ARTICLE

Pallister–Killian Syndrome

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Pallister–Killian syndrome (PKS) is characterized by craniofacial dysmorphism, pigmentary skin anomalies, congenital heart defects, congenital diaphragmatic hernia, hypotonia, intellectual disability, and epilepsy. PKS is caused by extra copies of chromosome 12p, most characteristically a marker isochromosome 12p that demonstrates tissue-limited mosaicism. The cytogenetic diagnosis of PKS is often cumbersome due to the absence of the isochromosome in lymphocytes requiring sampling of other tissues. The mechanism by which the isochromosome 12p results in the constellation of multiple congenital anomalies remains largely unknown. In this review, we summarize the background of, and recent advances in, the clinical and molecular understanding of PKS. © 2014 Wiley Periodicals, Inc.

KEY WORDS: Pallister–Killian syndrome; chromosome 12p

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INTRODUCTION

Pallister–Killian syndrome (PKS) (OMIM#601803) is a multisystem developmental disorder caused, most typically, by mosaic isochromosome 12p, which exists as a supernumerary marker chromosome. The clinical manifestations of PKS include characteristic craniofacial dysmorphism, pigmentary skin anomalies, limb differences, congenital heart defects, congenital diaphragmatic hernia, hypotonia, intellectual disabilities, and epilepsy. Recently, with the advance of molecular diagnostics, our understanding of the causal effects of the isochromosome on individuals with PKS has deepened.

HISTORY

Dr. Pallister first described two institutionalized adult individuals with similar physical features [Pallister et al., 1976]. These individuals had strikingly similar phenotypes including profound intellectual disability, severe epilepsy, "coarse" facial features, kyphoscoliosis, flaccidity and spasticity, and cataracts. Although Dr. Pallister identified the presence of an extra marker chromosome, in the original article, the extra chromosome was described as an isochromosome of an F group (20) chromosome. Subsequently, in 1977, the supranumerary chromosome was correctly identified as isochromosome 12p [Pallister et al., 1977]. An additional patient with similar phenotypic features was described by Teschler-Nicola and Killian [1981] resulting in the most commonly used term for this diagnosis: PKS. This syndrome is also occasionally referred to as Pallister mosaic syndrome, isochromosome 12p syndrome, Killian syndrome, Killian/Teschler-Nicola syndrome or Teschler-Nicola/Killian syndrome and tetrasomy 12p.

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ETIOLOGY

PKS is caused by the presence of extra copies of the short arm of chromosome 12, which most commonly present as a supernumerary marker isochromosome 12p (Fig. 1). This isochromosome 12p is present in a tissue-limited mosaic pattern with highly variable levels of mosaicism. Somatic mosaicism is defined as the presence of two or more populations of cells with different genotypes in an individual who has developed from a single fertilized egg. In PKS, these two populations are karyotypically normal cells and cells containing the supernumerary isochromosome 12p. All reported cases of PKS are due to mosaic isochromosome 12p, and there has never been a report of nonmosaic tetrasomy 12p, which is likely embryonic lethal.

The mechanism leading to the isochromsome 12p cell lines remains to be determined, however, the majority of previously published studies suggest maternal meiosis II nondisjunction as a mechanism of mosaic tetrasomy 12p, although more rarely paternal nondisjunction has also been reported [Turleau et al., 1996; Cormier-Daire et al., 1997; Conlin et al., 2012]. Hence, the isochromosome 12p would be present in a sperm or ovum, which forms a PKS zygote. There is a maternal age effect observed in PKS similar to other autosomal aneuploidy syndromes such as Down syndrome [Wilkens et al., 2012], and in fact, isochromosome 12p is most often demonstrated to be of maternal origin similar to other autosomal aneuploidies [Struthers et al., 1999]. In our PKS research study, the average maternal and paternal ages at conception were 31.7 and 34.9 years old, respectively [Wilkens et al., 2012]. However, the exact mechanism by which the isochromosome 12p is generated during meiosis remains unknown. Although in most cases, meiotic origin of the isochromosome 12p is documented/presumed, previously, one report of a post-zygotic origin of the isochromosome 12p associated with uniparental disomy of chromosome 12 has been published [De Ravel et al., 2004].

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The mosaic ratio of the isochromosome 12p population varies quite significantly even within the same proband. Identification of the isochromosome 12p associated with PKS is complicated by the low frequency of the isochromosome 12p in phytohaemagglutinin (PHA) stimulated peripheral blood lymphocytes, and it frequently requires cytogenetic analysis of fibroblast cells necessitating skin biopsy. In addition to the loss of isochromosome 12p containing cells in the bone marrow over time (it is much less likely to identify the isochromosome in older children and adults in the peripheral blood) it has also been shown that the use of PHA in standard cytogenetic preparations to induce mitoses, promotes the growth of normal cell lines over the isochromsome 12p cells, which results in the difficulty of detecting isochromsome 12p cells in peripheral blood on standard cytogenetic evaluation. Recently, with the introduction of array based cytogenetic analysis such as array comparative genomic hybridization (CGH) and single-nucleotide polymorphism (SNP) arrays, the improved detection of tetrasomy 12p in peripheral blood has been reported [Ballif et al., 2006; Powis et al., 2007; Conlin et al., 2012]. These new diagnostic methodologies have the advantage of being performed on direct DNA preparations from peripheral blood (no stimulation required) and can also more readily detect lower levels of mosaicism. However, even with the use of CGH and SNP array, the detection of iso12p in blood is rarely accomplished in the first year of life, and thereafter, it becomes very difficult to detect iso12p cells in blood. The mosaic ratio in skin fibroblast samples remains relatively stable over time [Conlin et al., 2012].

Marker chromosomes constituted of partial tetrasomy12p [Dufke et al., 2001; Vermeesch et al., 2005; Huang et al., 2007] and chromosomal duplication of 12p are also known to result in a PKS-like phenotype, suggesting the presence of dosage sensitive genes on 12p, which are critical for the pathogenesis of PKS (see the discussion below) [Izumi et al., 2012].

Interestingly, a similar isochromosome 12p has been consistently found in testicular germ cell tumors [Looijenga et al., 2003]. Since many congenital developmental disorders are caused by mutations in genes that have also been implicated in tumorigenesis, the fact that iso12p is often found in testicular germ cell tumors supports the presence of developmentally important genes in 12p.

GENETIC COUNSELING

All reported cases of PKS have been sporadic, and there has yet to be a report of familial recurrence. Hence, empirically the recurrence risk is as close to that of the general population. Theoretically, a recurrence risk could be possible if a parent presented with iso12p germline mosaicism; however this has never been reported. Since a PKS phenotype can be caused by chromosomal duplications inclusive of 12p, if a 12p duplication is identified and results from an imbalanced translocation, parental carriers of the balanced form should be excluded [Izumi et al., 2010]. Therefore, cytogenetic discrimination between mosaic iso12p and 12p duplication is essential in genetic counseling.

There have been many reported cases of prenatal detection of isochromosome 12p by chorionic villi sampling or amniocentesis [Doray et al., 2002]. However, systematic evaluations of outcomes and prognosis of prenatally diagnosed probands has not been reported. With the realization of a wide phenotypic spectrum of PKS, counseling based on a prenatal detection of isochromosome 12p is complicated and the decision process should take into consideration the presence or absence of

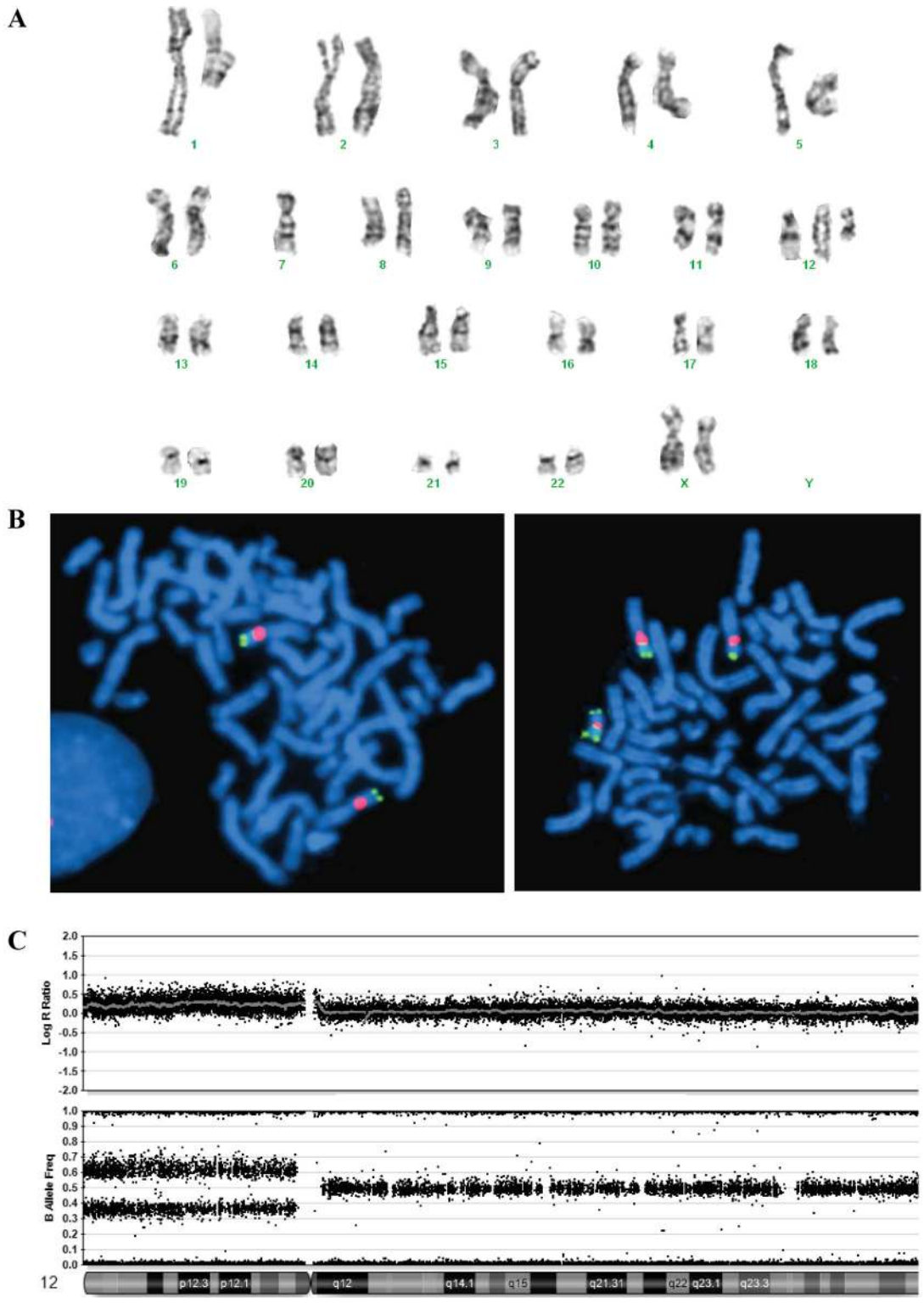

Figure 1. Representation of the supernumerary marker i(12p) chromosome using various diagnostic methods. (**A**) Standard G-banded karyotype. (**B**) Fluorescent in situ hybridization (FISH) image on left shows a normal cell and image on right shows an iso 12p cell (red probe = 12 centromere; green probe = 12p telomere). (**C**) Single nucleotide polymorphism (SNP) array.

major structural birth defects such as congenital diaphragmatic hernia.

INCIDENCE

A prevalence of 1/20,000 has been estimated based on an analysis of liveborn infants resulting from pregnancies with prenatally identified marker chromosome [Brøndum-Nielsen and Mikkelsen, 1995; Bartsch et al., 2005]; however it is very likely that PKS is underdiagnosed due to the difficulty of making a cytogenetic diagnosis from peripheral blood. To date more than 100 cases have been reported, and all cases have been sporadic.

CLINICAL MANIFESTATIONS

The manifestations of PKS can potentially involve any of the body organ systems. The facial features are very characteristic and most useful for diagnostic consideration (Fig. 2). Frequently reported facial features in PKS are frontal bossing, characteristic frontoparietal pattern of alopecia, sparse eyebrows, prominent cupid bow lip of upper vermilion lip, depressed nasal bridge, long philtrum, micrognathia, large mandible, telecanthus, ear pits, thickened ear helices, posterior rotated ears, low-set ears, ear tags, cleft or high palate, bifid

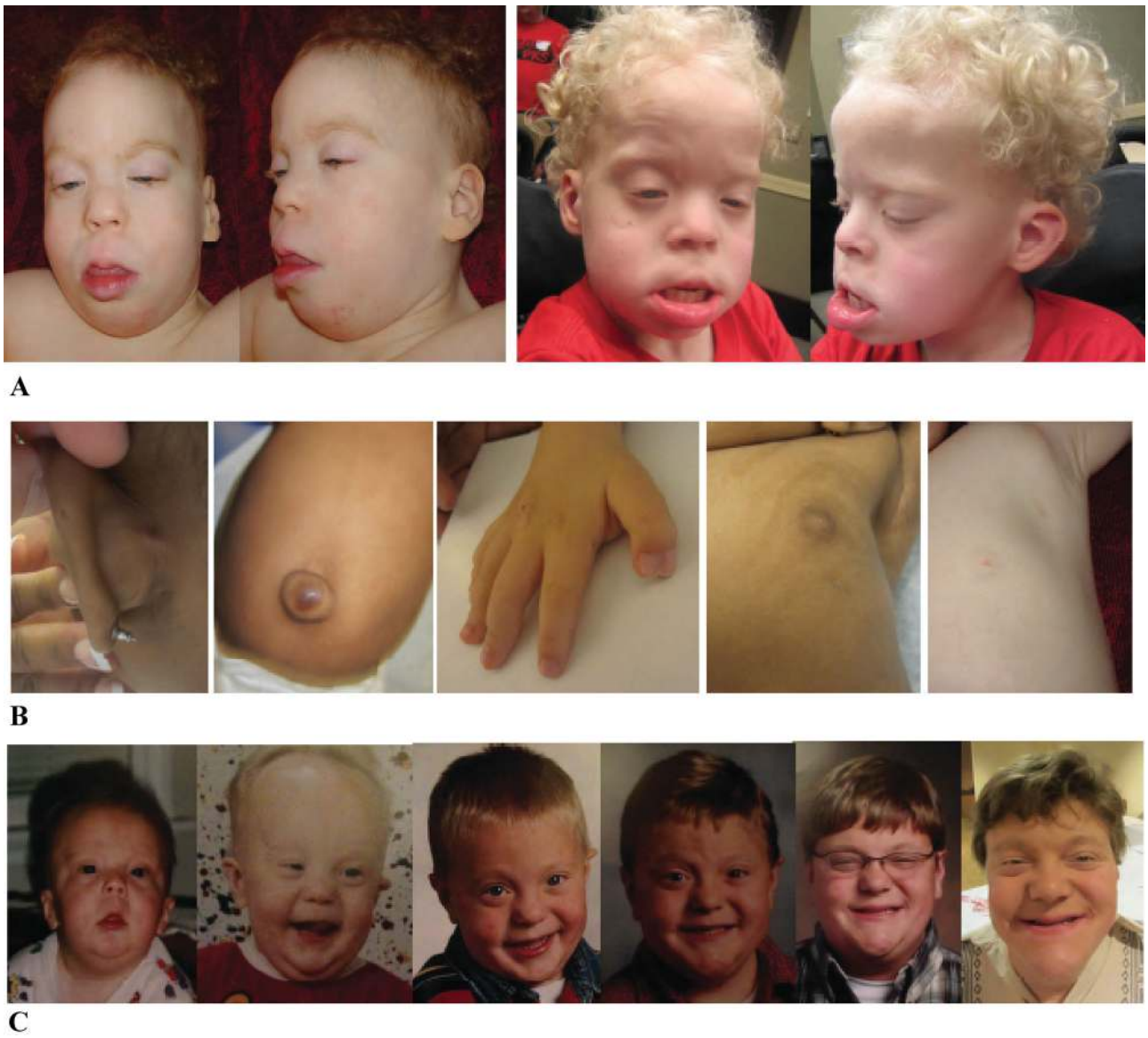

Figure 2. Clinical features of PKS. (**A**) Typical facial appearance in two unrelated children with PKS. Note fronto-parietal sparseness of hair, telecanthus, hypotonic facies, prominent cheeks, eversion of lower lip and invasion of vermilion of upper lip by philtral skin ("Pallister" lip). (**B**) From left to right: Posterior helical ear pit, umbilical hernia, duplicated thumb, swirly hyperpigmentation of skin, supernumerary nipple. (**C**) Evolution of the facial features with age. From left to right: 9 months, 1 year, 5 years, 10 years, 15 years, and 18 years.

uvula, and short neck. Extension of the philtral skin into the vermilion border of the upper lip (termed the "Pallister lip") was seen in 100% of the probands with PKS [Wilkens et al., 2012]. The facial features tend to coarsen over time and the typical pattern of scalp alopecia seen in younger children tends to resolve by older childhood and adolescence making recognition of the diagnosis more difficult in older individuals. Supernumerary/accessory nipples are frequently found. Commonly occurring limb differences are lymphedema, increased soft tissue of the extremities, broad thumbs and first toes and preaxial polydactyly [Wilkens et al., 2012].

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Neurological system

Seizures and structural brain malformations are often seen in PKS. Epilepsy occurs in 53% of probands with PKS, and among the probands who experienced seizures, 85% of them had seizure onset prior to 3.5 years of age. The mean age at seizure onset was 2 years and 4 months [Candee et al., 2012]. Seizure types frequently seen in PKS include myoclonic (56%), generalized convulsions (48%), and clustered tonic spasms (30%) [Candee et al., 2012]. Structural brain defects are variable, and have been reported in up to 60–70% of PKS probands. Clinically, most PKS probands have hypotonia during infancy, although variable spasticity and hypertonia can be seen in older individuals [Wilkens et al., 2012].

Cardiac System

Structural heart differences are seen in around 40% of the probands. Septal defects such as atrial or ventricular septal defects (15% of PKS cohort) were the most commonly seen congenital heart differences. Other structural difference frequently found in PKS include bicuspid aortic valve, aortic dilatation, PDA and PFO [Tilton et al., 2014]. Complex congenital heart disease has been reported mainly in the prenatally ascertained PKS cases [Gilgenkrantz et al., 1985; Wilson et al., 1994; Grech et al., 1999; Langford et al., 2000; Doray et al., 2002]; however, the incidence of such complex congenital heart disease seems to be very low at least in PKS probands who survive the neonatal period [Tilton et al., 2014]. One of the rare but potentially life-threatening cardiac complications in PKS is later onset cardiomyopathy [Ward et al., 1988; Tilton et al., 2014].

Ophthalmologic System

Ophthalmologic involvement is seen in 87% of individuals with PKS. In our previous study, 75% had some degree of visual impairment including strabismus, nystagmus or myopia, and 19% of the probands were diagnosed as legally blind [Kostanecka et al., 2012; Wilkens et al., 2012].

Auditory System

Hearing loss is common in PKS with 77% of individuals having varying degrees of hearing impairment. The frequency of sensorineural, conductive, and mixed hearing loss is 38%, 29%, and 33%, respectively. In most instances, the hearing impairment is bilateral [Wilkens et al., 2012].

Gastrointestinal System

Gastrointestinal system involvement was found in 52% of individuals with PKS. Intestinal malrotation and congenital diaphragmatic hernia represents the most commonly reported gastrointestinal malformations, and reported in 12% and 11% of individuals with PKS, respectively. Umbilical hernias and displacement of the anus were also frequently seen. Functional gastrointestinal manifestations are also common, and these manifestations include feeding difficulty, dysphagia, constipation, and gastroesophageal reflux disease [Wilkens et al., 2012].

Genitourinary System

The most commonly identified genitourinary manifestation was cryptorchidism. Other manifestations identified in PKS include hypospadias, small genitalia and hydrocele [Wilkens et al., 2012].

Musculoskeletal System

Polydactyly, joint contractures and hip dislocations have all been consistently reported in PKS [Wilkens et al., 2012].

Dermatologic System

Skin pigmentation differences (hypopigmentation/hyperpigmentation) indicative of the mosaic chromosomal abnormality is found in 45% of the probands with PKS [Wilkens et al., 2012].

Skin pigmentation differences (hypopigmentation/ hyperpigmentation) indicative of the mosaic chromosomal abnormality is found in 45 of the probands with PKS.

Pulmonary System

In individuals with diaphragmatic hernias respiratory complication can arise from resultant lung hypoplasia [Wilkens et al., 2012].

Growth Patterns

PKS individuals show a very unique growth pattern characterized by prenatal overgrowth and postnatal growth deceleration. Birth measurements including weight, length and head circumference are above 50th centile in most individuals; however, after birth, many PKS probands demonstrate growth deceleration, dropping into the lower centiles in the first few years of life [Wilkens et al., 2012].

Developmental History and Behavioral Characteristics

Most individuals with PKS manifest severe to profound developmental delay,

although there have been an increasing number of mildly affected individuals with PKS reported [Kostanecka et al., 2012]. Average ages for achieving motor milestones in PKS include: rolling—10.8 months, sitting independently—21.2 months, walking—38.8 months. Speech initiation was at 36 months, although there are many individuals with PKS who do not attain speech [Wilkens et al., 2012]. Repetitive hand and body movements were frequently noticed (75%), and self-injurious behaviors were also common (25%).

PHENOTYPIC SPECTRUM

The full phenotypic spectrum has yet to be full characterized. An increasing recognition of a milder end of the spectrum has been partially enabled by new diagnostic methodologies such as array based copy number detection. CGH and SNP arrays more readily detect low levels of mosaicism in samples and can more readily identify the isochromosome 12p in peripheral blood. Still, a diagnosis of PKS often requires a clinical suspicion and, even with array- based diagnostics, many times requires testing of tissue other than blood to establish a diagnosis. As the milder end of the PKS spectrum, and the adult phenotype, is not well recognized by clinicians often a negative blood test is the end of testing as buccal or skin biopsy testing is not considered. We recently reported on two milder individuals [Kostanecka et al., 2012]. One of these two individuals had IQ composite score of 69 on the Kaufman Brief Intelligence Test and was only diagnosed based on some mild skin pigmentary differences that led to chromosomal testing on a skin biopsy. Therefore, the true extent and prevalence of the milder end of the phenotypic spectrum remains to be determined.

Life Expectancy

The life expectancy in PKS has not been formally evaluated. We know of individuals with PKS in their 40s and 50s (unpublished data), and it is probable that there are many older PKS individuals who have never been diagnosed, since many adults with intellectual disability have not been formally evaluated by clinical geneticists.

Genotype–Phenotype Correlation

Previous studies have demonstrated the absence of a correlation between the mosaic ratio and clinical severity [Tilton et al., 2014; Wilkens et al., 2012]. One possibility explaining this absence of the correlation is the difficulty of extrapolating the mosaic ratio in the organ, whose abnormality directly leads to the symptom. For example, there has been no report of examining mosaic ratios in the brain tissue of variably affected PKS individuals. As exemplified by the absence of iso12p in the blood sample of PKS individuals, percent mosaicism is different among the different tissues/organs in a single individual. Furthermore, percent mosaicism can change as the proband grows.

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MOLECULAR ETIOLOGY

12p Minimum Critical Region

Chromosome 12p is 34.3 Mb in length, and contains approxiamtley 350 genes. Many biologically important genes exist on 12p including cancer-associated genes such as *KRAS* and *ING4*, and developmental genes such as *Nanog*, *CHD4*, and *SOX5*. Since variable interstitial duplications of 12p duplication can manifest a PKS phenotype, there likely exists a critical genomic region on 12p, an extra copy of which leads to the PKS phenotype. Based on the experience of a patient with PKS features due to microduplications of 12p13.31, we have previously defined a critical region for PKS [Izumi et al., 2012]. This proband had many clinical features of PKS including facial dysmorphia, congenital heart defect, limb defects and neurological features. These two microduplications were located at 12p13.31 and included 26 genes, all of which represents potential candidate genes for the PKS phenotype. Among these 26 genes, three genes, *ING4* and *CHD4* represent strong candidates, given their known function. *ING4* belongs to the family of inhibitor of growth (ING), which plays important roles in transcriptional regulation through associations with various binding partners including trimethylated histones and histone modifiers [Nozell et al., 2008; Hung et al., 2009]. The overexpression of *ING4* negatively regulates cell growth resulting in cell cycle arrest, and enhanced cell apoptosis [Zhang et al., 2004]. *CHD4* is a chromodomain helicase DNA binding protein, and constitutes a catalytic subunit of the nucleosome remodeling deacetylase (NuRD) transcriptional repressor complex, which plays an important role in chromatin remodeling [Tong et al., 1998].

Transcriptome Alteration in PKS

The tetrasomic state of critical genes on 12p results in misexpression of multiple downstream genes that are in turn responsible for the constellation of cognitive and structural birth defects seen in PKS. Identification of these downstream effectors will result in insights into the pathogenesis of PKS. In hopes of identifying these downstream-effector genes, we have performed genome-wide expression array analysis using samples obtained from PKS probands [Kaur et al., 2014]. The most statistically significantly dysregulated genes on 12p mapped to within the PKS defined critical region we defined on 12p13.31, further supporting the notion that 12p13.31 encompasses the genes important for the PKS phenotype. From the lists of significantly dysregulated genes in PKS, we were able to identify several genes whose expression alteration that may be directly related to the

phenotype of PKS. For example the most significantly down regulated gene was *ZFPM2*, mutations in which are known to cause congenital heart defects and congenital diaphragmatic hernia [Pizzuti et al., 2003; Ackerman et al., 2005]. *GATA6* was also demonstrated to be downregulated in PKS samples. Mutations of *GATA6* are associated with various types of CHD; hence, *GATA6* may also be associated with the pathogenesis of CHD in PKS [Kodo et al., 2009]. *IGFBP2* was the second most significantly upregulated gene. IGFBPs are known to have a function in modulating the IGF signaling pathway, therefore, upregulation of IGFBP2 represents a strong candidate gene whose dysregulation may be related to the unique growth phenotype seen in PKS [Hoeflich et al., 1999]. The involvement of microRNAs located on 12p was also evaluated in relation to the transcriptomic abnormality in PKS [Izumi et al., 2014]. Among the several 12p microRNAs, miR-1244 was significantly up-regulated in PKS. The molecular targets of miR-1244 include *MEIS2* whose haploinsufficiency causes congenital heart defects and cleft palate [Crowley et al., 2010]. Therefore, it is possible that the overexpression of microRNAs located on 12p contribute to the pleiotropic phenotype of PKS as well.

CONCLUSION

The ground breaking work by Dr. Philip Pallister and others in clinically recognizing, characterizing and identifying the underlying cytogenetic cause of what has been termed PKS, has led to decades of work in more fully understanding the medical and clinical issues faced by affected individuals. The resultant improved diagnostic and management guidelines, coupled with the establishment of PKS-specific family support groups (PKS Kids [http://www.pkskids.net], PKS Kids Italia [http://www.pksitalia.org]), have dramatically improved the lives of affected individuals and their families. Our understanding of PKS has deepened significantly over the last decade thanks to the utilization of recent advance in molecular diagnostics, however, the full phenotypic spectrum and precise understanding of the underlying molecular mechanism remains to be determined.

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