RESEARCH ARTICLE

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# Novel Clinical Manifestations in Pallister–Killian Syndrome: Comprehensive Evaluation of 59 Affected Individuals and Review of Previously Reported Cases

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Pallister–Killian syndrome is a rare, multi-system developmental diagnosis typically caused by tetrasomy of chromosome 12p that exhibits tissue-limited mosaicism. The spectrum of clinical manifestations in Pallister–Killian syndrome is wide and includes craniofacial anomalies, clefts, ophthalmologic, audiologic, cardiac, musculoskeletal, diaphragmatic, gastrointestinal, genitourinary, and cutaneous anomalies in association with intellectual disability and seizures. Growth parameters are often normal to elevated at birth with deceleration of growth postnatally. No formal estimate of the prevalence of Pallister–Killian syndrome has been made. Here, we report the clinical findings in 59 individuals with Pallister–Killian syndrome who were ascertained at Pallister–Killian syndrome Foundation family meetings held in the summers of 2006, 2008, 2009, and 2010. In addition, the clinical findings of 152 cases reported in the medical literature were reviewed and compared to the cohort examined here. Several novel clinical characteristics were identified through detailed dysmorphology examinations of this cohort and reassertion of a mild developmental variant is described. This report expands the clinical manifestations of Pallister–Killian syndrome and highlights the variable expressivity of this diagnosis with important implications for diagnosis and counseling. 

**Key words:** Pallister–Killian syndrome; PKS; Teschler-Nicola–Killian syndrome; tetrasomy 12p; isochromosome 12

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## INTRODUCTION

Pallister–Killian syndrome (PKS) was first described in 1977 by Dr. Phillip Pallister in two institutionalized adult patients with similar clinical phenotypes that included multiple congenital anomalies, intellectual disability, and seizures [Pallister et al., 1977]. Maria Teschler-Nicola and Wolfgang Killian reported a similar clinical phenotype as a novel ectodermal dysplasia in 1981 without a known associated cytogenetic abnormality [Teschler-Nicola and Killian, 1981]. This was followed by another case reported by Schroer and Stevenson [1983] and a case series in 1983 of five children demonstrating the same phenotype [Killian et al., 1983], which by this time, was referred to as the Teschler-Nicola/Killian syndrome. Although these children were noted to have phenotypic overlap with partial trisomy 12, chromosomal

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studies on all patients were normal. Initial analyses in fibroblasts prior to the availability of standard G-banding diagnosed the etiology of PKS to be trisomy of chromosome 20 [Pallister et al., 1976]; however, further studies in both blood and fibroblasts correctly identified the marker chromosome as an isochromosome 12p [Warburton et al., 1987]. As additional cases were reported, fibroblast cultures were performed and the two entities known as "Pallister mosaic syndrome" and "Teschler-Nicola/Killian syndrome" began to merge into a single diagnosis. Difficulty with case ascertainment persisted, however, both because of misidentification of the marker chromosome, as well as the apparent absence of the cytogenetic abnormality in lymphocytes analyzed by older testing methodologies.

Although extensive research has investigated the cytogenetic cause of this diagnosis and hypothesizes on the origin of the isochromosome, the rarity of the diagnosis has led to few formal clinical and developmental analyses of a large cohort of PKS individuals. The most common clinical features of this diagnosis based on case reports include craniofacial dysmorphism, pigmentary skin anomalies, broad and short hands and fingers, hypotonia, intellectual disability, and epilepsy [Schinzel, 1991]. The characteristic facial appearance includes bitemporal alopecia, hypertelorism, and abnormal ears [Schinzel, 1991]. Although almost universally described as a severe diagnosis with multiple congenital anomalies and severe to profound cognitive involvement, recent reports have described a milder phenotype [Bielanska et al., 1996; Schaefer et al., 1997; Genevieve et al., 2003]. Despite this documented clinical variability, there has not been any well-supported evidence for genotype-phenotype correlation based on either degree of mosaicism or genetic composition of the isochromosome.

To date, there have only been two reports documenting multiple patients' phenotypic features: a series of 11 patients [Reynolds et al., 1987] and a collaborative report of 19 children and fetuses [Mathieu et al., 1997]. We report patient information from 59 individuals with cytogenetically confirmed PKS who have participated in a study conducted by the Children's Hospital of Philadelphia (CHOP) and compare demographic, system-specific, growth, developmental and cytogenetic data to previously reported PKS data in the literature to further describe the wide phenotypic spectrum of PKS, and document novel clinical manifestations in the hope of facilitating further identification of patients with PKS and ultimately provide better anticipatory guidance for the medical complications seen frequently in these individuals.

## MATERIALS AND METHODS

The data represent the findings from children evaluated at the PKS family support group meetings held between 2006 and 2010. All subjects were enrolled under an IRB-approved protocol of informed consent held at CHOP. Family members answered a detailed clinical questionnaire with emphasis on the pregnancy, birth, pediatric, and family histories (see Intake form available in the Supporting Information online). In addition, we asked the parents to provide their child's medical records, imaging study reports and cytogenetic analyses for review. The individuals were comprehensively evaluated by clinicians trained in dysmorphology (including Dr. Phillip Pallister, who initially described this clinical entity) and, additionally, underwent formal developmental assessments. The results of the developmental evaluations are reported in the sister article by Kostanecka et al. [2012].

Reference cases were ascertained through searches of English language articles in PubMed and Medline using the following keywords: Pallister–Killian syndrome, Teschler-Nicola–Killian syndrome, tetrasomy 12p, and isochromosome 12p. All available relevant references from these articles were obtained even if the initial case was excluded. A total of 152 cases were found in the literature and represent a combination of fetuses, children, and adults. The references used in the literature review are available as "supplemental references." The observations and clinical findings of our 59 patients were then systematically compared to these 152 previously reported cases of PKS described in the literature.

For the purposes of consistency, inclusion was limited to individuals with complete tetrasomy 12p; individuals evaluated at the family meeting or reported in the literature with a variant form of PKS such as trisomy12p, partial isochromosome 12p or translocations involving a duplication of 12p with associated monosomic or trisomic regions of other chromosomes, were excluded from this report and from data analyses. Cases were not excluded based on lack of clinical information and each parameter was recorded as present, absent, unspecified or not applicable (as in the case of neonatal demise and developmental outcome, etc.), so as to provide an adequate denominator for analysis. We chose to include fetal cases of PKS in our literature cohort and compare them with the CHOP cohort, which is exclusively composed of postnatal cases, to demonstrate the spectrum of clinical variability, in that fetal demise was likely initiated by a more severe phenotype than the less complicated phenotypes seen in our patient population. In addition, not all measured parameters that we report on were available for either all CHOP participants or cases reported in the literature, thus denominators for both cohorts may differ for each variable.

## RESULTS

### Demographic Information

The male and female contributions of our cohort, as well as the average maternal and paternal ages are referenced in Table I. Pregnancy information including average gestational

**TABLE I. Demographic Characteristics in CHOP Cohort and Reported Literature**

| Demographic characteristics | CHOP | Literature |
|---|---|---|
| Gender of patient | N = 59 | N = 140 |
| Male | 32 | 69 |
| Female | 27 | 71 |
| Parental ages (years) | | |
| Avg. mat. age at gestation | 31.7 (N = 38) | 32.1 (N = 110) |
| Ave. pat. age at gestation | 34.9 (N = 32) | 34.2 (N = 48) |
| Avg. gestational age (weeks) | 37.4 | 36.7 |

age, complications and average age of diagnosis are also available. Seventy-three of the 152 cases in the literature resulted in either neonatal or fetal demise with seventy cases representing live-borns and nine individuals for whom the authors did not specify a living or deceased status. We chose to report the maternal and paternal ages of confirmed live births in the literature cohort. Overall, the demographic parameters were similar between cohorts.

## System Involvement (Tables II, III, IV)

***Neurologic involvement.*** Seizures in our cohort were observed less frequently than those in the literature. The most commonly reported seizure types were similar between both cohorts, as were the structural brain abnormalities confirmed either by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). The average age of patients with seizures in our cohort is 81.2 months

**TABLE II. Comparison of System Involvement Between CHOP Cohort and Cases Reported in Literature**

| Type of involvement | # of CHOP cases (# pt surveyed) | % | Number of cases (# for which data reported) | % |
|---|---|---|---|---|
| Neurologic involvement | 26 (48) | 54 | 27 (39) | 69 |
| Structural defects | 24 (33) | 73 | 55 (87) | 63 |
| Seizures | 23 (47) | 48 | 37 (46) | 80 |
| Hypotonia | 45 (49) | 92 | 14 (38) | 37 |
| Cardiac involvement | 19 (44) | 43 | 30 (76) | 39 |
| PFO + ASD | 7 (19) | 37 | 4 (30) | 13 |
| Bicuspid aortic valve | 3 (19) | 16 | 1 (30) | 3 |
| PDA | 3 (19) | 16 | 5 (30) | 16 |
| RVH | 1 (19) | 5 | 2 (30) | 7 |
| LVH | 1 (19) | 5 | 1 (30) | 3 |
| VSD | 1 (19) | 5 | 4 (30) | 13 |
| Bradycardia | 1 (19) | 5 | 0 (30) | 0 |
| Renal involvement | 5 (46) | 11 | 17 (52) | 33 |
| Structural anomalies | 4 (45) | 9 | 9 (52) | 17 |
| Renal dysplasia | 0 (46) | 0 | 2 (53) | 4 |
| Decreased renal function | 1 (12) | 8 | 1 (6) | 17 |
| Gastrointestinal involvement | 25 (48) | 52 | 53 (68) | 78 |
| Intestinal malrotation | 5 (42) | 12 | 6 (17) | 35 |
| Displacement of anus | 8 (40) | 20 | 6 (23) | 26 |
| Diaphragmatic hernia | 5 (45) | 11 | 11 (38) | 29 |
| Umbilical hernia | 7 | | 12 (21) | 57 |
| Functional manifestations | | | | |
| Feeding difficulty | 32 (48) | 67 | | |
| Dysphagia | 13 (44) | 30 | | |
| Constipation | 31 (48) | 65 | | |
| GERD | 18 (48) | 37 | | |
| Genitourinary involvement | 15 (47) | 32 | 31 (59) | 53 |
| Hypospadia | 1 (45) | 2 | 1 (27) | 4 |
| Small genitalia | 1 (12) | 8 | 7 (27) | 26 |
| Cryptorchidism | 10 (45) | 8 | 16 (27) | 59 |
| Hydrocele | 1 (12) | 8 | 1 (27) | 4 |
| Musculoskeletal involvement | 15 (48) | 31 | 81 (91) | 89 |
| Dermatologic involvement | 38 (48) | 79 | 48 (89) | 54 |
| Hypopigmentation | 21 (47) | 45 | 24 (89) | 27 |
| Pulmonary involvement | 37 (48) | 77 | 9 (38) | 24 |
| Ophthalmologic involvement | 39 (45) | 87 | 10 (38) | 26 |
| Auditory involvement | 36 (47) | 77 | | |
| Sensorineural | 8 (21) | 38 | | |
| Conductive | 6 (21) | 29 | | |
| Mixed | 7 (21) | 33 | | |
| Bilateral | 30 (36) | 83 | | |
| Unilateral | 2 (36) | 6 | | |
| Unspecified | 4 (36) | 11 | | |

CHOP case number is based on the detailed clinical questionnaire answered by the family.
PFO, patent foramen ovale; ASD, atrial septal defect; PDA, patent ductus arteriosis; RVH, right ventricular hypertrophy; LVH, left ventricular hypertrophy; VSD, ventricular septal defect.

TABLE III. Physical Characteristics (CHOP Cohort)

| Physical exam (N = 43) | # of individuals exhibiting notable features | % | Notable clinical features |
|---|---|---|---|
| General facial features | 43 | 100 | Frontal bossing (23), alopecia (29), spare eyebrows (29), cupid bow lip (8), upturned nostril (2), depressed nasal bridge (8), long philtrum (11), bifida uvula (3), short neck (33), micrognathia (18), large mandible (9) |
| Skin | 24 | 56 | Hyperpigmentation (1), accessory nipples (19), hypopigmentation (1), weeping cyst on face (1) |
| Eye | 31 | 72 | Palpebral fissure (31), proptosis (1), ptosis (1), epicanthal folds (1), telecanthus (12) |
| Ear | 20 | 47 | Ear pits (12), thick helices (3), helical notch (1), posterior rotated (5), low set (2), tag (2), folded lobe (1) |
| Palate | 17 | 40 | Cleft palate (6), high arch (11) |
| Extremities | 35 | 81 | Lymphedema (22), abnormal extension (1), whorl (13), syndactyly (1) |
| Spine/sacral area | 13 | 30 | Dimple (10), deep dimple (1), two blinded dimples (1), sacral tag (1) |
| Genitalia | 2 | 25 | |
| Male | 1 | 20 | Undescended testes (1) |
| Female | 1 | 33 | Small clitoris and labia minora (1) |
| Anteriorly placed anus | 8 | 19 | |

and represents an older population of individuals than the seizure-free patients whose average age is 31.5 months. A detailed description of seizure types and other neurology-specific information can be found in Candee et al. [2012].

***Cardiac involvement.*** The percentages of individuals with PKS who had cardiac anomalies are similar in both our patient population and those reported in the literature. The specific cardiac anomalies reported as most common in our cohort were also to those in the literature cohort and included patent foramen ovale (PFO), atrial septal defects (ASD), and patent ductus arteriosis (PDA). However, our cohort reported a greater frequency of bicuspid aortic valve, whereas the literature cohort reported a greater number of ventricular septal defects (VSDs).

***Ophthalmologic involvement.*** Although structural and visual acuity differences were described in both our cohort and in the PKS literature, the percentage of individuals with these differences were noted with higher frequency in our patient population.

***Auditory involvement.*** Hearing loss was a common finding reported in our cohort, in which the majority presented with bilateral loss with a similar distribution among sensorineural, conductive and mixed hearing loss. A comparison between our patient population and the PKS literature is difficult to establish, however, as little emphasis was placed on the exact clinical description of the hearing loss in the literature cohort. Despite this discrepancy sensorineural hearing loss does appear to be the predominant type.

TABLE IV. Comparison of Observed Craniofacial Differences Between the CHOP Cohort and Literature Probands

| Craniofacial differences | # of CHOP cases (# of cases examined) | % | Number of cases (# of cases reported) | % |
|---|---|---|---|---|
| Frontal bossing | 23 (43) | 53 | 9 (36) | 25 |
| Frontal temporal alopecia | 29 (43) | 67 | 57(73) | 78 |
| Hypertelorism | 38 (43) | 89 | 65 (79) | 82 |
| Depressed nasal bridge | 8 (43) | 19 | 12 (36) | 33 |
| Long philtrum | 11 (43) | 26 | 12 (36) | 33 |
| Short neck | 33 (43) | 77 | 10 (36) | 28 |
| Micrognathia | 18 (43) | 42 | 11 (71) | 15 |

***Gastrointestinal involvement.*** Gastrointestinal anomalies were reported significantly less in our study than previously reported in the literature. Despite the dissimilarity in frequency, both cohorts reported the same structural differences such as intestinal malrotation and congenital diaphragmatic hernia as occurring most commonly. Functional gastrointestinal manifestations were commonly described in our patient population and were not specifically denoted in the PKS literature.

***Genitourinary involvement.*** Although both our cohort and the PKS literature report genitourinary anomalies, our patient population had fewer cases reported overall. The most commonly reported abnormalities, however, did overlap in description with those seen in the literature. Decreased renal function and structural renal anomalies were also seen in both cohorts, but is a less common finding overall for individuals with PKS.

***Musculoskeletal involvement.*** Musculoskeletal differences were significantly less common in our patients than in the literature, however, the most commonly described anomalies between both cohorts included polydactyly, contractures and hip dislocation.

***Dermatologic involvement.*** Dermatologic differences (described as hyper- or hypo-pigmentation) were reported more commonly in our cohort than observed in the literature.

***Pulmonary involvement.*** Pulmonary abnormalities were found in the majority of our patients and notably not described in any of the living children with PKS in the literature, as the pulmonary complications seen the literature were associated with CDH leading to demise.

## Growth Information

Birth weight, length and head circumference (HC) measurements reported by the family members or reported in medical records were analyzed and calculated based on gestational age (Fig. 1). The birth weight, height and HC of females with PKS are more evenly distributed than those in males (Fig. 1). The majority had a height and weight in a lower centile at the time of the clinical exam than that of birth and most patients whose growth parameters fell below the 25th centile were 12 months or older (Fig. 2).

## Physical Characteristics

Dysmorphology exams were conducted on the majoirty of our patients and all individuals demonstrated facial dysmorphism already known to be associated with the PKS phenotype, including

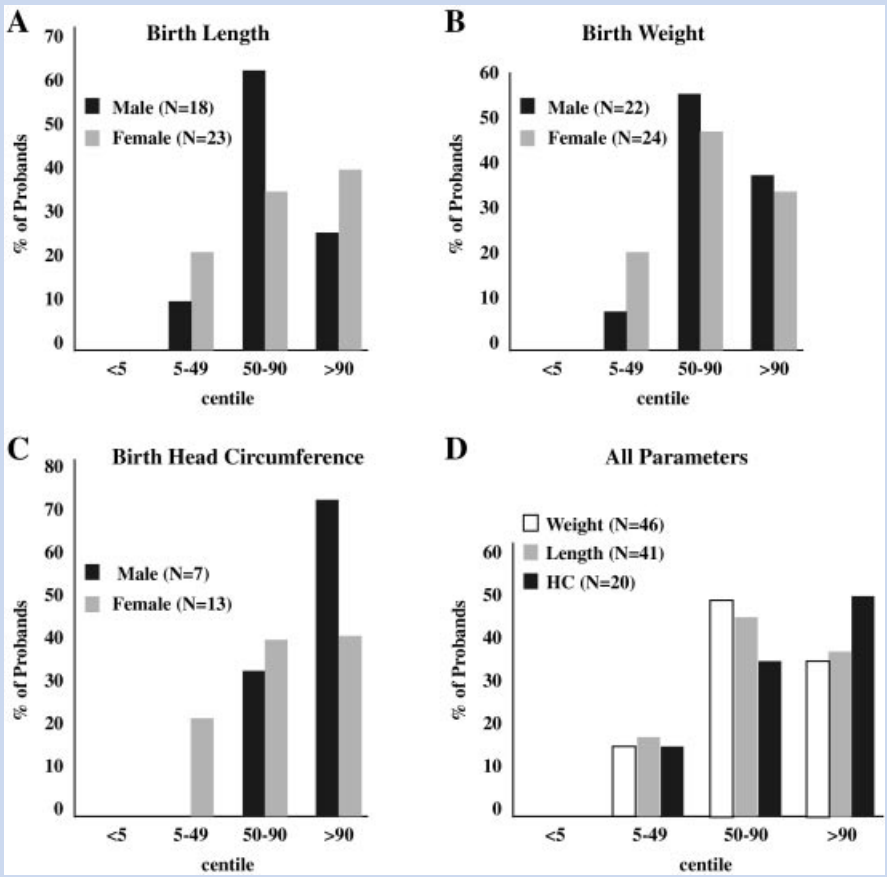


**FIG. 1. A: Distribution of birth length, (B) weight, and (C) head circumference (HC) in our PKS cohort, and (D) all parameters. Birth weight, length, and HC reported by the family members or reported in medical records were analyzed and calculated based on gestational age.**

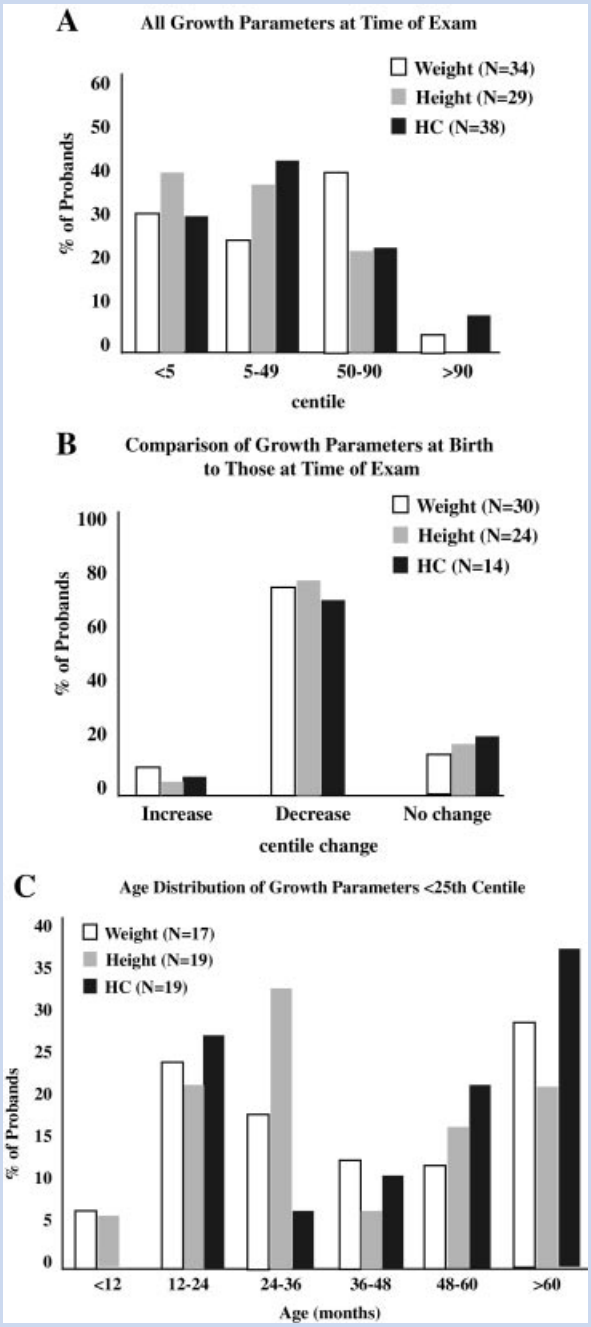


**FIG. 2. A: Distribution of weight, height, and HC at the time of examination in PKS cohort, (B) comparison of birth weight and length to weigh and length at time of examination, and (C) age distribution of patients with growth parameters less than 25th centile in PKS cohort. Growth information was requested in the PKS intake form for our cohort, or obtained at the time of examination and included 34 individuals for whom we have information on weight, 29 individuals for whom we have height, and 38 individuals for whom we have head circumference (HC) information.**

frontal bossing, alopecia, and sparse eyebrows/eyelashes (Fig. 3; Tables III and IV). For three patients, we collected the pictures of the face at various ages, demonstrating the progression of the facial features (Fig. 4). Fewer individuals in our cohort and in the literature showed other associated differences including shorter neck, micrognathia and a deperessed nasal bridge with anteverted nares. Long philtrums were a common characteristic reported in the literature, and were also prominent in our patients. Other common abnormalities in both populations were those of the skin, eyes, ears, palate, extremities, sacrum, and anus. Notable differences between the two popualtions included fewer individuals with cleft palates in our cohort and a higher incidence of supernumerary nipples as compared to the literature (Figs. 5 and 6). Features that were not assessed in the literature but were frequent in our cohort included telecanthus (Fig. 7), extension of the philtral skin into the vermilion border of the upper lip (we term the "Pallister lip"; Fig. 8), lymphedema/increasesd soft tissue of the extremities (Fig. 9), limited extension of the elbows, posterior ear pits (Fig. 10) and a propensity of whorls on dermatoglyphics (of which ~50% have >5 whorls on exam). Umbilical hernia was seen frequently in our cohort (Fig. 11). Middle finger and foot length measurements demonstrated that brachydactyly and small feet are common in our cohort (Supplemental Fig. 1).

## Developmental History

Developmental milestones were examined in our study participants and the average age of acquisition for several motor and language developmental milestones are reported (Table V). The average ages of milestone acquisition were significantly older in all developmental skills (Table V).

## Cytogenetic Data

While all patients included in our study had documented tetrasomy 12p, we had 50 cytogenetic results available for review from a total of 34 participants (Table VI). Sixteen of the 34 individuals included had cytogenetic mosaicism information on both lymphocyte and fibroblast samples. Among the 34 individuals, two were diagnosed prenatally and reports were based on chromosomal analysis of amniocytes. A variety of tissues were tested from those reported in the PKS literature with 50 lymphocyte samples and 84 fibroblast samples obtained from fetal, infant (birth–12 months) or childhood (>1 year) tissues (Table VII).

As is the case in our cohort, the data from the literature also suggest lymphocytes obtained from peripheral blood showed a higher percentage of chromosomally normal cells and lower percentage of isochromosome 12p mosaicism. Conversely, fibroblasts more often indicated the mosaic presence of the isochromosome (Fig. 12).

# DISCUSSION

Pallister–Killian syndrome is a rare, multisystem genetic diagnosis caused by tissue limited mosaic tetrasomy 12p. This report expands the clinical manifestations of PKS and highlights the variable expressivity of this diagnosis with important implications for

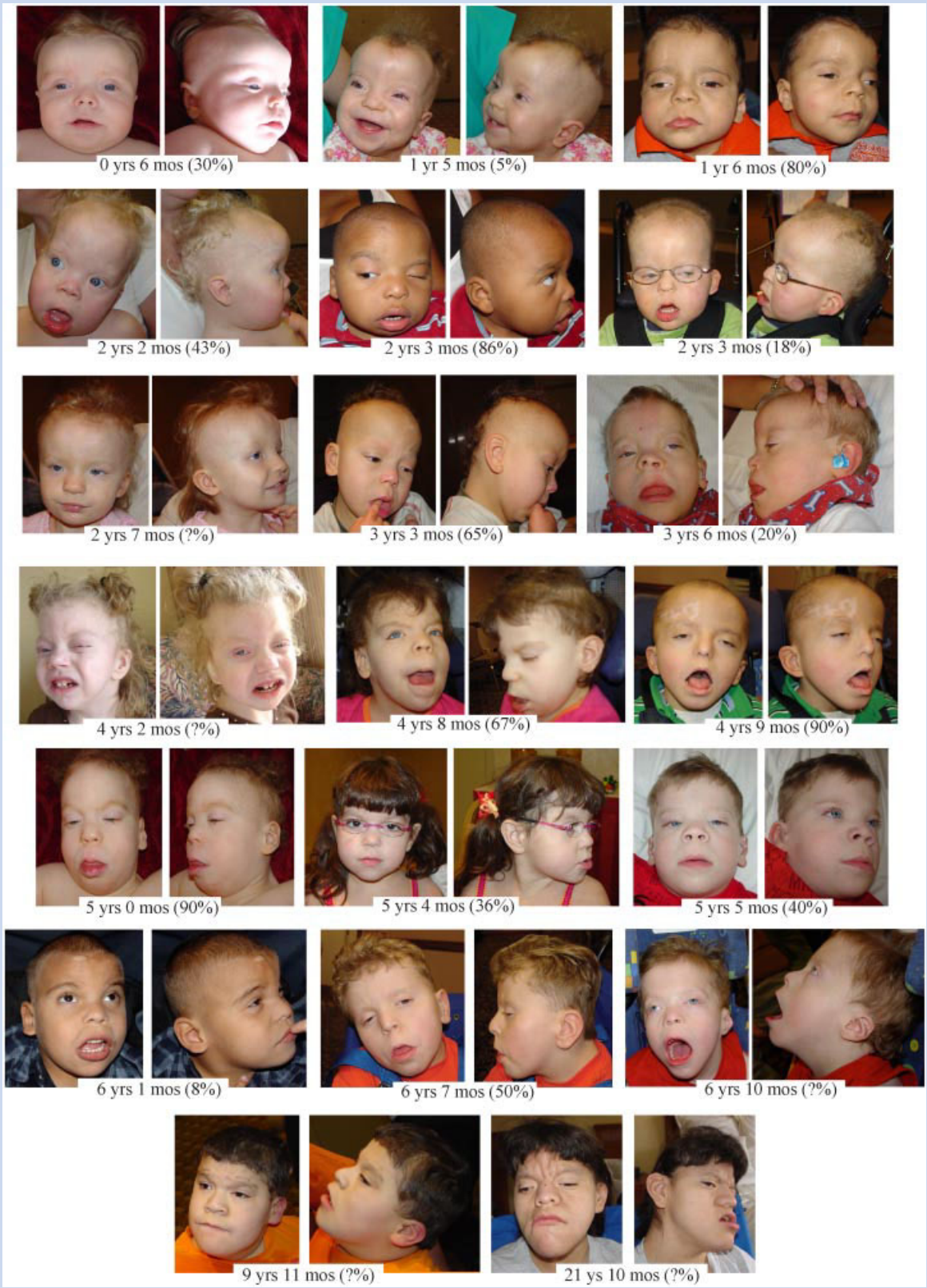


**FIG. 3. Facial characteristics with age at examination and percent (%) mosaicism for the i(12p) marker chromosome identified. Note consistency of facial features across genders, ages and ethnic backgrounds. There is a tendency towards improved hair growth in the temporal areas, increased prominence of the chin (prognathism) and coarsening of facial features with age. In some cases there was only verbal confirmation of i12p testing from parents and the level of mosaicism is unknown (?%).**

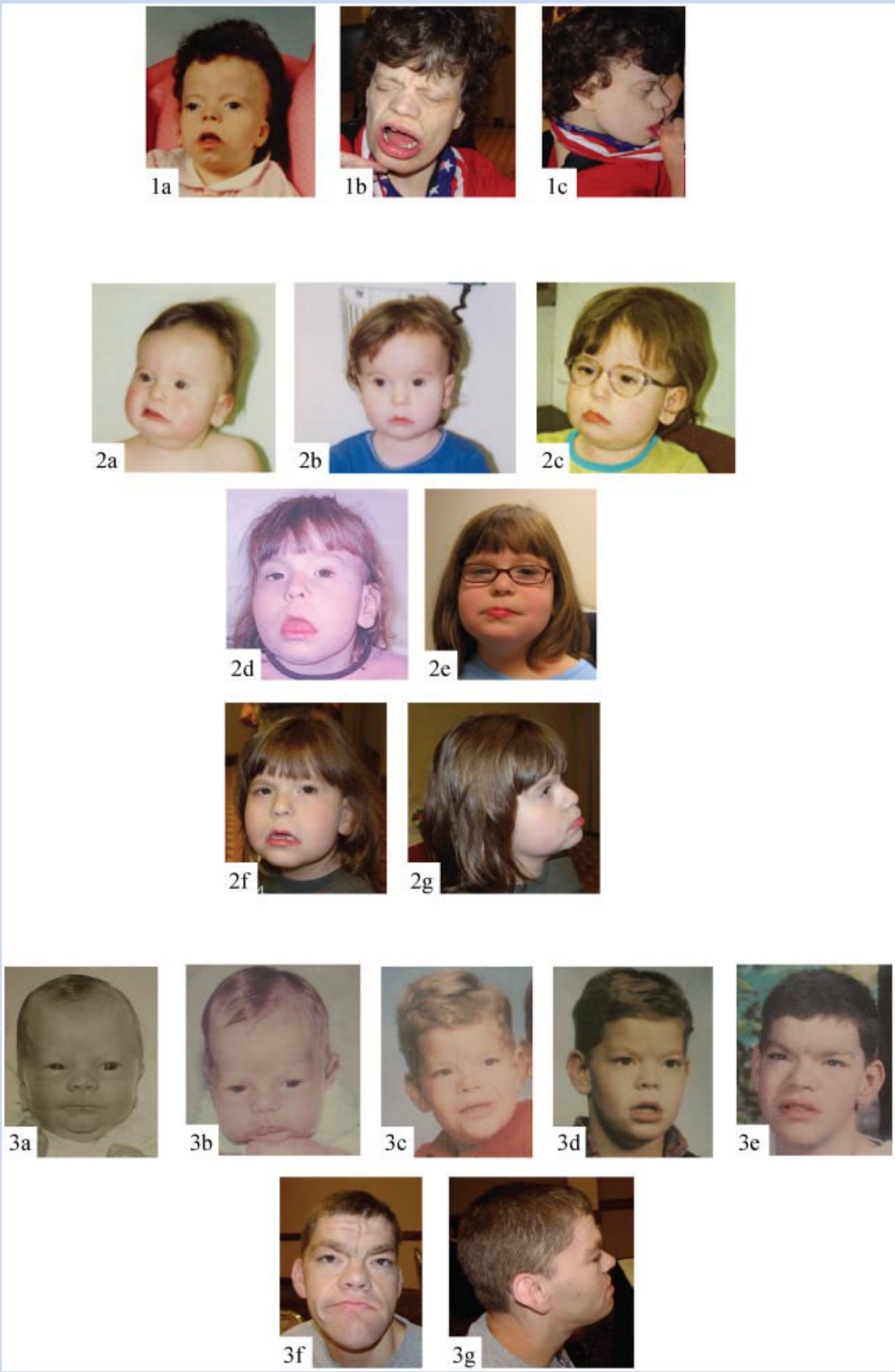


FIG. 4. Progression of the facial features in three PKS patients. A female at 6 months (1a) and 20 years (1b,c). Another female at 1 year (2a), 2 years (2b), 4 years (2c), 5 years (2d), 7 years (2e), and 8 years (2f,g). A male at 3 months (3a), 1 year (3b), 3 years (3c), 5 years (3d), 8 years (3e), and 26 years (3f,g).

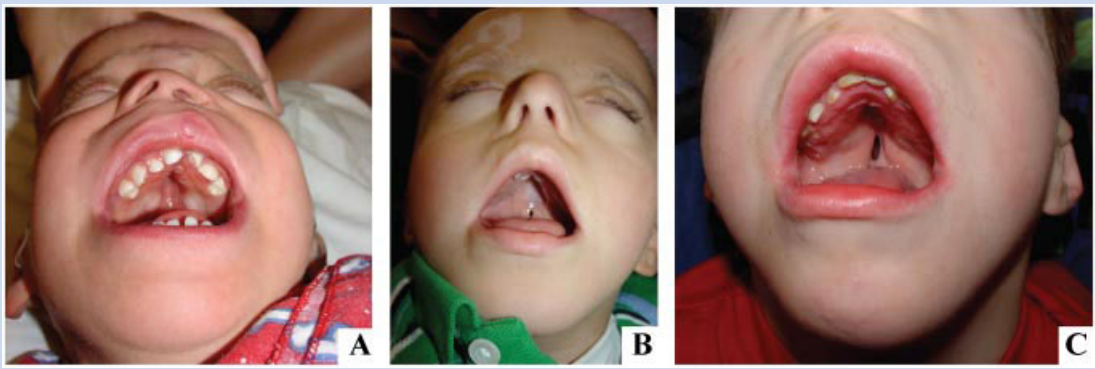


FIG. 5. Palatal clefts in three patients with PKS.

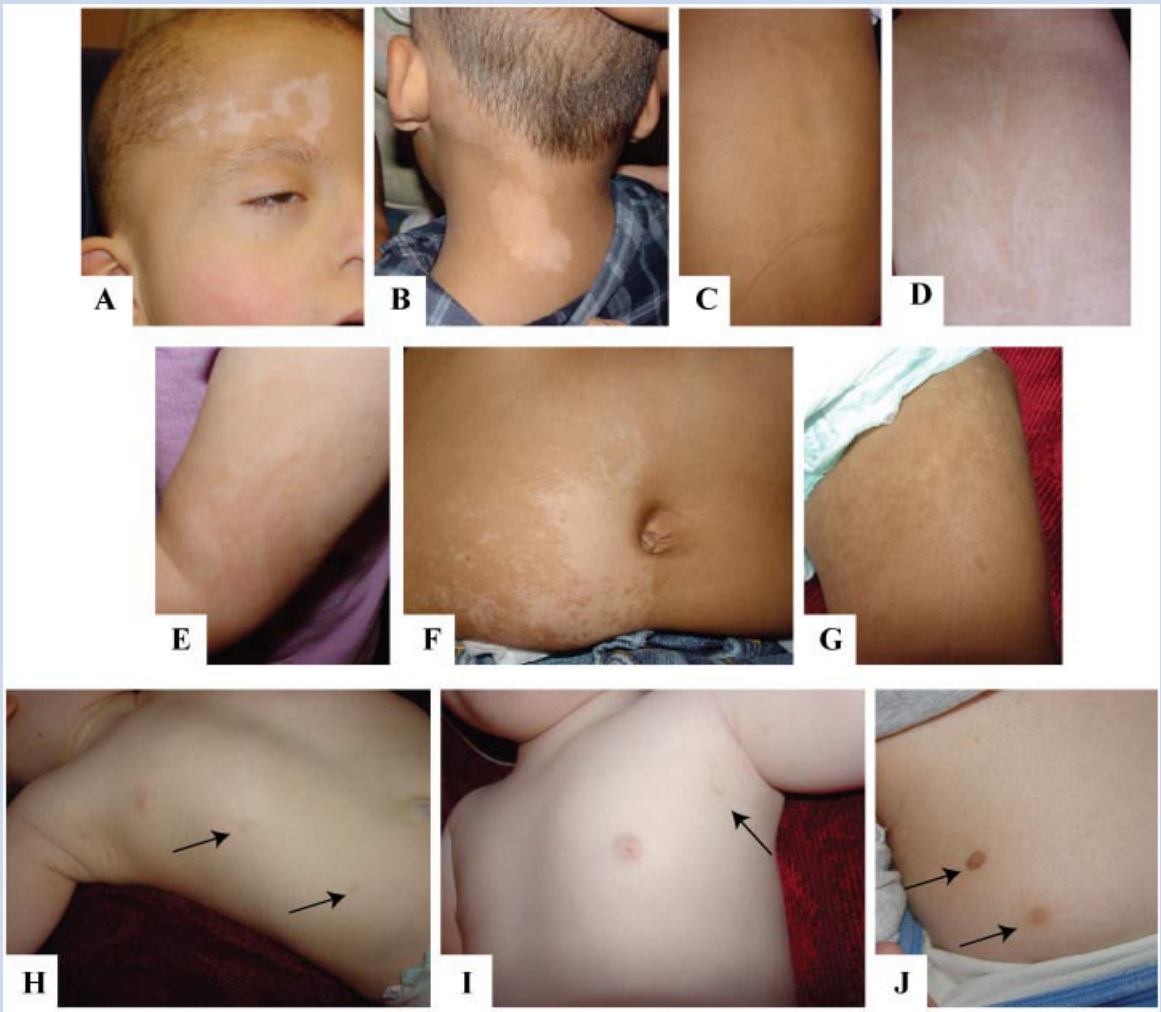


FIG. 6. Skin involvement in PKS. Skin anomalies have were identified in 56% of patients in our cohort, with hypo- and hyper-pigmentation noted as the most common (A–G). Unlike those reported in literature, we observed accessory nipples more frequently (44% in our cohort vs. 12% in literature; indicated by arrows in H–J).

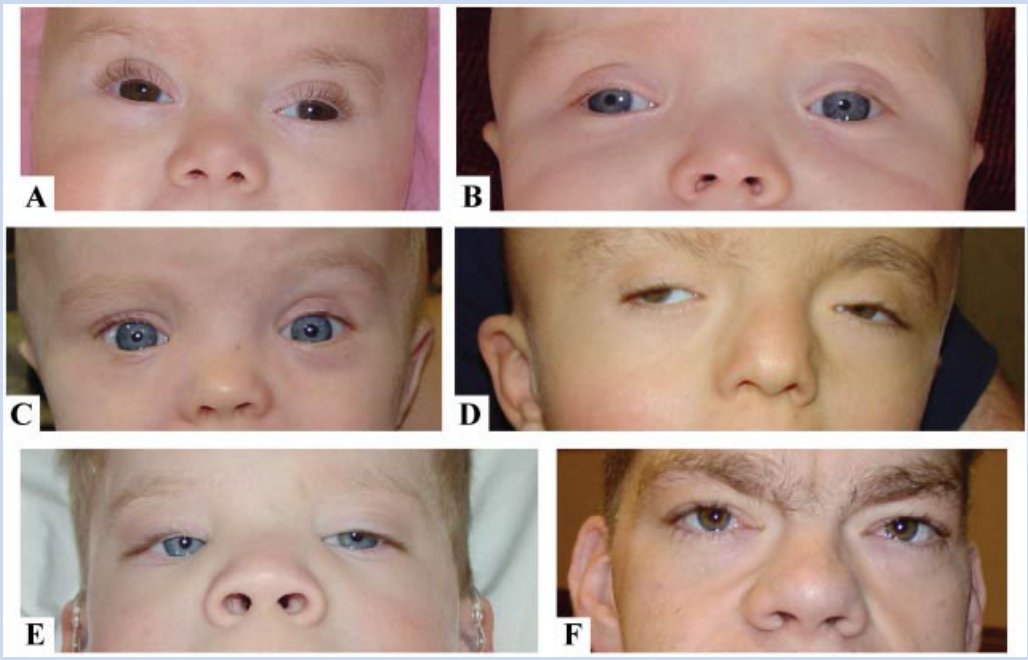


FIG. 7. PKS eyes. Note hypertelorism in all four individuals as well as telecanthus (most notable in B–D), downslant (B) of palpebral fissures and inverted epicanthi (C).

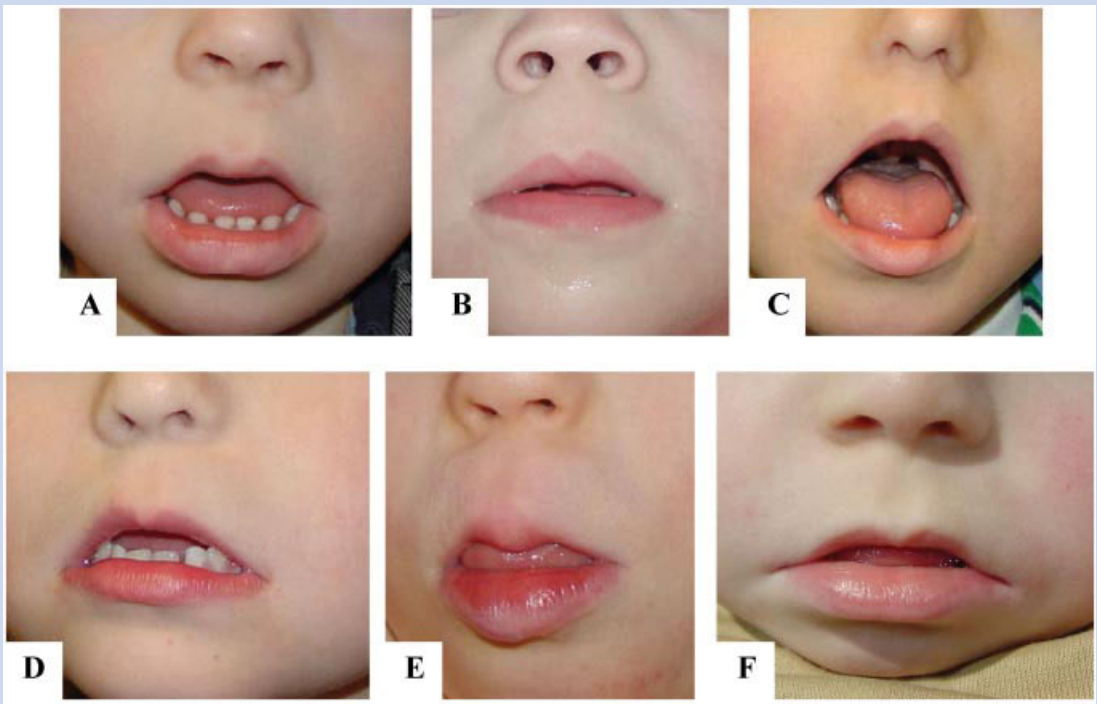


FIG. 8. "Pallister Lip." Typical appearance of the upper lip in six patients with PKS displaying extension of the philtral skin into the vermilion border of the upper lip (a feature we have termed the "Pallister lip").

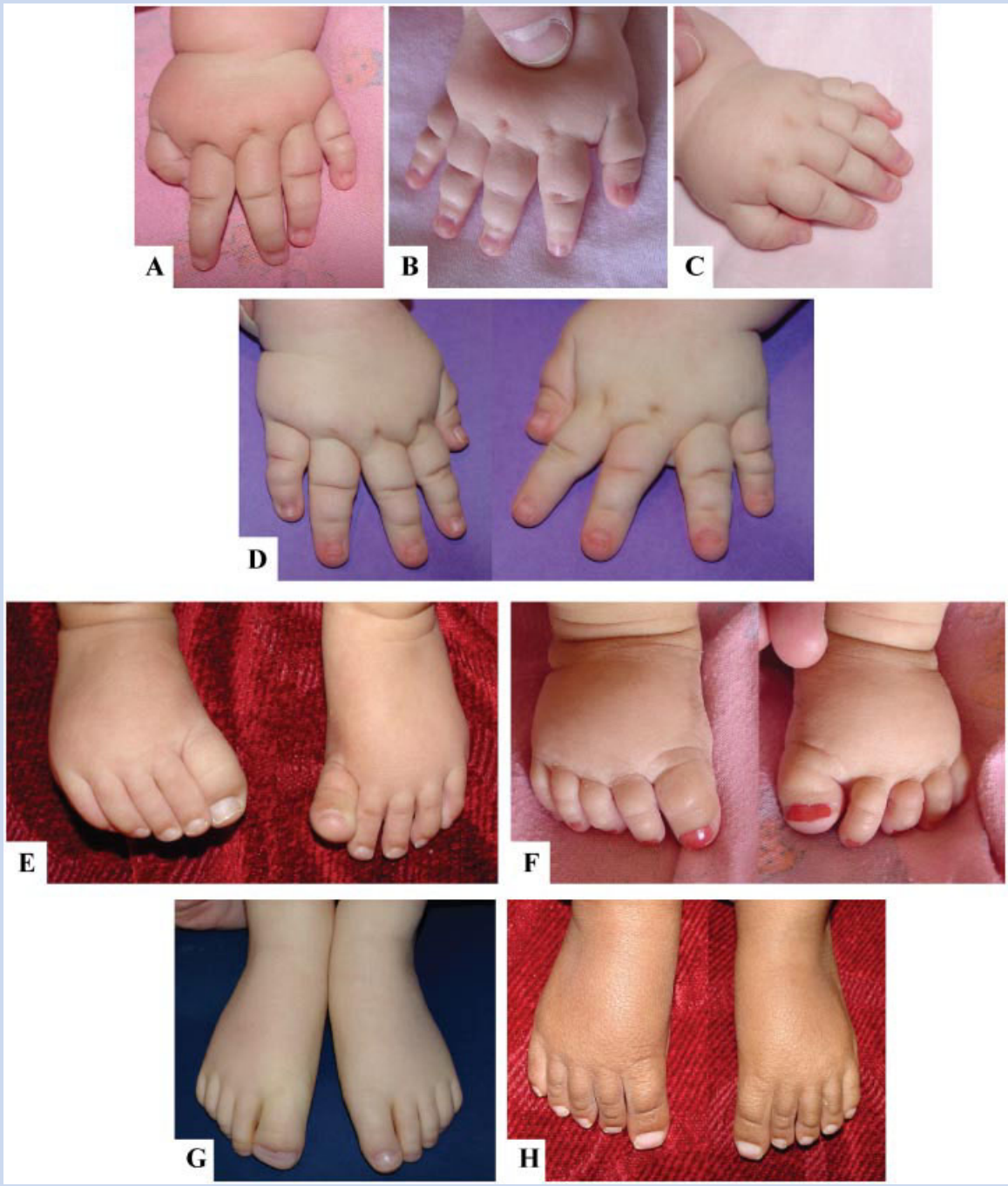


**FIG. 9. Hands and feet in PKS. Eighty-one percent of CHOP patients in this series had extremity differences including lymphedema/increased soft tissue of the extremities (A–H). Broad thumbs and 1st toes were consistently seen in the Our cohort with duplication of the 1st toe seen in two (F,G).**

diagnosis and counseling. While our cohort of 59 patients demonstrated similar findings as seen in the literature, with respect to demographic information, pregnancy history, system-specific manifestations, growth history, developmental outcomes and cytogenetic data, there were novel findings that emerged within both groups or between both cohorts.

## Pregnancy

The most notable pregnancy-related finding in both cohorts included earlier gestational ages at birth as compared to the standard 40 weeks gestation, therefore suggesting later prematurity as a potential pregnancy complication associated with PKS. Although

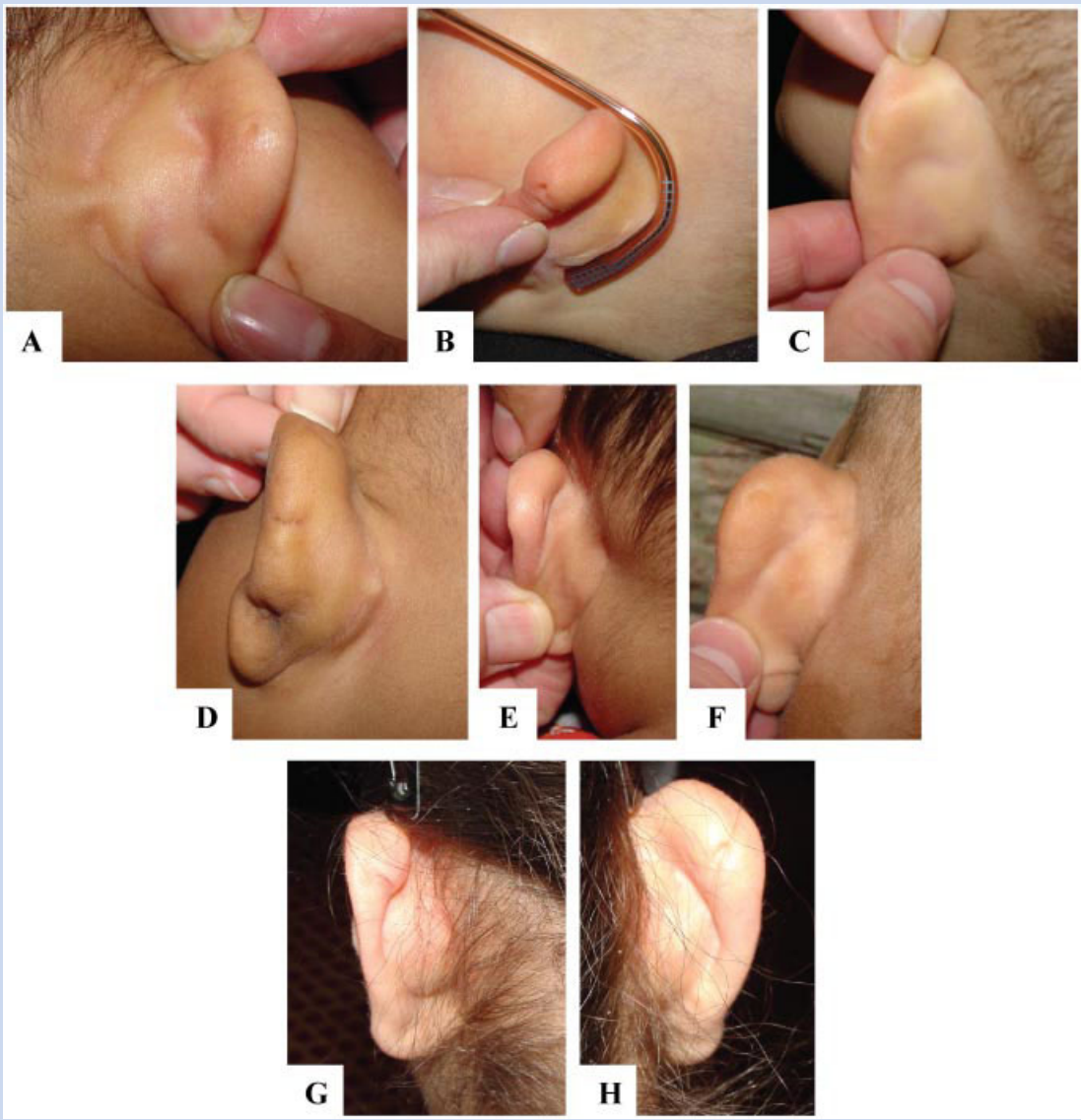


FIG. 10. Posterior ear pits in PKS patients.

it is difficult to establish a causal relationship at this time, we propose that fetal macrosomia may influence premature birth, as prematurity is already a documented finding associated with macrosomia induced by other causes, such as diabetes mellitus [Hay, 2012]. Another potential mechanism leading to prematurity is polyhydramnios, which can be associated with preterm delivery [Tough et al., 2003]. Although we did not collect the information about the amount of amniotic fluid systematically, at least, greater than 47% of the PKS pregnancies were associated with polyhydramnios. In addition, the average maternal age of the mothers in our cohort is 31.7 years and represents an older population of mothers as compared to the mean age at delivery of women overall in the United States (http://esa.un.org/unpd/wpp/). Given that the cellular division error proposed to form the isochromosome is thought to be due to non-disjunction—an error implicated in other chromosomal aneuploidies, such as trisomies, is associated with advanced maternal age. Therefore, non-disjunction as it relates to the formation of an isochromosome is also predicted to be influenced by advanced maternal age [Shen et al., 2010].

## Systemic Manifestations

While our cohort demonstrates previously reported neurologic, cardiac and structural kidney and pigmentary differences with similar frequencies as those in the literature, there are notable system-specific differences identified in each cohort that were not as concordant. Seizure involvement, for example, was reported less frequently in our cohort as compared to the literature cohort which could be a result of a difference in the age of the two populations. Within our cohort, the average age of patients with seizures

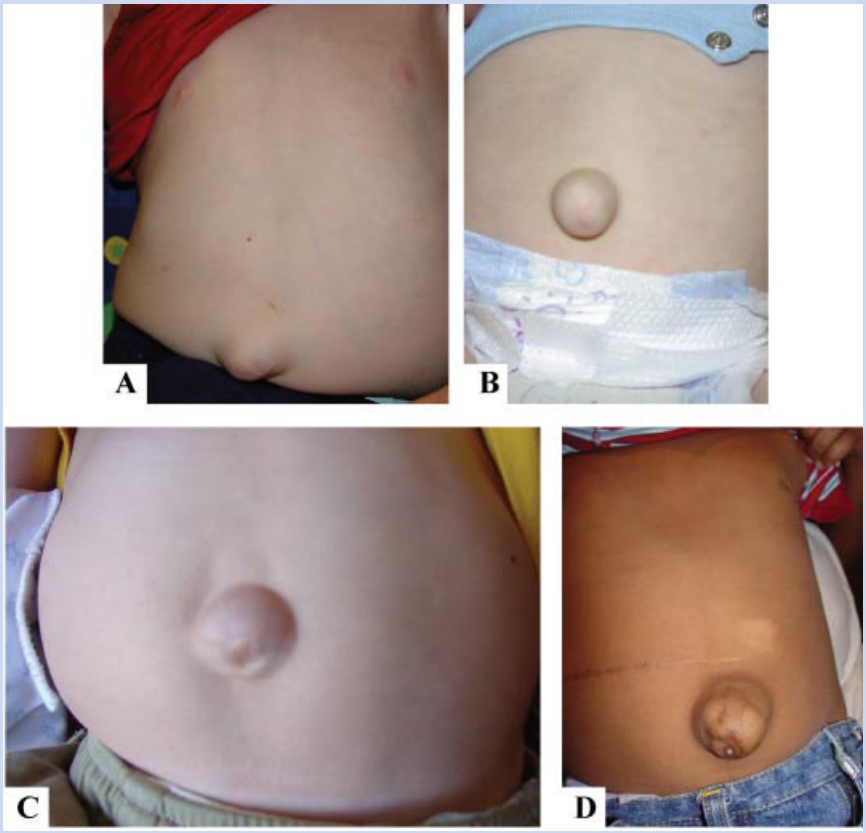


FIG. 11. Umbilical hernias in four PKS patients.

TABLE V. Developmental Outcomes in PKS Cohort

| Development milestones | # probands (# case exam) | % | Average age (months) |
|---|---|---|---|
| Rolling | 36 (48) | 75 | 10.8 |
| Sitting independently | 23 (47) | 49 | 21.2 |
| Walking | 8 (48) | 17 | 38.8 |
| Talking | 6 (47) | 13 | 36 |

TABLE VI. Cytogenetic Data for CHOP Probands (N = 50)

| | | | Degree of mosaicism (%) | | | |
|---|---|---|---|---|---|---|
| Tissue | # tested | Normal (%) | 1–25% | 26–50% | 51–75% | 76–100% |
| Lymphocytes | 24 | 12 (50) | 6 (25) | 3 (13) | 0 | 3 (13) |
| Infant (birth–1 year) | 14 | 7 (50) | 3 (21) | 3 (21) | 0 | 1 (7) |
| Child (>1 year) | 10 | 5 (50) | 3 (30) | 0 | 0 | 2 (20) |
| Fibroblasts | 24 | 1 (4) | 1 (4) | 6 (25) | 9 (38) | 7 (29) |
| Infant | 8 | 0 | 0 | 2 (25) | 3 (38) | 3 (38) |
| Child | 16 | 1 (6) | 1 (6) | 4 (25) | 6 (38) | 4 (25) |
| Amniocytes | 2 | 0 | 0 | 2 (100) | 0 | 0 |

TABLE VII. Cytogenetic Data for Available Literature

| Tissue | Number tested | Normal (%) | Degree of mosaicism (%) | | | |
|---|---|---|---|---|---|---|
| | | | 1–25% | 26–50% | 51–75% | 76–100% |
| Lymphocytes | 43 | 7 (16) | 26 (60) | 7 (16) | 1 (2) | 2 (4) |
| Fetal | 13 | 1 (8) | 7 (54) | 3 (23) | | 2 (15) |
| Infant (birth–1 year) | 26 | 3 (12) | 18 (69) | 4 (15) | 1 (4) | |
| Child (>1 year) | 4 | 3 (75) | 1 (25) | | | |
| Fibroblasts | 84 | 2 (2) | 4 (5) | 14 (17) | 10 (12) | 54 (64) |
| Fetal | 11 | 1 (9) | | | 1 (9) | 9 (82) |
| Infant | 35 | 1 (3) | 1 (3) | 6 (17) | 4 (11) | 23 (66) |
| Child | 38 | | 3 (8) | 8 (21) | 5 (13) | 22 (58) |
| Buccal cells | 14 | | 9 (64) | 1 (7) | 3 (21) | 1 (7) |
| Chorionic villi | 8 | 1 (12) | 5 (63) | | | 2 (25) |
| Amniocytes | 36 | 2 (6) | 4 (11) | 9 (25) | 5 (14) | 16 (44) |
| Other[a] | 14 | 2 (14) | | 1 (7) | 1 (7) | 10 (71) |
| Percentage not reported[b] | 19 | | | | | |

[a]Testis (5), lung (3), kidney (2), bone marrow (1), eye (1), liver (1), spleen (1).
[b]Amniocytes (7), fibroblasts (5), tissue not reported (5), bone marrow (1), lung (1).

represents an older population of individuals than the seizure-free patients, thus the increased frequency of seizures in the literature cohort could be due to an enrichment for older individuals. However, this hypothesis cannot be confirmed, as there was limited data regarding age at ascertainment for the literature cohort or age of seizure onset.

Interestingly, congenital diaphragmatic hernia (CDH), one of the hallmark features that often lead clinicians to entertain the diagnosis of PKS, was seen in far fewer individuals in this cohort versus the PKS literature. The discrepancy in frequency between populations is likely a reflection of the ascertainment process; patients in our patient population are enrolled at family meetings and are therefore less likely affected by the potential complications of CDH, which can include, but are not limited to pulmonary compromise, fetal or early neonatal demise. Therefore, the frequency of CDH is likely more commonly associated with PKS than what our cohort would suggest. The ascertainment bias described above is also likely to account for other observations in severity of features between our cohort and the literature, as those with more complications associated with morbidity and mortality were unlikely to attend to the family meetings.

With that said, individuals in the literature previously recognized as having PKS are likely those with a more "classic" or severe phenotype; individuals who were more likely to be clinically diagnosed first, and molecularly confirmed second, rather than individuals today who may be less involved but for whom molecular analysis indicates the diagnosis. Therefore, the frequency of CDH and other PKS features associated with morbidity and mortality is likely somewhere in the middle—not as frequent a finding as in the literature, but potentially more common than in our cohort. Lastly, the advancement of molecular/array technology and imaging devices in the last decade has improved diagnostic capabilities of not only identifying the presence of the isochromosome, but also the diagnostic capability of recognizing less severe system-specific differences, that had until recently, been less commonly associated with PKS.

## Physical Features

The physical features observed on dysmorphology exams were consistent across patients of different ethnic groups, including children of Caucasian, African American, Asian Indian, Hispanic, and Asian backgrounds. However, this may be influenced by an ascertainment bias since all patients examined had a known diagnosis. Overall, with advancing age, the facial features tend to coarsen with filling in of the temporal hair and a more prominent chin (prognathism). Notable findings in our cohort included the "Pallister lip", first pointed out to us by Dr. Pallister at the first family meeting in 2006, which is different from the classic "cupid's bow" lip in the diffusion of the philtral skin into the vermilion border rather than a sharply demarcated border, as well as hypertelorism, telecanthus. Other clinical exam features noted in our cohort included supernumerary nipples, increased subcutaneous tissue of the extremities, posterior ear pits and a propensity of dermatoglyphic whorls.

## Growth Parameters

More recent growth information was requested in the PKS intake form and the overall trend suggests that individuals with PKS are born with relatively high-normal growth parameters (weight, height, and HC) followed by postnatal growth deceleration, seen typically in the first 3 years of life. The reason for such a unique growth pattern remains unknown to date, yet it has been suggested that it may be due to the growth advantage of chromosomally normal cells over the cells with the isochromosome. Individuals who have had positive molecular confirmation of the isochromosome in peripheral blood by array were younger, whereas the older

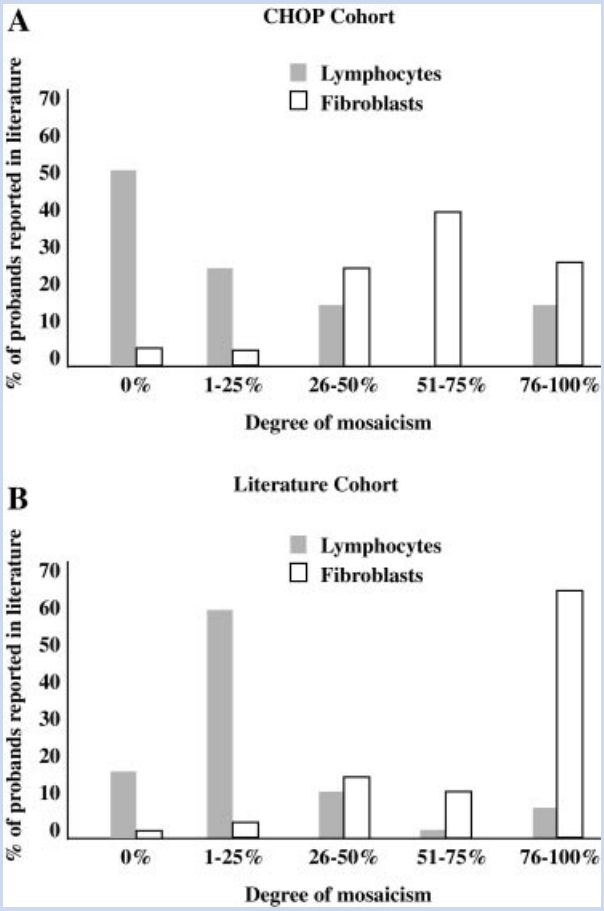


**FIG. 12. Mosaicism in lymphocytes and fibroblasts in PKS. A: CHOP PKS cohort mosaicism data. Of the 24 lymphocyte reports, 50% (or 12 samples) had detection of i(12p) mosaicism. The average percent mosaicism of i(12p) detected in the lymphocytes was ~19%. Ten individuals (45%) had chromosome analysis completed on lymphocytes for which no i(12p) mosaicism was detected. For these 10 individuals, all had i(12p) detected by fibroblast chromosomal analysis. In only one instance was the detection of i(12p) detected only in the lymphocytes and not in fibroblasts. Of the 24 fibroblast samples, 96% (or 23 samples) had detection of i(12p) mosaicism. The average percent mosaicism of i(12p) detected in fibroblasts was ~60%. B: Literature mosaicism data. In general, lymphocytes obtained from peripheral blood showed a higher percentage (16%) of chromosomally normal cells and lower percentage of isochromosome 12p mosaicism (60% of samples showed only 1–25% mosaicism). Conversely, fibroblasts more often indicated the mosaic presence of the isochromosome, as 64% of samples showed the presence of isochromosome 12p in 76–100% of cells karyotyped or arrayed.**

the individual, the less likely it was to find the presence of the isochromosome—representing a decline in mosaic ratio over time [Conlin et al., this issue]. Therefore, it is plausible that the increased presence of the isochromosome earlier on in an affected child's life influences the increased growth initially, but due to the declining mosaic ratio of the isochromosome even within the first year of life, the child then undergoes postnatal growth deceleration.

## Developmental Outcomes

Overall, the milestones of individuals with PKS show both motor and speech delay. However, two patients in our cohort had a relatively high level of functioning, which resulted in delayed diagnosis [Kostanecka et al., 2012]. Both of these school-aged females were ambulatory and verbal at the time of our evaluation. One had an IQ of 69, which is within the range of mild intellectual disability. By comparing the developmental outcomes between individuals with different degrees of mosaicism, we did not find that the level of mosaicism in any particular tissue to be predictive of the severity of neurodevelopmental outcome. Part of the difficulty in determining severity based upon degree of mosaicism detected in fibroblast or blood lymphocytes is due to the tissue specific mosaicism and the difficulty in extrapolating the level of mosaicism in the blood to that of the brain and other internal organ tissues.

## Cytogenetic Data

The cytogenetic data indicate that a higher percentage of chromosomally normal cells and lower degree of mosaicism are present in lymphocytes as compared to fibroblasts, thus confirming that chromosomal analysis by karyotype on fibroblasts is a more sensitive way to detect i(12p) in affected individuals. See Conlin et al. [this issue], for a more formal discussion of isochoromsome detection by microarray technology.

In summary, among our cohort, several previously unreported clinical features were observed including a high prevalence of dermatoglyphic whorls not present in the patients' parents, telecanthus, the "Pallister lip," posterior ear pits, and prenatal macrosomia followed by postnatal growth deceleration. Broad and duplicated thumbs and first toes, although previously described, were seen fairly frequently in this cohort and may be an underappreciated finding in PKS. These novel clinical features were consistently identified among our cohort and may prove to be useful clinical diagnostic aids. In addition, the patients in our cohort demonstrated greater variability in phenotypic spectrum with some displaying milder impairment than the typically described profound intellectual disability. The presence of a milder phenotype underscores the clinical variability and need for careful physical examination and lower threshold for performing skin biopsies in higher functioning individuals with less striking, atypical, mild or less classic clinical presentations who have had normal peripheral blood karyotypes or microarrays.

Additional investigations into the basic genetic and molecular mechanisms of PKS are necessary in order to provide for more comprehensive insights into the underlying genetic variability, downstream targets of the up-regulated genes on 12p, and delineation of a PKS critical region. While there is currently no recognized genotype-phenotype association for PKS, further molecular studies may provide insight into underlying genetic variability among children with differing degrees of severity and presence or absence of medical complications and structural abnormalities associated with this important human developmental diagnosis.

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