REVIEW ARTICLE

# Prenatal Sonographic Features of Pallister-Killian Syndrome

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Pallister-Killian syndrome (PKS), which is characterized by mental retardation, seizures, pigmentary skin lesions and dysmorphic facial features, is a rare chromosomal anomaly with the mosaic presence of an extra tissue-specific isochromosome 12p (mosaic tetrasomy 12p). Advanced maternal age is believed to be a risk factor for PKS. Ultrasound is a useful tool in the prenatal detection of characteristic findings associated with PKS. This article provides an overview of the prenatal sonographic features of PKS, including congenital diaphragmatic hernia, polyhydramnios, abnormal extremities, increased nuchal translucency or nuchal edema, cardiovascular anomalies, central nervous system anomalies, an abnormal facial profile, and other rare anomalies. Appropriate tissue samples and laboratory analytic techniques should be selected for an accurate prenatal diagnosis because of the instability of isochromosome 12p and the potentially incorrect interpretation as tetrasomy 21q on the traditional G-banded technique. Fryns syndrome, which has phenotypic overlap with PKS, is also discussed. Increasing awareness and knowledge of various anomalies of PKS on prenatal ultrasound would be helpful for the early detection of PKS. Definite diagnosis of fetuses with PKS could help clinical physicians in the decision-making process during the prenatal or postnatal periods.

**KEY WORDS** — Pallister-Killian syndrome, prenatal ultrasound

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## Introduction

Pallister-Killian syndrome (PKS, OMIM No. 601803), described by Pallister et al [1] and Killian et al [2], is a rare and sporadic chromosomal anomaly with the mosaic presence of a supernumerary tissue-limited isochromosome 12p [i(12p)] (mosaic tetrasomy 12p) [3]. Clinical features of postnatal PKS include mental retardation, seizures, pigmentary skin lesions, and dysmorphic facial features such as sparse anterior scalp hair, hypertelorism, short nose, flat nasal bridge, short neck and flat occiput [4]. However,

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the mosaic level of i(12p) is not correlated with the severity of congenital anomalies [5].

Prenatal diagnosis of PKS is difficult because of a wide range of abnormalities in fetuses with PKS and tissue-specific distribution of i(12p). To date, there have been more than 60 reported cases of prenatally-diagnosed PKS. Among these cases, some fetuses with PKS were diagnosed as an incidental finding after karyotyping for advanced maternal age, which is thought to be a risk factor for PKS. In addition, ultrasound detection of fetal anomalies could be another useful tool in the diagnosis of PKS. We review here the associated sonographic features in fetuses with PKS and the reported prenatal sonographic findings including congenital diaphragmatic hernia (CDH), polyhydramnios, abnormal extremities, increased nuchal translucency (NT) or nuchal edema, cardiovascular anomalies, central nervous system (CNS) anomalies, abnormal facial profile, and other rare anomalies. Accurate prenatal diagnosis is made by the identification of i(12p) in specific tissue samples by using appropriate analytic techniques. Fetuses of PKS can have similar structural anomalies to those of Fryns syndrome (FS) and the differential diagnosis is discussed. Early diagnosis of PKS is important for genetic counseling and obstetric management.

## Prenatal Sonographic Features

Gilgenkrantz et al [6] reported the first case of prenatally detected PKS based on abnormal sonographic findings. Currently, ultrasound is thought to be a valuable tool in the prenatal detection of characteristic findings associated with PKS. Prenatal sonographic features of published PKS cases are summarized in Table 1 [5–43]. Prenatally diagnosed PKS cases without abnormal sonographic reports were excluded in this review.

### *Congenital diaphragmatic hernia*

Identification of abdominal organs in the chest indicates CDH. Left-sided CDH is more common and typically characterized by the heart and the mediastinum deviated to the right side, and the possible presence of a gastric bubble or bowel peristalsis in the chest. Right-sided CDH is more difficult to diagnose because of the similar echogenicity between the lung and a herniated liver on prenatal ultrasound. Doppler study of the umbilical vein or hepatic vessels and visualization of the gall bladder may be helpful for diagnosis of CDH. Prenatal ultrasound can detect CDH as early as 15 weeks [44]. In Table 1 [5–43], 27 fetuses with PKS had CDH, a condition highly specific and frequently found in PKS, diagnosed prenatally. The occurrence of CDH might be the major cause of perinatal or postnatal death of PKS due to lung hypoplasia [13]. Several reports have shown that only 10–15% of PKS cases have CDH [18,45,46]. However, Mowery-Rushton et al [26] suggested that 50% or more of PKS cases might have CDH due to undiagnosed and lethal cases with PKS.

### *Polyhydramnios*

Table 1 shows 25 fetuses with PKS that had polyhydramnios, also the most consistent ultrasound finding. The reason for the development of polyhydramnios in association with PKS is unknown, but it may be associated with the presence of CDH due to inappropriate swallowing of amniotic fluid [25]. Only one fetus with PKS was reported to have oligohydramnios accompanied by short femurs, cerebral ventriculomegaly and intrauterine growth restriction.

### *Abnormal extremities*

Micromelia is the main feature suggestive of PKS, especially the shortness of the femurs and humerus. As shown in Table 1, prenatal ultrasound has detected rhizomelic micromelia or short femurs in 19 fetuses of PKS. In addition to micromelia, other skeletal anomalies such as bilateral talipes, club feet, club hands and clenched hands have been observed in fetuses of PKS.

### *Increased NT or nuchal edema*

Fetal NT refers to the sonographic finding of a subcutaneous collection of fluid behind the fetal neck in the first trimester. Increased NT is significantly

**Table 1.** Literature review of prenatal sonographic features, prenatal and postnatal molecular cytogenetic results and outcome of published PKS cases [5–43]

| Ref. | Maternal age (yr) | CDH | PHA | NT | Prenatal sonographic features | | | | | Prenatal diagnosis* | Postnatal diagnosis* | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Extremities | Heart | CNS | Face | Others | | | |
| 6 | 36 | | (+) | Nuchal edema | RM, club feet | Ebstein's anomaly | Agenesis of the vermis, cerebellar hypoplasia | Hypertelorism | | Amniocyte (100%) | Cord (1%), fibroblast (98%) | TOP |
| 7 | 35 | | (+) | | | | | | Hydrops | | Skin (+) | TOP |
| 8 | 21 | (+) | (+) | | | | | | | | Muscle (90%) | Neonatal death |
| | 42 | (+) | | | | | | | | Amniocyte (18%) | Villi (0%) | IUFD |
| 9 | 33 | | (+) | | RM | | | Hypertelorism | Omphalocele | Amniocyte (100%) | | Preterm, died |
| 10 | N/A | (+) | (+) | | | | | Hypertelorism | IUGR | | | |
| 11 | 37 | | | Nuchal edema | Short femurs | | | | | Amniocyte (75%) | Blood (5%), lung and testis (78–93%) | TOP |
| 12 | 37 | | | | | | | | Hydrops | Villi (93%) | | TOP |
| 13 | 28 | (+) | (+) | | | | | | | Villi (100%), amniocyte (73%) | Skin | TOP |
| 14 | 33 | | (+) | | | | Prominent cisterna magna | | Hypoplastic stomach, hydronephrosis | Amniocyte (79%) | Skin (97%), blood (5%) | Preterm, died |
| 15 | 28 | | (+) | | Short femurs | | | | Omphalocele | Amniocyte (88%) | Skin (95%), cord blood (3%) | Preterm, died |
| 16 | 32 | (+) | (+) | | | | | | | Amniocyte (70%), cord blood (13%) | Skin (100%) | Preterm, died |
| 17 | 37 | (+) | | | Short femurs | | | | | Amniocyte (80%) | Skin (100%), blood (80%), placenta (30%), chorion (50%) | TOP |
| 18 | 38 | (+) | (+) | | | | | | | Amniocyte (81%), cord blood (0%) | | TOP |
| | 36 | (+) | (+) | | | | | | | Amniocyte (+), cord blood (35%) | | Neonatal death |
| | 38 | (+) | (+) | | | | | | | Cord blood (0%) | | Neonatal death |

(*Contd*)

**Table 1.** (*Continued*)

| Ref. | Maternal age (yr) | CDH | PHA | NT | Prenatal sonographic features | | | | | Prenatal diagnosis* | Postnatal diagnosis* | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Extremities | Heart | CNS | Face | Others | | | |
| 19 | 22 | (+) | (+) | | | | | | | Amniocyte no growth, cord blood (49%) | | Preterm, died |
| 20 | 31 | (+) | | Nuchal cyst | Talipes | | Ventriculomegaly, cervical spina bifida | | | Villi (0%, 7%) | | TOP |
| 21 | 33 | (+) | (+) | | Short femurs | Double-outlet right ventricle | Flat face, abnormal ears | Overgrowth | | Amniocyte (89%) | | TOP |
| 22 | 45 | | (+) | | | | | | | Villi (0%) | Skin (100%), blood (0%) | DD, 18 mo |
| 23 | 37 | | | Hygroma | | | | | | Amniocyte (+) | | TOP |
| 24 | N/A | | (+) | | | | | | | Amniocyte (100%) | 30% | TOP |
| 25 | 35 | (+) | (+) | | | | | | | Amniocyte (38%) | Cord blood (0.5%), skin (70%), cord (48%), placenta (8%) | Preterm, died |
| 5 | 44 | (+) | | | | | Ventriculomegaly | Flat face | | Villi (22%), amniocyte (23%, 12%) | Cord (100%) | IUFD |
| | 28 | | (+) | | | | | | | Cord blood (0%) | Blood (3.5%), tendon (93%) | Preterm, died |
| 26 | 38 | (+) | | | | | | | | Amniocyte (0%) | Cord, villi, skin interphase FISH(+), normal G-banding | Preterm, died |
| 27† | | (4/11) | (2/11) | Hygroma (1/11) | Short limbs (5/11) | Right-sided enlargement, pulmonic stenosis (1/11) | | | Hydrops (2/11) | Amniocyte (92%)<br>Amniocyte (38%)<br>Amniocyte (36%) | Blood (0%), skin (92%)<br>Skin (10%)<br>Blood (7%), skin (58%) | TOP (5/11)<br>IUFD (4/11) |

(*Contd*)

**Table 1.** (*Continued*)

| Ref. | Maternal age (yr) | CDH | PHA | NT | Prenatal sonographic features | | | | | Prenatal diagnosis* | Postnatal diagnosis* | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Extremities | Heart | CNS | Face | Others | | | |
| 27† | | | | | | | | | | Amniocyte (100%)<br>Amniocyte (100%)<br><br>Amniocyte (90%)<br>Amniocyte (35–71%)<br>Amniocyte (100%)<br>Amniocyte (11–74%)<br><br>Amniocyte (0%) | Skin (73%)<br>Skin (100%), blood (8%),<br>Blood (0%)<br><br><br><br>Blood (0%), skin (82%)<br>Blood (0%) skin (0–99%) | |
| 28 | 34 | (+) | | | | Atrioventricular septal defect | | SUA, ambiguous genitalia | | Amniocyte (0%), cord blood (0%) | | IUFD |
| 29 | 39 | | (+) | | RM | | Ventriculomegaly | Frontal bossing | | Amniocyte (25%), cord blood (14%) | Blood (14%), amniotic fluid (31%), skin (33%) | TOP |
| 30 | NA | | | | | | | | Overgrowth | Amniocyte (0%) | Blood (0%), skin (26%) | MR, 20 mo |
| 31 | 30 | (+) | | 10.4 mm | RM, bilateral talipes | Left heart hypoplasia | | | Hydrops | Villi (6%) | Testis (100%), skin (97%) | TOP |
| 32 | 40 | (+) | (+) | | RM, clenched hands | | Ventriculomegaly | Small nose, thin lip, protruding lip | | Amniocyte (50%), cord blood (12%) | | TOP |
| 33 | 35 | (+) | (+) | | | | | | | Cord blood (0%) | Skin (65%) | DD, 2 yr |
| 34 | 27 | (+) | | | RM, club hands | Tetralogy of Fallot, pericardial effusion | Dandy-Walker malformation | | | Amniocyte 1 cell, cord blood (0%) | Cord (9%) | TOP |
| 35 | 40 | (+) | | Hygroma | | | | | Omphalocele | Short (–), long (+)‡ | | TOP |

(*Contd*)

**Table 1.** (*Continued*)

| Ref. | Maternal age (yr) | CDH | PHA | NT | Prenatal sonographic features | | | | | Prenatal diagnosis* | Postnatal diagnosis* | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Extremities | Heart | CNS | Face | Others | | | |
| 36 | 31 | (+) | (+) | 8.5 mm | RM, club feet | | Macrocephaly | Flat face, small nose, protruding lips | Overgrowth | | Cord blood (23%) | Preterm, died |
| 37 | 42 | | | 4.2 mm | | Left heart hypoplasia, ventricular septal defects, tricuspid regurgitation | | | | Amniocyte (+) | | TOP |
| 38 | 33 | | | Hygroma | | | | | | Amniocyte (+) | | TOP |
| | 30 | | | 3.2 mm | RM | | | | SGA, echogenic bowel | Amniocyte (72%, 75%) | Cord (12%) | TOP |
| 39 | 34 | (+) | | 5.4 mm | Micromelia | | | | | Villi (50%) | Tendon (90%) | TOP |
| 40 | 25 | | Oligo | | RM | | Ventriculomegaly | | IUGR | Amniocyte (+), cord blood (0%) | | TOP |
| 41 | 38 | | | | | Right ventricular dilation, pulmonic stenosis | Lemon sign | | SGA | Amniocyte (80%) | | TOP |
| 42 | 39 | | (+) | | | | | Retrognathia, long philtrum, turned up nose | | Amniocyte (24%) | Blood [0%, 4% (FISH)], placenta (10%), brain [12% (FISH)], pancreas [13% (FISH)], testicle [15% (FISH)], thymus [11% (FISH)] | TOP |
| 43 | 40 | | | | | | Macrocephaly | Hypertelorism, flat face, small nose, protruding lips | | Amniocyte (64%) | Cord (100%) | TOP |

**The numbers in brackets are the percentage of tetrasomy 12p in examined cells; †the authors only summarized the sonographic features of 11 fetuses with PKS; ‡tetrasomy 12p detected in long-term culture of villi but not in short-term culture of villi. CDH = congenital diaphragmatic hernia; PHA = polyhydramnios; NT = nuchal translucency; CNS = central nervous system; DD = delayed development; IUFD = intrauterine fetal death; IUGR = intrauterine growth restriction; MR = mental retardation; oligo = oligohydramnios; RM = rhizomelic micromelia; N/A = not available; SGA = small for gestational age; SUA = single umbilical artery; TOP = termination of pregnancy; FISH = fluorescence in situ hybridization.*

associated with chromosomal abnormalities [47]. Increased NT, nuchal edema or hygroma coli have been reported in 12 fetuses with PKS (Table 1 [5–43]). Among these cases, five had CDH and three had cardiovascular anomalies, but four had no detectable cardiac anomalies or CDH. The mechanism of increased NT in PKS is unknown, but the simultaneous presence of cardiac anomalies and/or a diaphragmatic hernia has been considered a possible cause [48,49].

### *Cardiovascular anomalies*

Only eight fetuses with PKS have been found with cardiovascular defects (Table 1 [5–43]). Various anomalies have been reported including Ebstein's anomaly, double outlet right ventricle, atrioventricular septal defect, hypoplastic left heart, tetralogy of Fallot, right ventricular hypertrophy, ventricular septal defects, tricuspid regurgitation and pulmonic stenosis. All of the PKS fetuses with cardiac anomalies also have other structural anomalies. Therefore, cardiac anomalies might not be the only feature for prenatal diagnosis of PKS.

### *CNS anomalies*

Ten fetuses with PKS have been found with CNS anomalies including ventriculomegaly, agenesis of the vermis, cerebellar hypoplasia, enlarged cisterna magna, cervical spina bifida, lemon sign, and Dandy-Walker malformation (Table 1 [5–43]). Among these features, ventriculomegaly is the most common.

### *Abnormal facial profile*

Abnormal facial features are the main manifestations of postnatal PKS cases including sparse anterior scalp hair, hypertelorism, short nose, flat nasal bridge, short neck and flat occiput. Ten fetuses with PKS were found to have an abnormal facial profile including hypertelorism, flat face, abnormal ears, frontal bossing, small nose, thin lip with protruding lower lip, retrognathia, long philtrum, and turned up nose (Table 1 [5–43]). Paladini et al [32] first described the typical facial abnormalities, including a small nose and a thin upper lip with a protruding lower lip, in a fetus with PKS on mid-trimester ultrasound. They believed that the diagnosis of PKS should be considered when the above typical facial features were present in fetuses with diaphragmatic hernia and short limbs. Sananes et al [42] reported that a 3D examination of the fetal face may be useful for diagnosing PKS.

### *Rare anomalies*

Chen [50] reported that omphalocele was found in cases of PKS with mosaic tetrasomy 12p. Three PKS fetuses with omphalocele have also been found with other anomalies such as polyhydramnios, rhizomelic micromelia, cystic hygroma and CDH (Table 1 [5–43]). Fetal overgrowth has been observed in three cases of PKS. Zollino et al [30] speculated that unexplained fetal overgrowth could be an indicator for karyotypic analysis. However, being small for gestational age and intrauterine fetal growth restriction are also distinct findings reported in several fetuses of PKS (Table 1). Fetal hydrops associated with PKS is not common but it has been reported in five fetuses (Table 1). The mechanism of fetal hydrops is thought to be associated with other anomalies such as fetal cardiac defects and CDH [31]. The least common reported features include hydronephrosis, ambiguous genitalia, a single umbilical artery, echogenic bowel and hypoplastic stomach (Table 1).

## Molecular Cytogenetic Analysis

PKS is diagnosed with the cytogenetic presence of an extra i(12p) in tissue-limited mosaicism. Based on traditional G-banded analysis, it is difficult to differentiate the extra i(12p) from inv dup 21q (tetrasomy 21q) [14,51–53]. The addition of targeted fluorescence *in situ* hybridization using chromosome 12-specific DNA probes [14,29] or other molecular genetic analyses such as micro-satellites and comparative genomic hybridization are useful adjuncts to making an accurate diagnosis.

The mosaic level of i(12p) varies in different tissue samples [54]. The i(12p) can be easily identified in cell cultures from skin fibroblasts, chorionic

villous cells and amniocytes, but it is rarely detected in rapidly growing cells such as peripheral blood lymphocytes or cord blood [28,29]. In addition, a dramatic decrease in mosaic i(12p) levels has been observed after subculture or long-term cultures of various fetal tissues such as blood lymphocytes, amniocytes, chorionic villi and fibroblasts [16,55]. It is important to select the appropriate samples and culture types for karyotypic analysis with implications for prenatal and postnatal diagnosis (Table 1 [5–43]). Interphase fluorescence *in situ* hybridization can remove the need for cell culture to easily detect the signal of i(12p) [14,21]. Currently, array comparative genomic hybridization based on genomic DNA extracted directly from uncultured blood cells can efficiently identify this mosaic i(12p) [56].

The origin and mechanism of formation of i(12p) have been studied previously [57,58]. Parental study of i(12p) has shown that most cases with PKS are of maternal origin and are related to advanced maternal age, which is considered as the main factor for isochromosome formation [35,59]. Either a prezygotic origin or a postzygotic origin of i(12p) has been proposed [35,60–62]. As there is no difference between PKS phenotypes of paternal origin i(12p) and those of maternal origin i(12p), therefore, PKS is not considered a genomic imprinting disorder [5,23,24,60].

**Table 2.** Prenatal sonographic features and differential diagnosis of Pallister-Killian syndrome

| |
|---|
| **Prenatal sonographic features** |
| Congenital diaphragmatic hernia |
| Polyhydramnios |
| Abnormal extremities |
| Rhizomelic micromelia, club feet, club hands, clenched hands and talipes |
| Increased nuchal translucency, nuchal edema or cystic hygroma |
| Cardiovascular anomalies |
| Ebstein's anomaly, double outlet right ventricle, atrioventricular septal defect, hypoplastic left heart, tetralogy of Fallot, right ventricular hypertrophy, ventricular septal defects, tricuspid regurgitation and pulmonic stenosis |
| Central nervous system anomalies |
| Ventriculomegaly, agenesis of the vermis, cerebellar hypoplasia, enlarged cisterna magna, cervical spina bifida, a lemon sign, and Dandy-Walker malformation |
| Abnormal facial profile |
| Hypertelorism, flat face, abnormal ears, frontal bossing, small nose, thin lip and protruding lower lip, retrognathia, long philtrum and turned up nose |
| Rare anomalies |
| Omphalocele, fetal hydrops, macrosomia, born small for gestational age, intrauterine fetal growth restriction, hydronephrosis, hypoplastic stomach, ambiguous genitalia, echogenic bowel and single umbilical artery |
| **Differential diagnosis** |
| Fryns syndrome |

## Differential Diagnosis

Fetuses with PKS can have CDH, polyhydramnios, abnormal extremities, increased NT or nuchal edema, cardiovascular anomalies, CNS anomalies, abnormal facial profile and other rare anomalies. Because of these common anomalies in PKS, differential diagnosis should include FS, the manifestations of which include CDH, lung hypoplasia, distal limb hypoplasia, polyhydramnios, craniofacial anomalies, cardiac defects and internal malformations [63–65]. FS is an autosomal recessive disorder and is usually lethal. The recurrence risk is higher in FS than in PKS. Structural anomalies such as CDH, polyhydramnios and cardiac anomalies can be detected in both syndromes but dysmorphic facial features are different. Micrognathia and cleft lip/palate are commonly seen in FS, but hypertelorism, small nose, flat and broad nasal root, and thin upper lip with a protruding lower lip are often seen in PKS [32]. Clinically, ultrasound detection of the different facial features can distinguish between these two syndromes but it is difficult to clearly visualize the difference in early pregnancy. Hence, molecular and cytogenetic demonstration of mosaic i(12p) on

prenatal tissue samples is still required to make a definite diagnosis of PKS.

## Conclusion

The present article provides an overview of prenatal sonographic features of PKS. Prenatal detection of CDH, polyhydramnios, rhizomelic micromelia, increased NT or nuchal edema, cardiac anomalies, CNS anomalies, abnormal facial profile and other rare anomalies should alert clinicians to the possibility of PKS (Table 2). Recognition of these congenital anomalies in association with PKS may lead to the selection of appropriate tissue samples for chromosome analysis because mosaic i(12p) might only be identified in specific tissues by selective molecular cytogenetic analyses. If the traditional cytogenetic result is normal but prenatal sonographic findings remain suggestive for PKS, alternative tissue samples or additional diagnostic tools should be available for further study. FS having phenotypic overlap with PKS should be differentiated. Accurate diagnosis of fetuses with PKS could be beneficial for genetic counseling and clinical management.

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