ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Functional Abilities in Children and Adults With the CDKL5 Disorder

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Manuscript Received: 19 December 2015; Manuscript Accepted: 17 June 2016

Functional abilities in the CDKL5 disorder have been described as severely impaired, yet some individuals are able to run and use phrases for speech. Our study investigated gross motor, hand function, and expressive communication abilities in individuals with the CDKL5 disorder. Data for 108 females and 16 males registered with the International CDKL5 disorder database and with a pathogenic CDKL5 mutation were analyzed. Relationships between functional abilities, age, genotype, and gender were analyzed using regression models. Over half of the females could sit on the floor and nearly a quarter could walk 10 steps. Fewer males could complete these tasks although one boy was able to sit, walk, and run. Most females and few males were able to pick up a large object. Females mostly used gestures to communicate while males mostly used other forms of non-verbal communication. Compared to those with no functional CDKL5 protein, individuals with truncating variants after aa 781 were more likely to be able to stand (OR 5.7, 95%CI 1.2, 26.6) or walk independently (4.3, 95%CI 0.9, 20.5), and use more advanced communication methods such as words (OR 6.1, 95%CI 1.5–24.2). Although abilities were markedly impaired for the majority with the CDKL5 disorder, some females and a few males had better functional abilities. This variability may be related to underlying gene variants, with females with a late truncating variant having better levels of ability than those with no functional protein. 2016 Wiley Periodicals, Inc.

Key words: functional abilities; genotype; epileptic encephalopathy; CDKL5; disability

How to Cite this Article:
Fehr S, Downs J, Ho G, de Klerk N, Forbes D, Christodoulou J, Williams S, Leonard H. 2016. Functional abilities in children and adults with the CDKL5 disorder.
Am J Med Genet Part A 9999A:1–10.

INTRODUCTION

The CDKL5 disorder is caused by variants in the cyclin-dependent kinase-like 5 (*CDKL5*) gene [Kalscheuer et al., 2003; Weaving et al., 2004a; Fehr et al., 2013]. Clinical features identified to date include early-onset seizures (generally within the first 3 months of life), severe global developmental delay, abnormal muscle tone, hand stereotypies, gastrointestinal problems, and bruxism [Fehr et al., 2013]. Most studies of the CDKL5 disorder have been limited to case studies or small case series and while functional abilities have mostly been described as severely impaired [White et al., 2010; Liang et al., 2011; Olson and Poduri, 2012; Fehr et al., 2013; Hagebeuk et al., 2013], variability in the clinical features has also been reported. It appears that some individuals are less severely affected, in terms of motor abilities and are able to walk [Weaving et al., 2004a; Martínez et al., 2012; Pini et al., 2013] and even run [Bartnik et al., 2011]. Expressive communication seems to be mostly limited to vocalizations and babble [Tao et al., 2004;

Conflict of interest: none.
Grant sponsor: NHMRC; Grant number: #572742; Grant sponsor: NHMRC Senior Research Fellowship; Grant number: #572568; Grant sponsor: International Rett Syndrome Foundation; Grant sponsor: International Foundation for CDKL5 Research.
Abbreviations: CDKL5, cyclin-dependent kinase-like 5; aa, amino acid; OR, odds ratio.
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Article first published online in Wiley Online Library (wileyonlinelibrary.com): 00 Month 2016
DOI 10.1002/ajmg.a.37851

Evans et al., 2005; Nemos et al., 2009; Artuso et al., 2010; Jähn et al., 2013], although some girls are able to use words in phrases [Weaving et al., 2004b; Archer et al., 2006; Martínez et al., 2012]. Hand function has been less well documented [Bahi-Buisson et al., 2008; Bartnik et al., 2011; Martínez et al., 2012; Olson and Poduri, 2012; Hagebeuk et al., 2013; Pini et al., 2013], but would appear to be absent or limited for most [Tao et al., 2004; Evans et al., 2005; Nemos et al., 2009; Artuso et al., 2010; Jähn et al., 2013].

Despite this apparent variability in the functional abilities, there have been no large studies investigating the spectrum. We recently used time to event analysis to investigate specifically the attainment of developmental milestones in the CDKL5 disorder [Fehr et al., 2015]. Approximately two thirds of females and one third of males learned to sit. A quarter of females had attained independent walking by four and a half years but independent walking was rare in males. One in 10 females was able to produce single words by 18 months of age but only one of 18 males acquired use of words [Fehr et al., 2015]. This is the extent of the information available on functional abilities in these and other domains in children and adults of various ages with the CDKL5 disorder and there is limited understanding of any relationship with genotype. There is a need to increase knowledge about this disorder to inform the natural history and guide clinical management. The aim of this study was to describe current functional abilities in detail in individuals with the CDKL5 disorder and to investigate the relationships with genotype, age, and gender.

METHODS

The International CDKL5 Disorder Database was established in 2012 and collects information from caregivers of a child with the CDKL5 disorder in the form of online or paper-based questionnaires. Data collection tools were developed in consultation with a consumer reference group, experienced clinicians, and review of the literature [Fehr et al., 2015]. Caregivers who had previously provided data to the International Rett Syndrome Phenotype Database (InterRett) were recontacted [Fehr et al., 2013] and invited to participate in this new CDKL5 disorder-specific database [Fehr et al., 2015]. Cases were included in this study, if their *CDKL5* variant affected protein function and information on current functional abilities had been provided.

Because of the marked heterogeneity in individual *CDKL5* mutations within our sample, they were grouped according to their predicted structural and functional consequences [Bertani et al., 2006] to investigate the relationship between genotype and functional ability. These groups were (1) variants resulting in no functional protein (including variants causing loss of the functional components in the catalytic domain before amino acid [aa] 172 and full gene deletions); (2) missense/in-frame variants within the catalytic domain (includes any missense variants within the protein's kinase active region or in-frame variants); (3) truncating variants located between aa 172 and aa 781 (includes any variants resulting in a truncation such as nonsense or frameshift variants potentially resulting in maintaining kinase activity but loss of the C-terminal region); and (4) truncating variants occurring after aa 781 (maintains kinase activity and majority of the C-terminal region). All identified variants have been listed [Fehr et al., 2015] and were submitted to RettBASE: http://mecp2.chw.edu.au/cdkl5/cdkl5_variant_list.php. Age was categorized as <1.5 years; >1.5 to <7 years, >7 to <13 years; and >13 years. These age groupings were based on broad expected developmental abilities of children in these age groups.

To investigate gross motor abilities for the children <1.5 years, a modified version of the Chailey Levels of Ability was used for skills in prone and supine lying, floor and stool sitting, and standing [Pountney et al., 1999]. The scale was modified to allow completion by caregivers and we asked them to indicate which of six alternatives best described their child's gross motor ability in each position.

The Rett Syndrome Gross Motor Scale comprises 15 gross motor skills scored on a 4-point scale [Downs et al., 2008] and is suitable for children with a severe disability. For the current study, caregivers were asked to indicate the level of assistance needed by their child. Each item was then coded as needing no assistance; needing some assistance; or unable to complete/needing maximal assistance. The more basic motor skills were described for individuals aged 18 months or older, and the more complex skills of getting up from the floor, bending to touch the floor, and running were described for individuals aged 3 years and older. This avoided children being scored on tasks that were too complex for their chronological age.

Seventeen binary (Yes/No) questions were used to ascertain hand function in relation to skills such as pressing a switch and grasping large and small objects, enabling scoring based on the Rett Syndrome Hand Function Scale [Downs et al., 2010]. The Rett Syndrome Hand Function Scale comprises eight levels ranging from levels 1 (no grasping ability present) to 8 (able to pick up small objects using a precise pincer grip and transfer objects from one hand to the other) [Downs et al., 2010]. If responses were not clearly indicative of a level, further information was sourced from caregiver comments about hand function and the most likely conservative category was assigned. For description and analyses, hand grasping abilities were grouped as follows: none or limited grasping abilities (level 3 or lower); able to grasp a large but not a small object (level 4); and able to grasp both large and small objects (level 5 and higher).

Expressive communication was investigated using questions modeled on two areas of the communication matrix [Rowland and Fried-Oken, 2010]. Caregivers were asked to indicate the methods of communication their child used to convey either refusal or when requesting an object or experience. Communication methods included early sounds (such as laughing, screaming, and grunting), facial expression, body language (such as twisting body away and kicking), simple gestures (such as tapping an item or pushing it away), complex gestures (such as shaking their head and giving back unwanted item), vocalizations (such as "uh uh"), concrete symbols (pictures), single words, signs, and language (more than one word or sign language). Each individual was then assigned to one of the three categories based on their most complex method of expressive communication: (1) no observed or simple methods of communication (body language, early sounds, facial expressions, and simple gestures); (2) complex gestures,

vocalizations, and concrete symbols; and (3) spoken language (single words and more than one), sign language, and abstract symbols. For statistical analysis relating to communication skills those under 2 years were excluded, as it would be less likely for them to have attained language.

Approval for this study was provided by the University of Western Australia Human Research Ethics Committee, Perth, Western Australia, Australia (RA/4/1/5024).

Statistical Analyses

Descriptive statistics were used to explore the distribution of functional abilities across gender, age, and mutation groups. The variables describing sitting on the floor for 10 sec, standing for 20 sec, and walking forward 10 steps were re-categorized as a binary variable (no assistance needed/assistance needed or unable). Logistic regression was used to assess the relationships between these gross motor skills, mutation group, age group, and gender. Multinomial logistic regression was used to assess relationships between the three levels of hand grasping ability and mutation group, age group, and gender. Ordinal logistic regression was used to assess relationships between the three communication levels and mutation group, age group, and gender, with the odds ratio (OR) for each predictor variable being interpreted as the relative odds of an individual having a higher outcome in the functional ability variable.

RESULTS

As of May 2014, there were 124 individuals (57 had previously provided data to InterRett [Fehr et al., 2013]) who were eligible for this study. Of these, 108 (87%) were female (median age 6 years, range 3 months to 29 years) and 16 (13%) were male (median age 5 years 3 months, range 10 months to 22 years 8 months). Data on developmental regression were available for 119 individuals, 25 of whom had previously experienced loss of hand function and/or communication skills. This regression coincided with severe bouts of epilepsy or changes in epilepsy management for 17 (68%) of this group.

Gross Motor Function of Children Aged 1.5 Years and Younger

Eleven girls and one boy were aged 1.5 years or younger and had modified Chailey Levels of Ability scores. For the girls, six were able to roll from supine onto their side or three from prone to supine and back again. In prone lying, eight were able to lift their head and five could take weight through their arms. Eight

TABLE I. Level of Assistance Needed to Undertake Gross Motor Tasks for Females and Males

	Females (n, %)				Males (n, %)			
Gross motor task	No assistance	With assistance	Maximal assistance/ unable	Total number	No assistance	With assistance	Maximal/ unable	Total number
Sitting[a]								
On the floor for 10 sec	65 (67)	9 (9)	23 (24)	97	4 (27)	1 (7)	10 (67)	15
On a chair for 10 sec	51 (54)	18 (19.0)	26 (27)	95	2 (13)	2 (13)	11 (73)	15
On a stool for 10 sec	30 (31)	30 (31)	37 (38)	97	1 (7)	1 (7)	13 (87)	15
Standing[a]								
3 sec	29 (30)	27 (28)	41 (42)	97	1 (7)	1 (7)	12 (86)	14
10 sec	24 (25)	25 (26)	48 (50)	97	1 (7)	1 (7)	12 (86)	14
20 sec	24 (25)	22 (23)	51 (53)	97	1 (7)	2 (13)	12 (80)	15
Transition[a]								
From sitting to standing	20 (21)	21 (22)	56 (58)	97	1 (7)	3 (20)	11 (73)	15
10 steps forward	22 (23)	14 (14)	61 (63)	97	1 (7)	0 (0)	14 (93)	15
Walking[a]								
Side-steps (to step around furniture)	21 (22)	14 (14)	62 (64)	97	1 (7)	0 (0)	14 (93)	15
Able to turn 180°	20 (21)	9 (9)	68 (70)	97	1 (7)	0 (0)	14 (93)	15
Up or down a slope	10 (10)	20 (21)	67 (69)	97	1 (7)	0 (0)	14 (93)	15
Stepping over an obstacle	15 (16)	14 (14)	68 (70)	97	1 (7)	0 (0)	14 (93)	15
Complex transition and running[b]								
From the floor to standing	19 (23)	17 (20)	48 (57)	84	1 (8)	1 (8)	10 (83)	12
Bending to touch floor and returning to standing	17 (20)	6 (7)	61 (73)	84	1 (8)	0 (0)	11 (92)	12
Running	11 (13)	4 (5)	69 (82)	84	1 (8)	0 (0)	11 (92)	12

[a]General gross motor tasks for individuals aged ≥1.5 years (females n = 97, males n = 15).
[b]Complex gross motor tasks for individuals ≥3 years (females n = 84, males n = 12).

could sit on the floor independently and one could sit on a stool and stand independently. The boy could roll from supine to prone, move into 4-point kneeling, and sit on the floor independently. He needed assistance to sit on a stool and balance in standing.

Gross Motor Scores for Individuals Aged Over 1.5 Years

Gross motor data were available for 97 females. Two thirds (n = 65, 67%) could sit on the floor without support, just over half (n = 51, 54%) could sit on a firm backed chair, and almost a third (n = 30, 31%) were able to sit on a stool independently (Table I). A quarter (n = 24) were able to stand for 20 sec, 20 (21%) were able to transition from sitting to standing with no assistance, and 22 (23%) could walk forward 10 steps. For the more complex tasks, nearly a quarter could get up from the floor to standing, 20% could bend over to touch the floor and return to standing, and 13% were reported to be able to run (Table I).

Gross motor data were available for 15 males. Most were unable to perform most tasks although four boys could sit on the floor with no assistance and one could complete all tasks independently (Table I).

Hand Function

Data on hand function were available for 105 females and 16 males. A category of hand grasping could be assigned to all but two of the females (Table II). Overall, 17% of the females had no ability to grasp objects including seven females who were reported only to be able to press a switch. These individuals were classified with individuals who needed assistance to grasp an object (35/105, 34%), as none could grasp an object independently. Otherwise, two thirds could either grasp and pick up a large object (>level 3) (27/103, 26%) or pick up a large or a small object 41% (>level 4) (41/103) (Table II).

Three quarters of the males in the study could not grasp objects, although a quarter could hold an object that was given to them. Otherwise, two could grasp and pick up a large object, and two could pick up small objects also (Table II).

Expressive Communication

Information on expressive communication skills was available for all but two of the females. Most females used a variety of methods to communicate although one was reported only to use facial expressions to communicate and two to have no expressive communication. The most frequently used methods of communication were body language (96%), facial expressions (94%), early sounds (91%), and simple gestures (89%). Over half (63%) used complex gestures, a quarter used single words, signs or abstract symbols (single words n = 9), one fifth used vocalizations, and eight could speak in sentences. After categorization by their most advanced communication method, the best level of communication used by females was spoken language, sign language and abstract symbols (26%), complex gestures, followed by vocalizations and concrete symbols (39%), and simple communication (33%) (Table II).

The males in the study also used multiple modes of expressive communication, although compared to females, fewer used complex gestures and vocalizations and three quarters used simpler communication methods (Table II).

TABLE II. The Distribution of Grasping Skills and Methods of Expressive Communication Methods for Females by Age Group and Males

	Females					Males
Grasping task	**≤1.5 years (n = 11)**	**1.5–7 years (n = 48)**	**7–13 years (n = 30)**	**13 years and over (n = 14)**	**All females (n = 103)**	**Total (n = 16)**
No ability to grasp or needs help to grasp a large object	5 (14.3%)	16 (45%)	9 (25.7%)	5 (14.3%)	35 (34.0%)	12 (75.0)
Can grasp, pick up, and hold at least one type of large object[a]	4 (36%)	16 (33%)	6 (20%)	1 (7%)	27 (26%)	2 (12.5)
Able to grasp a small[b] and a large object	2 (4.9%)	16 (39.0%)	15 (36.6%)	8 (19.5%)	41 (39.8%)	2 (12.5)
Communication method	**≤1.5 years (n = 11)**	**1.5–7 years (n = 49)**	**7–13 years (n = 31)**	**≥13 years (n = 15)**	**Total (n = 106)**	**Total (n = 16)**
No or simple communication	7 (64%)	16 (33%)	8 (26%)	6 (40%)	37 (35%)	12 (75%)
Complex gestures, concrete symbols, and vocalizations	3 (27%)	18 (37%)	15 (49%)	5 (33%)	41 (39%)	4 (25%)
Spoken language, signs, and abstract symbol	1 (9%)	15 (30%)	8 (26%)	4 (27%)	28 (26%)	0 (0%)

[a]A large object could be a cup, eating utensil, small toy, or a small ball.
[b]A small object could be a small piece of food such as a sultana or piece of apricot.

Relationships Between Age, Genotype, Gender, and Current Functional Abilities

Univariate and multivariate analyses for gross motor skills are shown in Tables III and IV. There were no apparent relationships between age and the abilities to sit, stand, or walk in those older than 18 months. Compared to individuals with no functional protein, those with a truncation after aa 781 had three times the odds (OR 3.33, 95%CI 0.56, 16.35) of sitting on the floor, five times the odds (OR 5.66, 95%CI 1.20, 26.64) of independent standing and four times the odds (OR 4.28, 95%CI 0.89, 20.50) of independent walking, taking into account the effects of age and gender. The odds of males being able to sit, stand, or walk were less than for females but this effect reduced when taking into account the effect of mutation group. However, males had 75% less odds (OR 0.25, 95%CI 0.07, 0.96) of being able to sit independently compared with females irrespective of age and mutation group (Tables III and IV).

Univariate and multivariate analyses for hand function skills are shown in Table V. There were no apparent relationships between age group and the ability to grasp large or small objects. In the univariate analysis, those with a truncation between aa 172 and aa 781 had increased odds of being able to hold a large object compared with those with no functional protein. Taking into account the effects of age and gender, significantly increased odds of being able to grasp a large object persisted for those with a truncation between aa 172 and aa 781 (OR 4.58, 95%CI 1.12, 18.75). Males were less likely to be able to grasp a small or a large object in the univariate analyses. Taking into account the effects of age and mutation group, males were more than 80% less likely to be able to grasp a small object (OR 0.19, 95%CI 0.36, 1.00) compared with females (Table V).

Univariate and multivariate analyses for communication skills are shown in Table IV. Again there were no relationships between age group and method of communication in the univariate or multivariate analyses in those older than 2 years. Taking into account the effects of age group and gender and compared to individuals with no functional protein, those with a truncation after aa 781 had 6.06 times (95%CI 1.52–24.18) the odds of using a more advanced form of communication such as use of words. Males were more than 80% less likely than females to be able to use advanced communication methods in the univariate analysis,

TABLE III. Univariate and Multivariate Relationships Between Genotype, Age, Gender, and the Gross Motor Skills of Sitting on the Floor and Standing

		Univariate models		Multivariate models		
	N (%)	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Sitting on floor 10 sec[a]							
No functional protein	35 (34.6)	Baseline		Baseline[b]		Baseline[c]	
Missense/in-frame variant within catalytic region	30 (29.7)	1.50 (0.54, 4.13)	0.432	1.45 (0.51, 4.08)	0.485	1.34 (0.46, 3.92)	0.590
Truncation after aa 172 and before aa 781	23 (22.8)	0.98 (0.34, 2.82)	0.963	0.94 (0.32, 2.80)	0.916	0.74 (0.24, 2.31)	0.607
Truncation after aa 781	13 (12.9)	4.12 (0.79, 21.45)	0.092	4.04 (0.77, 21.15)	0.098	3.33 (0.56, 16.35)	0.198
1.5–7 years	51 (50.5)	Baseline		Baseline[b]		Baseline[c]	
7–13 years	33 (32.7)	1.08 (0.46, 2.56)	0.859	0.97 (0.38, 2.48)	0.946	1.07 (0.40, 2.83)	0.888
13 years and over	17 (16.8)	0.76 (0.26, 2.23)	0.622	0.83 (0.26, 2.68)	0.753	0.81 (0.24, 2.69)	0.730
Female	89 (88.1)	Baseline		–		Baseline[c]	
Male	12 (11.9)	0.18 (0.05, 0.61)	0.006	–	–	0.25 (0.07, 0.96)	0.043
Stand 20 sec[a]							
No functional protein	35 (34.6)	Baseline		Baseline[b]		Baseline[c]	
Missense/in-frame variant within catalytic region	30 (29.7)	1.93 (0.49, 7.65)	0.345	1.98 (0.49, 8.05)	0.340	1.91 (0.46, 7.87)	0.372
Truncation after aa 172 and before aa 781	23 (22.8)	2.74 (0.68, 11.05)	0.158	2.62 (0.63, 10.92)	0.185	2.34 (0.55, 9.98)	0.252
Truncation after aa 781	13 (12.9	6.64 (1.47, 30.00)	0.014	6.51 (1.42, 29.82)	0.016	5.66 (1.20, 26.64)	0.028
1.5–7 years	51 (50.5)	Baseline		Baseline[b]		Baseline[c]	
7–13 years	33 (32.7)	1.88 (0.72, 4.94)	0.200	1.47 (0.50, 4.32)	0.482	1.53 (0.52, 4.56)	0.442
13 years and over	17 (16.8)	0.85 (0.21, 3.47)	0.826	1.07 (0.23, 4.85)	0.932	1.08 (0.23, 4.93)	0.925
Female	89 (88.1)	Baseline		–		Baseline[c]	
Male	12 (11.9)	0.22 (0.03, 1.74)	0.150	–	–	0.42 (0.05, 3.66)	0.431

[a]Restricted to individuals 18 months or older, n = 101;
[b]Adjusted for age or mutation group;
[c]Adjusted for age group, mutation group, and gender.

TABLE IV. Univariate and Multivariate Relationships Between Genotype, Age, Gender, and the Gross Motor Skill of Walking and Communication Method

	Univariate models			Multivariate models			
	N (%)	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Walk 10 steps[a]							
No functional protein	35 (34.6)	Baseline		Baseline[c]		Baseline[d]	
Missense/in-frame variant within catalytic region	30 (29.7)	1.94 (0.49, 7.65)	0.345	1.96 (0.48, 7.97)	0.348	1.89 (0.46, 7.80)	0.378
Truncation after aa 172 and before aa 781	23 (22.8)	2.15 (0.51, 9.06)	0.296	2.16 (0.50, 9.36)	0.305	1.95 (0.44, 8.66)	0.381
Truncation after aa 781	13 (12.9)	4.84 (1.05, 22.31)	0.043	4.85 (1.04, 22.63)	0.045	4.28 (0.89, 20.50)	0.069
1.5–7 years	51 (50.5)	Baseline		Baseline[c]		Baseline[d]	
7–13 years	33 (32.7)	1.42 (0.52, 3.87)	0.488	1.06 (0.35, 3.25)	0.917	1.10 (0.36, 3.41)	0.866
13 years and over	17 (16.8)	0.85 (0.21, 3.47)	0.826	1.05 (0.24, 4.72)	0.945	1.06 (0.24, 4.80)	0.937
Female	89 (88.1)	Baseline		–		Baseline[d]	
Male	12 (11.9)	0.24 (0.03, 1.96)	0.184	–	–	0.45 (0.05, 3.95)	0.474
Communication[b]							
No functional protein	31 (33.7)	Baseline		Baseline[c]		Baseline[d]	
Missense/in-frame variant within catalytic region	27 (29.4)	1.41 (0.53, 3.76)	0.448	1.41 (0.52, 3.86)	0.497	1.20 (0.42, 3.39)	0.737
Truncation after aa 172 and before aa 781	22 (23.9)	1.26 (0.44, 3.57)	0.768	1.26 (0.43, 3.64)	0.675	0.8 (0.29, 2.70)	0.829
Truncation after aa 781	12 (13.0)	8.69 (2.30, 32.90)	0.002	8.68 (2.26, 33.38)	0.002	6.06 (1.52, 24.18)	0.011
1.5–7 years	43 (46.7)	Baseline		Baseline[c]		Baseline[d]	
7–13 years	33 (35.9)	1.04 (0.48, 2.29)	0.912	1.04 (0.44, 2.46)	0.928	1.08 (0.44, 2.60)	0.871
13 years and over	16 (17.4)	0.75 (0.26, 2.13)	0.591	1.00 (0.32, 3.17)	0.997	0.91 (0.28, 2.93)	0.870
Female	80 (87.0)	Baseline		Baseline		Baseline[d]	
Male	12 (13.0)	0.16 (0.05, 0.53)	0.003	–	–	0.17 (0.04, 0.71)	0.015

[a]Restricted to individuals 18 months or older, n = 101;
[b]Restricted to individuals 2 years and older, n = 92;
[c]Adjusted for age or mutation group;
[d]Adjusted for age group, mutation group, and gender.

and this strong effect persisted after taking into account the effects of age and mutation group (OR 0.17, 95%CI 0.04, 0.71) (Table IV).

DISCUSSION

For most individuals with the CDKL5 disorder, functional abilities were severely impaired, although there was variability. Most of the youngest children in our study had difficulty with early mobility skills such as rolling, crawling, and standing. For those who were older than 18 months, age had little effect on functional abilities, but gross motor and communication skills were more severely affected in males. Independent standing and walking as well as more advanced communication skills were more likely in those with a truncation after aa 781 in comparison to those with no functional protein in the gene. This is the first paper to identify this pattern for relationships between genotype and phenotype in the CDKL5 disorder.

Our database has already provided information on the acquisition of developmental milestones where we found that two thirds of females learned to sit and 29% learned to walk [Fehr et al., 2015]. We now report functional abilities current at the time of ascertainment to the database where 23% were walking independently, 8% used single words, and 7% used sentences. In a previous small French case series (n = 20) [Bahi-Buisson et al., 2008], one female (5%) was able to walk independently, five (25%) were able to transfer an object from one hand to the other, five could use babble or single words (25%), and one girl could speak in sentences (5%) [Bahi-Buisson et al., 2008]. In terms of a milder phenotype, Archer et al. [2006] described a young woman who could walk and swim independently, feed herself using cutlery, and speak in phrases. More recently, a Spanish study reported on eight females of whom three learned to walk, four had some hand use, and two could speak using phrases [Martínez et al., 2012], but the pathogenicity of variants affecting two of these cases has not been confirmed [Ho et al., 2012; Diebold et al., 2014]. Reports of males with the CDKL5 disorder are rare, but in the largest previous study (n = 8) all boys had markedly impaired gross motor and communication skills [Mirzaa et al., 2013]. We also found that males were generally more severely affected than females although one male was able to run. Our findings support the thesis that a greater spectrum of functional abilities exists in the CDKL5 disorder than previously

TABLE V. Univariate and Multivariate Relationships Between Genotype, Age, Gender, and Hand Function (n = 109)

	No independent grasp	Able to grasp, pick up, and hold a large object					Able to grasp, pick up, and hold a small object				
			Univariate		Multivariate[a]			Univariate		Multivariate[a]	
	n (%)	n (%)	OR (95%CI)	*P* value	OR (95%CI)	*P* value	n (%)	OR (95%CI)	*P* value	OR (95%CI)	*P* value
No functional protein	20 (50)	5 (13)		Baseline			15 (37)		Baseline		
Missense/in-frame variant within catalytic region	10 (32)	10 (32)	4.00 (1.07, 14.89)	0.039	3.36 (0.85,13.28)	0.084	11 (36)	1.47 (0.49, 4.35)	0.490	1.42 (0.45,4.52)	0.548
Truncation after aa 172 and before aa 781	8 (32)	11 (44)	5.50 (1.44, 20.96)	0.013	4.58 (1.12,18.75)	0.034	6 (24)	1.00 (0.28, 3.50)	1.000	0.77 (0.20,2.89)	0.698
Truncation after aa 781	3 (23)	3 (23)	4.00 (0.61, 26.12)	0.148	2.97 (0.43,20.74)	0.271	7 (54)	3.11 (0.69,14.07)	0.140	2.34 (0.49,11.27)	0.289
Below 1.5 years	5 (42)	4 (33)		Baseline			3 (25)		Baseline		
1.5–7 years	17 (35)	17 (35)	1.25 (0.28, 5.47)	0.767	1.06 (0.22,5.21)	0.939	15 (30)	1.47 (0.30, 7.22)	0.635	1.36 (0.26,7.07)	0.715
7–13 years	12 (37)	7 (22)	0.73 (0.14, 3.65)	0.701	0.58 (0.10,3.31)	0.543	13 (41)	1.80 (0.35, 9.24)	0.478	1.93 (0.35,10.69)	0.450
13 years and over	7 (44)	1 (6)	0.18 (0.02, 2.12)	0.172	0.20 (0.02,2.64)	0.225	8 (50)	1.90 (0.33,11.01)	0.472	2.04 (0.34,12.39)	0.440
Female	32 (33)	27 (28)	Baseline				37 (39)		Baseline		
Male	9 (69)	2 (15)	0.26 (0.05, 1.32)	0.106	0.41 (0.07,2.30)	0.308	2 (15)	0.19 (0.04, 0.96)	0.044	0.19 (0.36, 1.00)	0.051

OR, odds ratio; CI, confidence interval.

[a]Effect of mutation group adjusted for age group and gender, effect of age group adjusted for mutation group and gender, effect of gender adjusted for mutation group and age group.

described and that males are usually more severely affected than females.

Investigating genotype–phenotype relationship in the CDKL5 disorder is challenging because of the abundance of unique variants [Bahi-Buisson et al., 2012] evident even in the current study with data on 124 confirmed cases included in the analyses [Fehr et al., 2015]. By grouping the variants, we found that those with a truncation after aa 781 were more likely to be able to stand or walk independently and had better expressive communication abilities than those with no functional protein. Only one other study has specifically examined genotype–phenotype relationships (n = 26, range per variant 1–5) [Bahi-Buisson et al., 2012]. In this study, the missense variant p. Ala40Val (n = 5) and the C-terminal nonsense variant p. Arg550* (n = 3) were associated with a milder phenotype, whereas the C-terminal frameshift variant c.2635_2636delCT (n = 3) was associated with a more severe phenotype. Our current study included two individuals with this latter variant of whom one could walk independently and the other could not. For our analyses, these individuals were grouped with others who also had a mutation in the C-terminal region (the truncation after aa 781 group), resulting in a much larger sample and greater potential to reduce sampling error. This mutation group was associated with better functional abilities across the gross motor and communication domains. Otherwise, we found that those with a truncation between aa 172 and aa 781 rather than those with a truncation after aa 781 were more likely to be able to pick up large object than those with no functional protein, although this apparent protective effect did not extend to more advanced hand function skills. Clearly, the impacts that different variants have on protein function and phenotype needs to be further investigated with even larger studies. However, we are the first to have described the findings that together suggest that those with a truncation after aa 781 are more mildly affected.

Severe developmental delay is a cardinal feature of the CDKL5 disorder [Fehr et al., 2013] and the gross motor impacts of the CDKL5 disorder would generally be considered more severe than for other disorders such as Rett syndrome. In a sample of 293 individuals with Rett syndrome, more than 90% learned to sit and nearly half (46%) learned to walk during early childhood [Fehr et al., 2011]. Gross motor skills in 99 females with Rett syndrome were then observed using video taken at a median age of 14 years 1 month [Downs et al., 2008]. Compared with Rett syndrome, fewer females with the CDKL5 disorder were able to sit on the floor (67% vs. 76%), stand for 20 sec (25% vs. 30%), and walk 10 steps forward with no assistance (23% vs. 43%). During early childhood, the likelihood of acquiring the ability to sit or walk was much higher for females with Rett syndrome than for females with the CDKL5 disorder. However, we have demonstrated that the ability to sit on the floor declined in 21% of 70 individuals over a 3 to 4-year period [Foley et al., 2011], and using longitudinal data on 363 individuals followed for up to 20 years, a proportion experienced deterioration in walking from independent or assisted walking to being unable to walk (n = 55, 15%) [Downs et al., 2016]. Sitting and walking skills can decline over time with any neurodevelopmental disability due to factors such as epilepsy, the development of deformity and general deconditioning, and the median age of the Rett syndrome cohort was older than for females with the CDKL5 disorder (median age 5 years) in the current study. We acknowledge that we did not see a relationship between gross motor skills and age but further follow up of individuals with the CDKL5 disorder would be important to understand the trajectories of gross motor skills.

In contrast to gross motor skills, hand grasping appeared stronger in the CDKL5 disorder, with a higher proportion of females able to grasp objects (83%) compared to those with Rett syndrome (70%, n = 144, median age 14 years 10 months) [Downs et al., 2010]. Loss of hand skills during a period of regression typically occurs in Rett syndrome (89%) [Fehr et al., 2010] and is a component of the diagnostic criteria [Neul et al., 2010]. Regression is less common in the CDKL5 disorder [Fehr et al., 2013] and could explain the better level of hand grasping skill. We previously found that the majority of those with the CDKL5 disorder did not meet the diagnostic criteria for Rett syndrome [Fehr et al., 2013]. Our current findings provide additional detail as to the differences in functional abilities between the two conditions.

It has been suggested that *CDKL5* variants cause early-onset infantile epileptic encephalopathy [Liang et al., 2011; Melani et al., 2011], implying that the epileptic activity contributes to the severe cognitive and behavioral impairment, "above and beyond that expected from the underlying pathology alone" [Berg et al., 2010]. The developmental processes occurring at the time are thought to influence the impacts of seizures [Nardou et al., 2013], with early-onset frequent seizures having the greatest impact on cognition [Vasconcellos et al., 2001]. Spontaneous seizures were not present in the first CDKL5 disorder mouse model, however, autistic-like behaviors and motor impairments were [Wang et al., 2012]. Therefore, these features may be a result of the underlying genetic abnormality rather than the seizures. It would be of interest to further investigate the factors associated with the severity of the functional phenotype and whether they relate to early seizure activity.

Our study included the largest number of individuals with the CDKL5 disorder reported to date, providing a better opportunity to capture the spectrum of clinical presentations. Only a small proportion of individuals in the current study experienced regression of hand and/or communication skills, a mandatory criterion for atypical Rett syndrome including the early seizure variant. We confirm that the CDKL5 disorder is an independent clinical entity [Fehr et al., 2013]. The International CDKL5 Disorder Database, used in this study, is the only global data collection developed specifically to collect comprehensive information on this disorder. Most previous studies have reported findings in the context of the CDKL5 disorder being part of the Rett syndrome spectrum, and mainly comprised individual case studies. Even our earlier study [Fehr et al., 2013] was primarily developed to collect information on Rett syndrome [Fyfe et al., 2003]. Therefore, we acknowledge that some of the measures we used in the current study were originally designed for Rett syndrome, but they are generally applicable to individuals with severe functional impairments allowing comparison across conditions. Our questionnaire was grounded in the expressed views of our consumer reference group who argued that detailed description of motor skills was critical to

understanding their child's condition. We acknowledge that our grouping of individual mutations may not be optimal and that future criteria for grouping may become evident with time. As the first comprehensive description of functional abilities, our study is based on parent-report data, with its use supported by previous findings that parent report of functional abilities is likely to be accurate [Bodnarchuk and Eaton, 2004; Harvey et al., 2010]. We coded data into broader categories which would be relatively crude but would have more validity. Therefore, we believe that we have captured some of the true variability present in the CDKL5 disorder. Planned future video data collection will assist in confirming our findings and where possible collection of clinical data. It is also likely that we may have an over-representation of families from higher socio-economic backgrounds because of the requirement for genetic testing to confirm the diagnosis. Although our study is the largest to date, the genetic heterogeneity still limits the power to identify genotype–phenotype relationships and therefore even greater numbers are needed.

In summary, we have provided information on functional abilities in the largest sample of individuals with the CDKL5 disorder to date. In doing so, we have confirmed that males are more severely impaired than females and found that there is little variation in skills with age. Our findings also highlight the variability within this disorder and particularly that milder developmental impairments may be associated with later truncations in the *CDKL5* gene. More research with regard to the effects of genotype and epilepsy are needed.

ACKNOWLEDGMENTS

The authors would like to acknowledge the families and caregivers who have participated in the International CDKL5 Disorder Database by completing questionnaires on their child. The authors would also like to thank the International Foundation for CDKL5 Research for their ongoing support and assistance and Dr Alison Anderson for her assistance in establishing and designing the database infrastructure. SF received an Australian Postgraduate Award, University of Western Australia Safety-Net Top-Up Scholarship, the Stan and Jean Perron Top-Up Scholarship, and the Stan and Jean Perron Award for Excellence. Data collection was also supported by an NHMRC Program Grant #572742 (Dr. Jenny Downs) and NHMRC Senior Research Fellowship #572568 (Dr. Helen Leonard). Dr Ho was supported by an International Rett Syndrome Foundation database support grant.

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