Knee extension, joint ROM (positive values for hyperextension)			
Median (IQR)	0 (7.5)	5 (10)	5 (6.25)
Normal	9 (82%)	14 (100%)	16 (100%)
Limited	2 (18%)	0 (0%)	0 (0%)
Knee extension, m hamstrings (Popliteal angle with contralateral knee extended)			
Median (IQR)	-45 (12.5)	-27.5 (27.5)	-37.5 (21.25)
Normal	3 (27%)	9 (64%)	8 (50%)
Limited	8 (73%)	5 (36%)	8 (50%)
Ankle dorsiflexion, m soleus (Silfverskiöld 90°)			
Median (IQR)	10 (10)	20 (8.75)	17.5 (10)
Normal	1 (9%)	3 (21%)	4 (25%)
Limited	10 (91%)	11 (79%)	12 (75%)
Ankle dorsiflexion, m gastrocnemius (Silfverskiöld 0°)			
Median (IQR)	5 (5)	10 (8.75)	10 (10)
Normal	1 (9%)	2 (14%)	4 (25%)
Limited	10 (91%)	12 (86%)	12 (75%)
Skeletal alignment			
Femoral anteversion (TPAT)			
Median (IQR)	25 (5)	30 (5)	30 (5)
Normal	8 (73%)	11 (79%)	14 (88%)
Increased anteversion	3 (27%)	3 (21%)	2 (13%)
Tibial torsion (bimalleolar angle)			
Median (IQR)	25 (7.5)	30 (5)	25 (10)
Normal	3 (27%)	3 (21%)	6 (38%)
Increased external torsion	8 (73%)	11 (79%)	10 (63%)
Foot posture index (FPI-6)			
Median (IQR)	6 (5.5)	5.5 (6.75)	6.5 (6)
Normal	5 (45%)	9 (64%)	10 (63%)
Increased pronation (planovalgus)	6 (55%)	4 (29%)	5 (31%)
Increased supination (cavovarus)	0 (0%)	1 (7%)	1 (6%)

Table 3: Physical examination of DS subgroups. All measures were compared to age-related norm values with mean \pm 1SD as cut-off to define deviations (Mudge et al. 2014; Redmond et al. 2008). Values in this table did not significantly differ between subgroups. IQR, interquartile range; TPAT, trochanteric prominence angle test; ROM range of motion.

APPENDIX

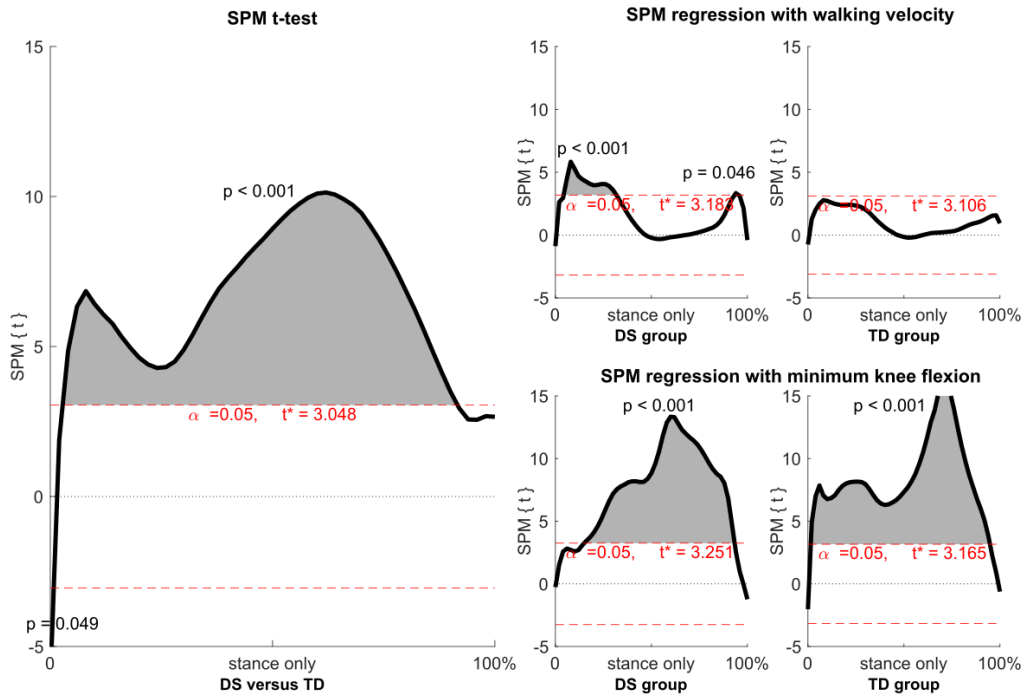


Figure A1: SPM inference curves accompanying figure 2: The support moment and its relation to walking velocity and knee flexion. Left: The SPM{t} curve of the t test statistics represents the difference between the support moment in the typically developing (TD) group and the Dravet Syndrome (DS) group over the stance phase. Right: The SPM{t} curve expresses the effect magnitude of non-dimensional walking velocity (upper) and minimum knee flexion angle in midstance (lower) on the support moment in both groups. Red dashed lines indicate the critical threshold (t^*) for $\alpha = 0.05$. Shaded areas with P values are clusters with significant differences (t -test) or association (regression).

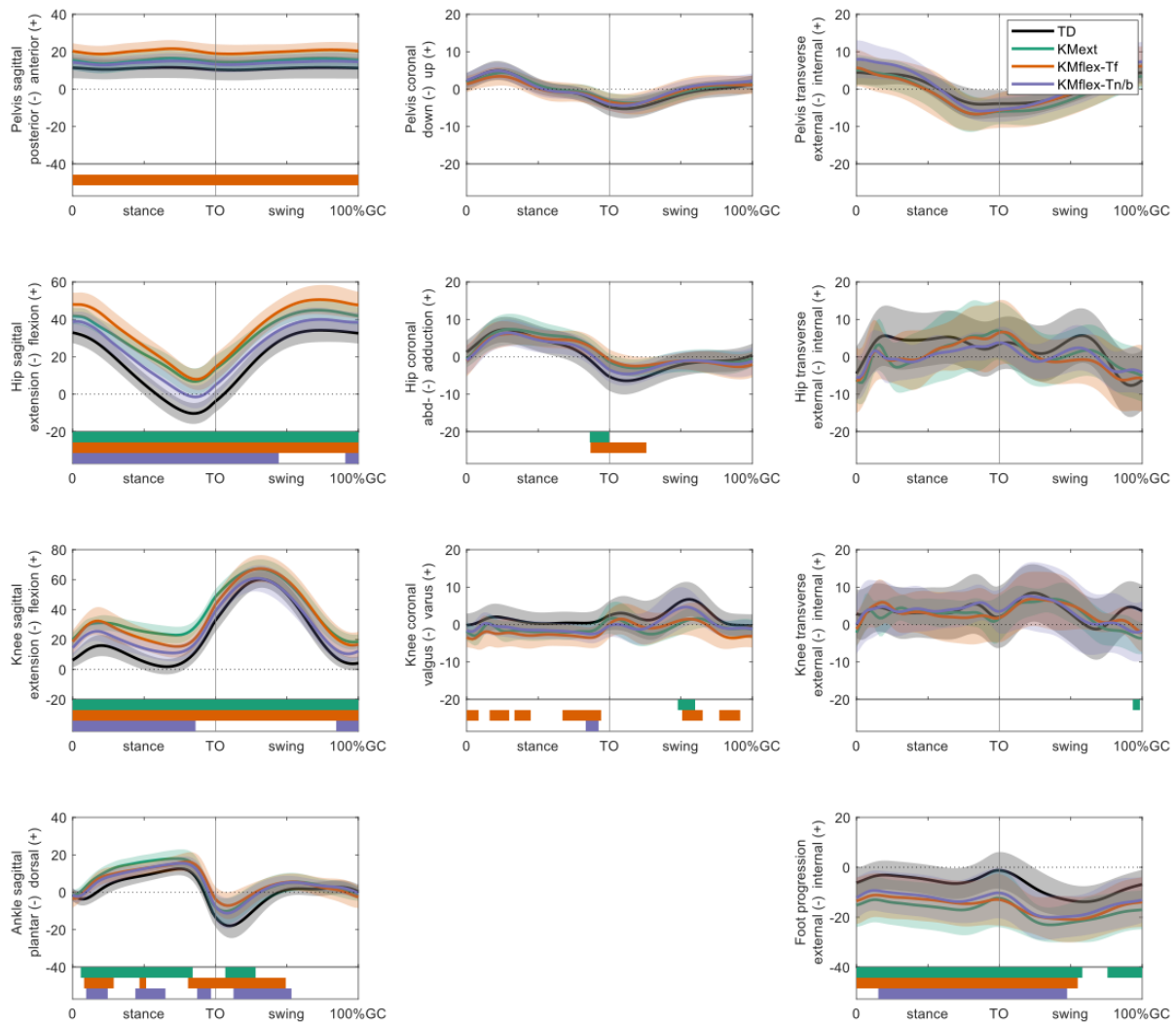


Figure A2: Comparison of kinematics in the three planes between Dravet Syndrome subgroups and typically developing (TD) controls. Group averaged curves and 1SD regions are plotted. Horizontal bars represent clusters with significant differences (SPM *t*-tests) comparing subgroups with the TD group. TO, toe off; GC, gait cycle.

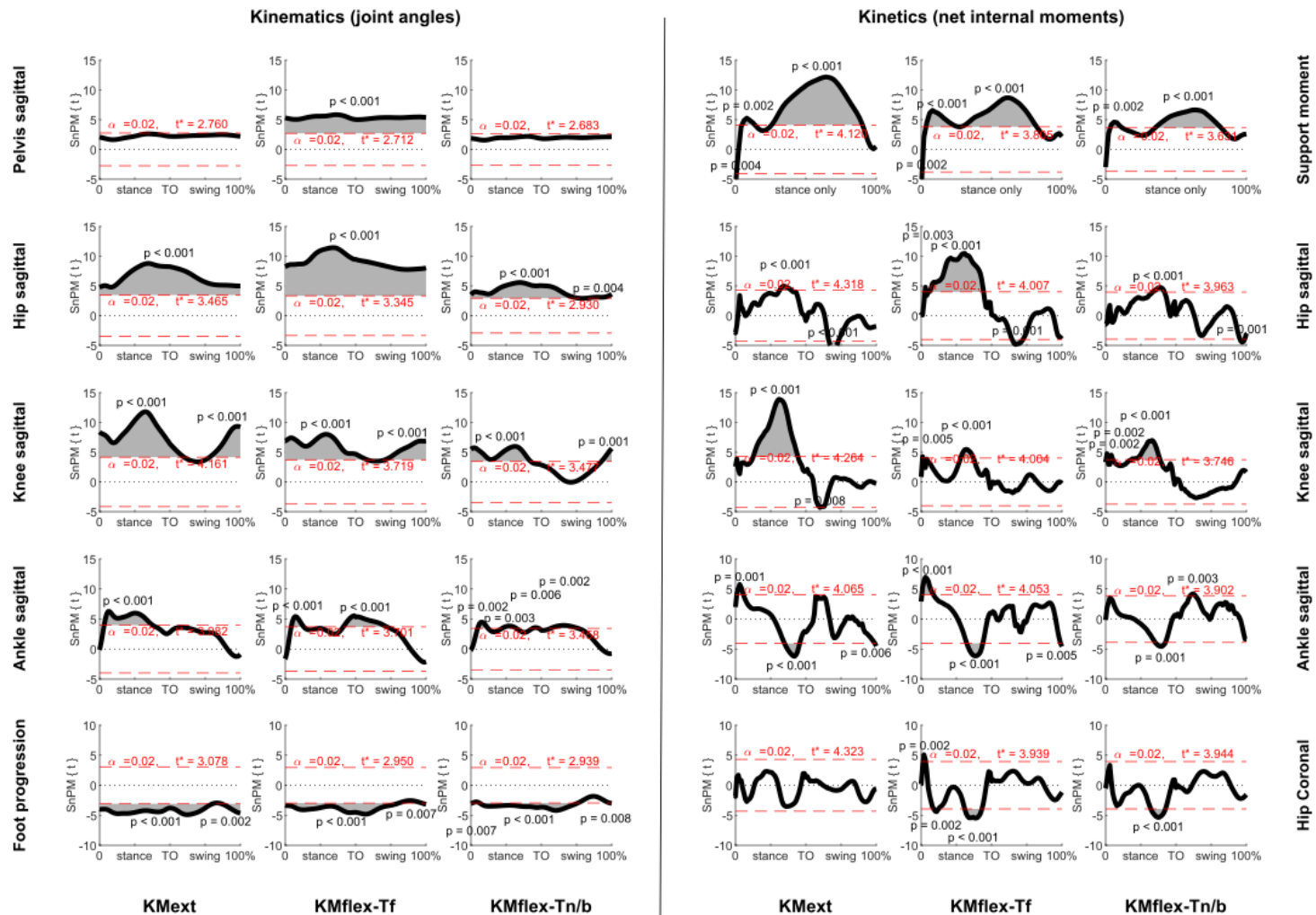


Figure A3: SPM inference curves accompanying figure 3: Comparison of kinematic and kinetic curves between Dravet Syndrome (DS) subgroups and typically developing (TD) controls. The SPM{t} curves of the t test statistics represent the difference between the DS subgroup (KMext, KMflex-Tf or KMflex-Tn/b) and the TD group. Red dashed lines indicate the critical threshold (t^*) for Bonferroni corrected $\alpha = 0.05/3$. Shaded areas with P values are clusters with significant differences. The gait cycle on the x-axis was normalized for stance (50%) and swing (50%) phase, except for the support moment, where only stance phase (100%) was analyzed. TO, toe-off

	Age (years) and gender	BMI	SCN1A mutation type	Nucleotide change	De novo	Age of onset epilepsy (months)	Current epileptic activity	Level of ID	Age of independent walking (months)	Walking distance	FMS
KMflex subgroup	6.4 m	14.3	missense	c.3714A>C	no	11	mild	mild	20	1km-3km	5/5/1
	7.4 m	14.7	frameshift	c. 5536_5539del	yes	4	mild	mild	18	1km-3km	6/6/6
	13.4 f	17.9	nonsense	c.4219C>T	unknown	8	severe	moderate	13	1km-3km	5/5/5
	16.1 f	27.0	missense	c.4294A>G	yes	3	mild	moderate	30	<1km	5/5/1
	17.1 f	29.3	missense	c.4168G>A	yes	4	free	mild	14	>3km	5/5/5
	17.1 m	14.3	missense	c.4223G>T	yes	8	mild	moderate	13	>3km	5/5/4
	19.2 f	23.7	deletion	c.1200_1202delTGA	yes	3	mild	severe	46	<1km	5/4/1
	19.8 m	24.0	missense	c.680T>G	unknown	3	severe	severe	27	<1km	5/5/1
	20.7 m	14.4	frameshift	c.4497delT	yes	6	severe	severe	18	<1km	5/4/1
	24.8 m	19.2	splice site	c.4338+1G>A	yes	5	severe	severe	13	>3km	5/5/4
	25.7 f	28.2	missense	c.1178G>A	yes	6	severe	severe	18	<1km	5/4/4
KMext-Tf subgroup	5.2 m	15.1	missense	c.5735G>C	yes	5	mild	moderate	18	1km-3km	4/4/1
	5.2 f	17.2	missense	c.2836C>T	unknown	4	mild	moderate	37	<1km	5/5/1
	5.6 m	16.3	missense	c.4346T>C	yes	6	mild	moderate	18	<1km	5/4/1
	6.7 m	13.7	nonsense	c.1348C>T	yes	8.5	severe	moderate	18	>3km	5/5/5
	7.2 f	19.7	intragenic deletion	(exon 1-7)	unknown	5	severe	severe	14	<1km	6/6/4
	7.5 m	13.2	missense	c.406T>C	yes	6	free	mild	18	>3km	5/5/5
	8.4 f	19.8	missense	c.1178G>A	yes	4	free	severe	18	<1km	5/5/1
	10.1 f	15.6	missense	c.296T>A	yes	4	mild	severe	36	<1km	5/4/1
	10.6 f	18.0	nonsense	c.1738C>T	yes	5	mild	severe	18	<1km	5/4/1
	10.8 m	13.4	nonsense	c.969T>G	yes	3	free	mild	19	>3km	5/5/5
	14.7 f	23.2	missense	c.4633A>G	yes	11	moderate	severe	unknown	1km-3km	6/6/5

	15.8 m	17.0	missense	c.5150T>C	yes	4	moderate	moderate	20	<1km	5/4/1
	17.0 m	25.7	frameshift	c.550dupT	unknown	8	mild	moderate	unknown	>3km	5/5/5
	22.1 f	26.4	missense	c.2902T>G	yes	11	moderate	severe	15	<1km	5/4/1
KMext-Tr/B subgroup	5.2 m	14.8	missense	c.2791C>T	yes	3	moderate	mild	16	>3km	6/6/6
	5.9 m	14.5	missense	c.301C>T	yes	3.5	free	moderate	16	<1km	5/4/1
	6.8 f	15.6	frameshift	c.4554dupA	yes	6	moderate	moderate	14	>3km	5/5/5
	8.4 m	13.5	nonsense	c.664C>T	yes	7	free	mild	15	>3km	6/6/6
	9.3 f	12.7	missense	c.1178G>A	unknown	4	free	moderate	14	>3km	5/5/5
	9.3 m	12.7	nonsense	c. 2134C>T	yes	5	mild	mild	20	>3km	5/5/5
	10.7 m	16.5	frameshift	c.657_658delAG	yes	6	severe	severe	22	1km-3km	5/5/1
	10.8 f	13.1	frameshift	c.3503dupT	yes	5	moderate	mild	18	>3km	5/5/4
	11.4 m	22.0	missense	c.2791C>T	yes	9	mild	mild	unknown	unknown	unknown
	11.9 f	19.3	frameshift	c.429_430delGT	yes	3	free	mild	15	1km-3km	5/5/4
	17.5 m	17.0	micro-duplication	c.3430-?_4002+?dup	unknown	4	severe	moderate	13	>3km	6/6/5
	17.6 f	27.3	frameshift; splice site	c.[1169InsC]; [1170+1G>A]	yes	4.5	mild	moderate	18	>3km	5/5/5
	19.2 f	26.3	nonsense	c.58C>T	yes	5	mild	moderate	14	>3km	5/5/5
	22.2 f	25.9	missense	c.5534A>C	no	10	moderate	moderate	16	>3km	5/5/4
	24.0 m	18.1	splice site	c.4853-1G>C	yes	7	free	severe	18	>3km	6/6/6
26.1m	15.8	missense	c.680T>C	yes	4.5	free	severe	unknown	1km-3km	6/5/5	

Table A1: Characteristics of individuals in the DS group. BMI = Body Mass Index, ID = Intellectual Disability, FMS = Functional Mobility Scale (5m/50m/500m), m = male, f = female

	KMext (n = 11)	KMflex-Tf (n = 14)	KMflex-Tn/b (n = 16)
	median (IQR)	median (IQR)	median (IQR)
Spatiotemporal parameters			
Walking velocity (m/sec)	1.08 (0.28)	1.04 (0.44)	1.00 (0.31)
Non-dimensional walking velocity	0.366 (0.106)	0.382 (0.159)	0.358 (0.115)
Cadence (steps/sec)	1.92 (0.27)	2.08 (0.53)	2.02 (0.56)
Non-dimensional cadence	0.600 (0.083)	0.599 (0.091)	0.562 (0.084)
Step length (m)	0.51 (0.17)	0.46 (0.11)	0.52 (0.14)
Non-dimensional step length	0.595 (0.156)	0.637 (0.213)	0.659 (0.101)
Step width (m)	0.21 (0.09)	0.17 (0.06)	0.16 (0.03)
Non-dimensional step width	0.221 (0.100)	0.249 (0.107)	0.203 (0.056)
Stance time (%GC)	61.7 (3.2)	60.9 (5.7)	59.6 (3.6)

Table A2: Spatiotemporal parameters did not significantly differ between subgroups. IQR, interquartile range; GC, gait cycle

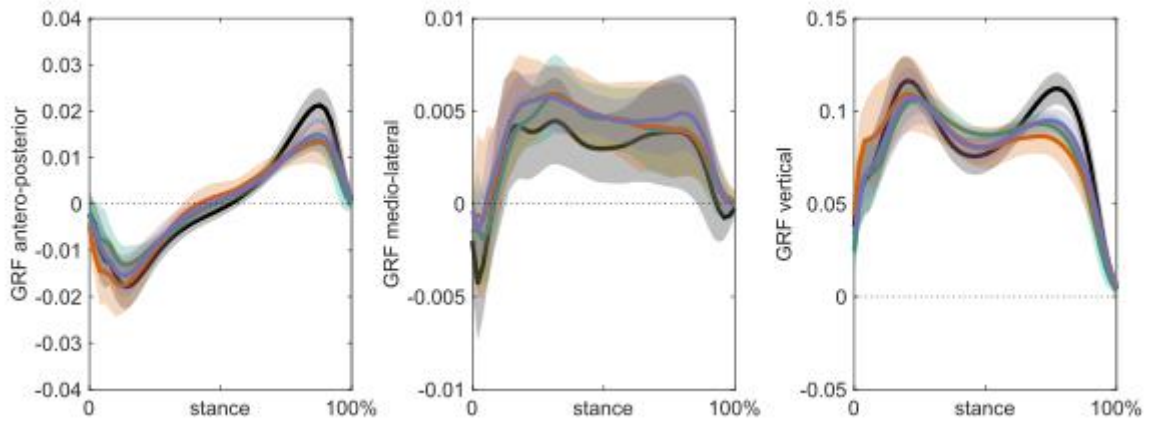


Figure A4: The three components of the ground reaction force (GRF) vector for the three subgroups (colours) and the TD group (black). Normalized for body weight.