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De novo unbalanced translocation of chromosomes 3 and 10 and associated phenotype in a twin gestation. M.S.Verp[1,2], C.J.De Ruiter[3] and R. Spiro[2]. [1]Dept. of Obstetrics and Gynecology, [2]Dept. of Human Genetics, and [3]The Pritzker School of Medicine,Univ. of Chicago, IL.

We report one fetus of a twin pregnancy with a de novo unbalanced translocation detected by elevated maternal serum alpha-fetoprotein(MSAFP) and an abnormal ultrasound examination.

A 33 year old African female was referred for genetic counseling at 19 weeks gestation because of a MSAFP of 4.3MOM She and the father, a 40 year old African male, had one normal child, and he had a second healthy child by another woman. Other family history was noncontributory. Ultrasound examination demonstrated a twin gestation. Twin A appeared structurally normal, Twin B showed omphalocele, echogenic focus in the left ventricle, single umbilical artery, polydactyly, and short femurs. Amniocentesis demonstrated normal chromosomes for Twin A; Twin B had an unbalanced translocation: 46, XY, der(3) t(3;10) (p25;q11.2), del(10) (q11.2).ish der(3) t(3;10)(p25;q11.2)(B47a2-) with deletion of both the 3p telomere and 10q11.2. Both parental karyotypes were normal.

The patient delivered at 29 weeks gestation . Twin A was a phenotypically normal 1140g female who died of Group B streptococcal sepsis. Twin B weighed 906g, w a s hypotonic, had low hairlines, widely open fontanelles, coarse facial features, short neck, distended abdomen, hypoplastic scrotum, rocker bottom feet, divarication of recti, postaxial polydactyly of all extremities, dilated right atrium, ventricle, and main pulmonary artery with a large patent ductus arteriosus. He developed respiratory distress syndrome (RDS), and increased abdominal distention, and died at age 14 days. Autopsy confirmed PDA, pulmonary changes of RDS, ascites and distended large bowel.

An unbalanced 3;10 translocation has not previously been reported. The net effect of the translocation was loss of portions of 3p and 10q. Terminal 3p deletion has been associated with severe mental retardation, low hairlines, postaxial polydactyly, dysmorphic facies and growth restriction. Del 10(q11.2) has been associated with microcephaly, short stature and megacolon or Hirschsprung syndrome. The phenotype in our case appears to be a result of deletions from both chromosomes.

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New syndromic association of male pseudohermaphroditism with female external genitalia and adrenal hypoplasia congenita suggests additional sex determining gene(s). E. Vilain[1,2], C. Quigley[3], J. Aisenberg[4], Y.-H. Zhang[2], G. Freidenberg[3], B.-L. Huang[2], E.R.B. McCabe.[2] Depts. of [1]Human Genetics & [2]Pediatrics, UCLA, LA, CA, [3]Dept. of Pediatrics, Indiana Univ., Indianapolis, IN, [4]St. Peter's Hosp., New Brunswick, NJ.

Genetic mechanisms of sex determination involve a network of interacting genes. Molecular analyses of rare patients with sex reversal or sexual ambiguities have been critical in the identification of new genes for sexual development. *SRY*, an HMG-box transcription factor, triggers male sex determination. When the dosage sensitive sex reversal (DSS) locus, containing the nuclear hormone receptor *DAX1*, is duplicated, the result is XY sex reversal and hypogonadotropic hypogonadism (HH); mutations in *DAX1* cause adrenal hypoplasia congenita (AHC). Here we describe two patients with a new clinical association of male pseudohermaphroditism with sex-reversed external genitalia and AHC. In both patients, normal female genitalia were noted at birth and each had an episode of adrenal insufficiency before two months of age. They had absent steroidogenesis, AHC and HH. Abdominal magnetic resonance imaging (MRI) showed adrenal hypoplasia or aplasia, and pelvic MRI revealed neither gonads nor any Mullerian structures. The patients' karyotypes were 46,XY. Molecular genetic studies revealed no mutations in *SRY*, *DAX1*, or *SF1*, another nuclear hormone receptor. We present alternative hypotheses to explain this unusual association: (1) one or more additional sex-determining genes within the *DSS* locus, possibly acting in synergy with *DAX1*; or (2) one or more genes not linked to *DSS* involved in both gonadal and adrenal development.

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Prenatal Diagnosis of Asymmetric Fetal Overgrowth: A Diagnostic Dilemma. V. Vincent[1], L. Seaver[2], A.M. Sanders[1], B. Allen[1], J.V. Dacus[1]. [1]Univ. S. Carolina, Columbia, SC, [2]Greenwood Genetics Center, Greenwood, SC.

We present a case of prenatal diagnosis of a fetus with asymmetric overgrowth and multiple cystic lesions in which the differential diagnoses include Proteus syndrome (PS) and Klippel-Trenaunay-Weber syndrome (KTW). The patient is a 40 year old G3P1A1 presenting at 18 weeks gestation due to advanced maternal age. Ultrasound exam revealed edematous right fetal hip, leg, and foot with irregular contour; edema of the left hip through the chest; and an enlarged right kidney. Follow up ultrasound performed at 21 weeks confirmed these findings along with possible cysts in the right kidney. Amniocentesis results revealed a 46,XY karyotype with an AFAFP of 2.72 MoM and a negative acetylcholinesterase. The patient terminated the pregnancy at 22 weeks. At autopsy the fetus was found to have multicystic masses and enlargement of the right foot and left thorax. Polydactyly of the phalanges of the right foot as well as hemorrhagic vascular tumors were associated with the overgrowth of the right leg. The fetus appeared macrocephalic. No other internal or external hamartomata were identified. No skin lesions (nevi) were identified, although this is not unusual in a mid gestation fetus.

Asymmetric overgrowth and vascular tumors are features of both KTW and PS. This fetus had features consistent with both conditions. The lack of other types of tumors and cutaneous or connective tissue nevi in the fetus makes it difficult to support a diagnosis of PS. However, many of the characteristic features of PS, which may allow differentiation from KTW, are not always present at birth or in the prenatal period.

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Atypical Down Syndrome phenotype with translocation Trisomy 21. J. Welch[1], K.Keppler-Noreuil[1], H. Major[1], Q. Qiau[1], C Epstein [2]and. [1]S. Patil[1] [1]Univ. Of Iowa, Dept. of Peds. Iowa City, IA and [2]Univ. of California, San Francisco Medical Center, San Francisco, CA

Down Syndrome (DS) is the most common chromosomal aneuploidy. Ninety-five percent of DS cases are due to free Trisomy while 3-4% are due to an unbalanced translocation. Generally, there are no phenotypic differences between these two causes of DS. We report an infant with Trisomy 21 due to 21q 21q translocation, who presented with an atypical DS phenotype.

The proband was an AGA 36-week gestation infant born by SVD to a 35y.o. G2P2AB1 woman following two normal prenatal ultrasounds and a normal MSAFP. Pregnancy, labor and delivery were uncomplicated. At 2.5 months, exam revealed ht at 10-25th %, wt and HC at <5th%, mild facial asymmetry, high mildly deviated nasal bridge, downslanting palpebral fissures, absent Brushfield spots, moderate micrognathia, left ptosis, low set ears with overfolded superior helices, right Bell's palsy, left torticollis. Other findings were dermatoglyphics: right WRWAU, left ARUUU, tapered fingers with positional clenching of fist, sacral dimple and neurological abnormalities of hypertonia and arching of the back. Vision, hearing and echocardiogram were normal. By diagnostic criteria published in the J. of Peds. (1982), she did not meet the diagnosis of DS. Chromosome analysis by two laboratories at band level K1 550 revealed: 46,XX, +21, der (21; 21)(q10; q10). Both parents had normal karyotypes. FISH analysis utilizing the TUPLE; LSI 13,21 probe confirmed the Trisomy 21 translocation. At 8 months, she has continued hypertonia and developmental delay with functioning at 5-6 months.

Our patient with Trisomy 21 due to translocation does not have the characteristic phenotype of DS. In 1977,. Avramopoulos et al (1997) reported a patient with full standard Trisomy 21, who also had atypical phenotypes for DS. Possible etiologies for these findings may include: 1) small molecular deletion of the critical region of chromosome 21, 2) disruption of a gene by gene- gene interaction or 3) mosaicism in other cell lines. Further molecular research studies are planned..