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Developmental and Behavioral Characteristics of Individuals With Pallister–Killian Syndrome

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Pallister–Killian syndrome is a sporadic disorder caused by the presence of mosaic tetrasomy of the short arms of chromosome 12. Case reports of children with Pallister–Killian syndrome have described a range of developmental and behavioral outcomes, but no systematic studies of these outcomes exist. The objective of this study was to describe developmental and behavioral characteristics of individuals with Pallister–Killian syndrome participating in a national meeting of families and their affected children. Sixteen individuals with Pallister–Killian syndrome, ages 16 months to 19 years, were studied using questionnaires and direct interview. Among the 16 patients enrolled in the study, 3 probands were between 16 and 19 months, and had severe developmental delay. Among the rest of the 13 probands older than 24 months, 11 children had a developmental level of less than 8 months age equivalent. They were non-ambulatory, non-verbal, and passive, requiring extensive assistance in daily living. There were two higher functioning children who were ambulatory, and verbal. One of these children met criteria for Autism on the Autism Diagnostic Interview-Revised. Thus, although most individuals with Pallister–Killian syndrome studied showed profound intellectual disability and sensory impairments, individuals with Pallister–Killian syndrome can have mild to moderate intellectual disability. Therefore, in individuals with physical examination findings of Pallister–Killian syndrome, formal diagnostic testing should be considered, even in individuals with mild to moderate intellectual disability. Further studies will be needed to determine if these higher functioning children with Pallister–Killian syndrome are at increased risk for autism.

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INTRODUCTION

Pallister–Killian syndrome (PKS) is a sporadic disorder most commonly caused by the presence of mosaic tetrasomy of the short arm of chromosome 12 [Peltomaki et al., 1987; Warburton et al., 1987]. This results in a variety of congenital abnormalities including facial features consisting of a high forehead, fronto-temporal alopecia, hypertelorism, hypotonia, streaks of hypo, and/or hyper-pigmented skin, seizures and psychomotor delay [Schinzel, 1991]. Additional reported congenital anomalies include diaphragmatic hernias [Bergoffen et al., 1993], oculoretinal changes [Birch et al., 1995; Graham et al., 1999], midface malformations, including cleft palate, macroglossia, prognathism [Horneff et al., 1993; Genevieve et al., 2003], and hearing loss [Bielanska et al., 1996].

The existing literature describes cytogenetic and molecular characteristics of PKS in detail [Reynolds et al., 1987; Mathieu et al., 1997; Leube et al., 2003], but there are limited developmental and behavioral features beyond noting severe psychomotor delay. There are case reports of individuals with PKS, who are higher functioning, having only mild speech and developmental delays and attending regular schools, suggesting the possibility that the spectrum of neuro-cognitive phenotype of PKS might be wider than

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that previously thought [Warburton et al., 1987; Bielanska et al., 1996; Schaefer et al., 1997; Genevieve et al., 2003; Stalker et al., 2006]. The purpose of this article is to describe the range of developmental and behavioral phenotype seen in a cohort of PKS probands ascertained at a PKS family support group meeting to further advance the understanding of its neuro-cognitive spectrum.

METHODS

Patients

The participants of this study were recruited from families attending the first "Face to Face" PKS Conference in Philadelphia, Pennsylvania, USA in July 2006. A detailed description of the medical history and demographics of all participants except Case 16 can be found in Wilkens et al. [2012]. Case 16 is not described in Wilkens et al. as genetic testing showed a marker chromosome with additional 12p and "additional genetic material" attached to the long arm of the marker chromosome that was not specifically identified at the time of testing. The study was approved by the Institutional Review Board of The Children's Hospital of Philadelphia. Informed consent was obtained from the caregivers of all participating individuals.

Developmental and Behavioral Evaluation

Families of the participants filled out developmental and behavioral questionnaires including the Aberrant Behavior Checklist (ABC), the Modified Checklist for Autism in Toddlers (M-CHAT), and/or the Social Communication Questionnaire (SCQ). The details of these questionnaires are described in Supplementary Table I (see Supporting Information online). During the meeting, using the following instruments: The Vineland-II Adaptive Behavior Scales were administered by directly interviewing each caregiver. Direct assessments of each child's adaptive, fine motor, gross motor, language, and personal-social skills were conducted using the Revised Gesell Developmental Schedules for children whose skills were less than 24 months. The Preschool Language Scale 4 (PLS4), the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI), and the Kaufman Brief Intelligence Test Second Edition (KBIT-2) were administered to those participants who had a developmental age of at least 24 months. For children scoring "at risk" for social skills delay on the M-CHAT or SCQ and who had a developmental age of 18 months or greater, telephone interview using the Autism Diagnostic Interview-Revised (ADI-R) was performed. Detailed description of these interview and assessment instruments can be found in Supplementary Table I (see Supporting Information online). The results from previous developmental and psychological evaluations, as well as pertinent medical history were also included in the data analysis.

RESULTS

Patient Characteristics

Sixteen children, 10 males and 6 females, ages 16 months to 19 years were eligible for the study, based on a documented diagnosis of PKS by genetic testing. Diagnoses were made by skin biopsy in 11 cases, by chromosome analysis of peripheral blood in four cases, and by chromosome analysis from amniocentesis in one case (Table I). The degree of mosaicism in skin fibroblast ranged from 5% to 100%.

Developmental Skills

Of the 16 participants, 14 individuals, whose age ranged from 16 months to 19 years, were non-verbal and non-ambulatory. Their skills assessment based on parental reports on Vineland interview and direct observation showed gross motor skills and fine motor skills at or below 7 months age equivalent (Table II). All of these 14 individuals had hypotonia, were unable to bear weight and needed to be supported in a sitting position. They had almost no purposeful

TABLE I. Age, Gender, and Chromosomal Abnormality

ID number	Age	Gender	Chromosomal abnormality: degree of tetrasomy 12p mosaicism.
1	6y7m	F	0% of peripheral lymphocytes at birth, mosaicism on skin biopsy
2	5y4m	F	36% of buccal cells, CGH positive for amplification of 12p signal, positive skin fibroblast testing
14	1y4m	F	Normal peripheral blood karyotype at birth, 5% of skin fibroblasts
10	1y6m	M	80% of skin fibroblasts
15	1y7m	M	66% of amniocytes
3	2y3m	M	18% of peripheral lymphocytes
4	2y3m	F	15% of peripheral lymphocytes
12	2y3m	M	Normal peripheral blood karyotype, 86% of skin fibroblasts
6	2y6m	M	2% of peripheral lymphocytes
16	2y7m	F	Positive skin biopsy with "additional genetic material"
13	2y9m	M	Normal peripheral blood karyotype at birth, 90% of skin fibroblasts
7	3y2m	M	Diagnosed from buccal smear, confirmed by skin biopsy
8	4y7m	M	0% of peripheral lymphocytes at 1 month, 100% of skin fibroblasts
11	6y11m	M	Normal peripheral blood karyotype, positive skin biopsy
9	9y11m	M	Present in blood and skin, no percentage given
5	19y8m	F	100% of skin fibroblasts

TABLE II. Vineland II and Aberrant Behavioral Checklist Results

		Vineland-II adaptive behavior scales							Aberrant behavioral checklist						
ID number	Age	Gender	Gross motor skills	Fine motor skills	Language receptive	Language expressive	Daily living skills	Play skills	Tactile defensiveness	Self-injurious behavior	Irritability	Lethargy	Stereotypy	Hyper-activity	Inappropriate speech
1	6y7m	F	19	25	23	21	19	12	None	None	*	—	***	—	—
2	5y4m	F	20	28	34	42	20	9	None	None	—	—	*	*	*
14	1y4m	F	4	7	8	9	4	10	Yes	None	*	**	***	—	N/A
10	1y 6m	M	5	4	3	4	5	<1	Yes	None	*	**	***	**	N/A
15	1y7m	M	4	1	<1	4	5	4	None	None	—	***	**	**	N/A
3	2y3m	M	1	3	<1	2	6	4	None	None	—	**	**	—	N/A
4	2y3m	F	4	4	9	9	7	6	Yes	None	—	*	—	—	N/A
12	2y3m	M	7	5	<1	7	6	6	None	—	—	—	—	—	N/A
6	2y6m	M	3	4	3	8	5	7	Yes	None	—	—	—	—	N/A
16	2y7m	F	6	6	6	6	7	6	None	None	—	*	**	—	N/A
13	2y9m	M	3	1	<1	3	4	4	Yes	None	*	***	***	**	N/A
7	3y2m	M	5	1	8	10	4	9	Yes	Hand biting	**	***	***	—	N/A
8	4y7m	M	6	4	<1	3	9	2	None	None	***	***	***	***	N/A
11	6y11m	M	6	5	<1	8	1	7	Yes	Hand biting	—	**	**	*	N/A
9	9y11m	M	7	6	<1	8	1	9	None	Hand biting	***	**	***	***	N/A
5	19y8m	F	3	4	<1	8	4	4	Yes	Hand biting	***	***	***	***	N/A
			Total	8/16	4/16	3/16	5/16	8/16	3/16						

*, mild; **, moderate; ***, severe; N/A, not applicable.
Numbers are months of the age equivalents.

movements of their hands. However, one 9-year 11-month-old male (case 9) was able to hold a cup and drink through a straw, and one 3-year 2-month-old female (case 16) was able to feed herself with her fingers.

Language skills in these 14 children were below 9 months age equivalent. These children had little to no communicative intent. They did not use words, word approximations or gestures. Parents reported recognizing different vocalizations that signaled different needs. The highest developmental quotient of 50 was achieved by the youngest participant; age 16 months (case 10). In addition, tactile defensiveness was noticed in 50% of the participants. The children withdrew their hands when examiners attempted to place a toy or other object in them. Similarly they withdrew their feet from touching the ground. Among the 16 individuals in the study, two participants who had relatively higher level of functioning will be described below.

Proband 1 was a 6-year 7-month-old female, whose tetrasomy 12p was not detected in blood but was found on skin biopsy at 21 months (Fig. 1A,B). Her Gross Motor Skills and Daily Living Skills were at 24 months age equivalent, according to parental report on the Vineland-II adaptive behavior scale. She started walking at 4 years of age. She was able to feed herself and dress with help. She was not toilet trained. On the Preschool Language Scale 4 the auditory comprehension and on both the auditory comprehension and expressive language sections, she received standard scores below 50, and age equivalent of 21 months. She was using approximately 20 words and gestures for communication. The Social Communication Questionnaire (SCQ) score did not indicate risk for autism spectrum disorder. She had good eye contact and social skills appropriate to her developmental age. She had a history of a single febrile seizure, strabismus, nystagmus, and normal hearing.

Proband 2 was a 5-year 4-month-old female, who was diagnosed with PKS at 4 years and 5 months of age by comparative genomic hybridization (CGH) testing with tetrasomy 12p detected in 36 percent of buccal cells and confirmed in skin fibroblasts (Fig. 1C,D). Her gross motor skills and daily living skills were at 24 months age equivalent, according to parental report on the Vineland-II

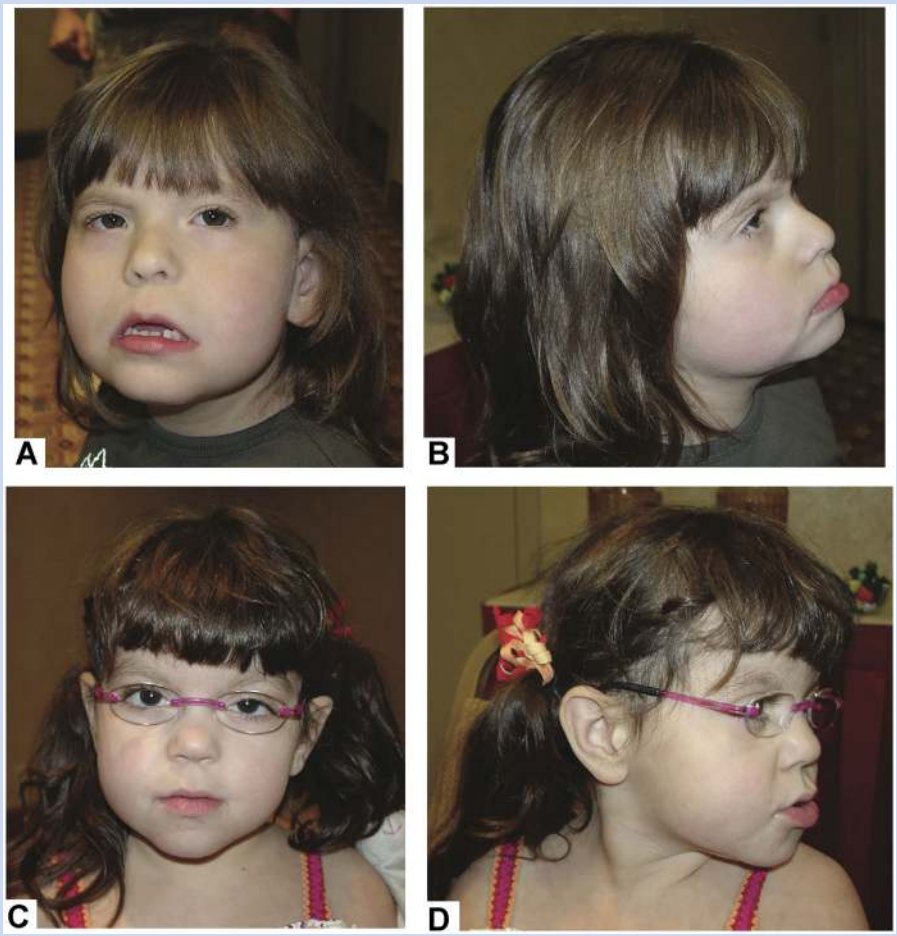

FIG. 1. Facial features of proband 1 (A,B) and proband 2 (C,D). The facial features characteristic of PKS are present in both children but more pronounced in proband 1 and include widely spaced eyes, short nose long philtrum with extension of philtral skin into the vermillion border of the upper lip, eversion of lower lip and prominent (or "droopy" appearing) cheeks.

Adaptive Behaivor Scales. She was able to walk and climb stairs. Her language evaluation, based on the Preschool Language Scale 4 showed at the chronological age of 4 years and 11 months, showed in auditory comprehension standard score of 81 (3 years and 9 months age equivalent) and in expressive communication standard score of 70 (3 years and 3 months age equivalent). She was able to speak in two to four word sentences, recognize letters and numbers. Her speech was characterized by rote patterns with limited voice modulation. She was able to follow two-step commands consistently. On the Kaufman Brief Intelligence Test 2, her IQ composite score was 69 (vocabulary standard score 85, matrices standard score of 59). On VMI, her standard score was 67 (2 years and 11 months age equivalent). On the Social Communication Questionnaire her score indicated concern for an autistic spectrum disorder. Autism Diagnostic Interview, Revised supported a diagnosis of autism.

Vision and Hearing Impairment

Twelve of 16 children (75%) had varying degrees of hearing impairment: two conductive, four mixed, and six sensorineural hearing loss. Twelve of 16 children (75%) had visual impairment including strabismus, nystagmus or myopia; and three (19%) were legally blind.

Behavioral Characteristics

The behavioral survey was conducted using the Aberrant Behavior Checklist (Table II). The questionnaire consists of five subscales: irritability (including self-injurious behavior), lethargy, stereotypy, hyperactivity, and inappropriate speech. Repetitive hand and body movements were noticed in 12 participants (75%). Self-injurious behavior, such as hand or finger biting and head banging were reported in 4 individuals (25%). Eleven of the children (68%) were reported as "lethargic and withdrawn" and five (31%) were "drowsy during daily activities". Child's sleep habits questionnaires were available for 15 subjects. Sleep problems were reported in five children: four reports of waking up at night and one of sleep apnea. Subjects tended to sleep long hours (range from 9.5 to 15 hr per day) and four of five subjects over the age of 5 reported usually taking naps (naps in younger children considered normal).

DISCUSSION

Here we describe behavioral and neuro-cognitive features of PKS and confirm the previous notion that PKS is usually associated with profound intellectual disability and sensory impairments, as evidenced by the majority of the subjects older than 2 years being diagnosed with severe developmental delay/intellectual disability. In younger patients, three children ages 16–19 months had significant developmental delays. The developmental trajectory of these youngest participants cannot be predicted with certainty, although a significant degree of cognitive impairment is anticipated.

However, there were two patients who showed relatively mild to moderate intellectual disability. A similar range of cognitive skills in individuals with PKS has been reported in the literature [Warburton et al., 1987; Bielanska et al., 1996; Schaefer et al., 1997; Genevieve et al., 2003; Stalker et al., 2006]. Since the diagnosis often depends on a skin biopsy, it is possible, that PKS is under diagnosed among individuals with milder phenotypes. There have been at least five cases reported in the literature of individuals with PKS showing only mild developmental disability (Table III), supporting the notion that individuals with PKS could present with mild neurocognitive phenotype. Therefore, we recommend that the diagnosis of PKS be considered in individuals with clinical features of PKS even in the presence of mild to moderate developmental delay/intellectual disability. The underlying mechanism of such wide phenotypic spectrum remains unknown, but could be related to the level of mosaicism, to differential expression in brain tissue or differential effects on the cellular processes involved in brain development. Unfortunately, our study did not provide an opportunity to test whether there is an association between the degree of behavioral findings and level of mosaicism, due to the variation of the age when the diagnosis of PKS was made and the use of different tissues for the identification of isochromosome 12p.

The behavioral concerns reported in the majority of the participants were lethargy and withdrawal. Such lethargy could also contribute to developmental delays, and impede developmental progress. The lower functioning children with PKS were very passive, appeared drowsy, and had extremely limited communicative intent. Their lack of internal drive to explore their surroundings might be partially explained by their visual and hearing impairments, but was not improved by compensation with corrective lenses or hearing aides. Hypotonia and the tactile defensiveness noted in many children might also explain this lack of ability and desire to explore their environment. Autism could also explain a lack of engagement with the environment, but is difficult to assess in individuals with such severe cognitive impairment. Not noted in the literature previously was the tactile defensiveness seen in 50% of study participants. Such defensiveness may further impede developmental progression, since children need to tolerate touching and manipulating objects in order to learn from them, and need to bear weight on their feet on a variety of surfaces and textures in order to walk.

In a group of individuals with this severe degree of cognitive disability, we found direct observation of skills and the Vineland's semi-structured interview more useful than more standard IQ testing. With standard tools most individuals would not achieve a basal score, and no appreciation for the quality of skills that they do display would be possible. In addition, compared to a standard score, age-equivalents can better chart the developmental progress the individual makes across time. The age equivalent estimate of the Vineland can be also useful to assess effectiveness of therapies [Williams et al., 2006].

This study has implications for early intervention. The inability to sit upright should not be allowed to interfere the acquisition of other skills. Appropriate supportive seating for infants and toddlers should be provided in order to maximize the child's ability to fully take part in their environment, and to aid with the development of fine motor and feeding skills. Also, the tactile defensiveness should be addressed with appropriate sensory activities. If autism is identified, then appropriate support for communication, social skills and play development needs to be provided in addition to other therapies.

TABLE III. Characteristics of Higher Functioning Individuals With PKS in This Study and in the Literature

ID number	Age	Gender	Degree of tetrasomy12p mosaicism.	Pigmentary skin changes	Seizures	Visual impairment	Hearing impairment	Motor skills	Language skills	Social skills	School setting
1. This report	6y7m	F	0% PBL mosaicism on skin biopsy	Yes	Single febrile	Strabismus, Nystag.	None	Walked at 4 years hypotonia	21 months age equivalent	Appropriate	Special Ed.
2. This report	5y4m	F	36% buccal positive skin fibro testing	Yes	None	Strabismus, Nystag. myopia	None	Walked at 27 months	39–45 months age equivalent	Autism spectrum disorder	Autism support class Full scale IQ 69
Stalker et al. [2006]	14 y	F	0% PBL; 79% fibro: 22.7% buccal	Yes	Single febrile	N/A	N/A	Walked at 15 months, hypotonia	Speech delay	Autism spectrum disorder	Full scale IQ 93
Genevieve et al. [2003]	15 y	M	37% fibro; normal PBL	Yes	None	N/A	None	Walked at 28 months	Able to talk at age 3 years	N/A	Special Ed. at 15 years
Schaefer et al. [1997]	7 y	M	50% fibro; normal PBL	Yes	None	N/A	Yes	Walked at 14 months	Speech delay	N/A	Mild mental retardation, regular class
Bielanska et al. [1996]	5 y	M	80% fibro; normal PBL	Yes	None	Strabismus, myopia	Yes	Delayed skills, hypotonia	Speech delay	Appropriate	Mild mental retardation
Warburton et al. [1987]	7 y	F	85% fibro; 11.5% PBL	Yes	N/A	N/A	N/A	Walked at 20 months	Speech delay	N/A	Mild mental retardation, special Ed.

N/A, data not available; PBL, peripheral blood lymphocytes; fibro, skin fibroblasts; Nystag., nystagmus; Ed., education.

Several limitations of our study exist, including the small number of subjects, although our cohort outnumbers previously described case series of PKS. The participants were a self-selected group of families, who were willing and financially able to come to Philadelphia, and thus may not reflect the general population of individuals with PKS. In addition, teachers and therapists were not surveyed, and so the behavioral characteristics reported by parents may not accurately reflect the probands' behavior in school or community settings. Except for the Aberrant Behavior Checklist, the questionnaires utilized, were standardized in a typical population, and thus may have limited validity in children with multiple disabilities. The Social Communication Questionnaire was found not to be applicable to the majority of subjects due to the degree of cognitive disability. The ABC was a useful tool to collect behavioral information in a systematic manner, even in children with this degree of disability, but has not been standardized for children under the age of 6. All children in our study, ages 3 and younger had scores on Modified Checklist for Autism in Toddlers (M-CHAT) indicating a concern for an autistic spectrum disorder. However, the degree of developmental delay in this group makes interpretation of these findings questionable. The M-CHAT is typically used in children ages 18–24 months as an autism screening tool.

In summary, our study demonstrated the wide neuro-cognitive spectrum of PKS. Further studies are needed to investigate whether children with PKS are at increased risk for autism and to investigate the prevalence of neurosensory deficits, tactile defensiveness, and lethargy, especially as they may relate to developmental impairments in children with PKS. Investigation into the cause of such findings may lead to better targeted intervention and better developmental outcome.

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