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A minimally invasive assay detects BRCA 1 germline mutations. T. J. Byrne[1], M. Reece[2], M. Lane[2], L. Adams[2] and G. Cohn[2]. [1]University of Massachusetts, Amherst Biomedical Collaborative Research Program, [2]Baystate Medical Center, Springfield, MA.

Previously, we described an antibody based assay which detects BRCA 1 gene alterations in surgical specimens from individuals with ovarian cancer. We also reported that this assay can detect BRCA 1 expression in human buccal cells and demonstrated BRCA 1 transcription in these cells using RT-PCR.

To determine whether this antibody based assay can detect protein truncations resulting from germline BRCA 1 gene mutations in buccal cells, a study was conducted in which immunohistochemical reactivity was compared with BRCA 1 genetic analysis.

Buccal cells of three individuals at high risk for developing heritable breast or ovarian cancer were collected. Mutation analysis was performed using PCR and SSCP followed by gene sequencing of unique polymorphisms. Immunohistochemical analysis of cytospin deposited buccal cells was performed using antibodies directed at the amino and carboxy ends of the BRCA 1 protein.

In two of three specimens, germline mutations were detected. This was consistent with the immunohistochemical results which showed reduced reactivity with the carboxy binding antibody, suggesting the presence for a protein truncation. In the third specimen, no BRCA 1 polymorphisms were detected and immunohistochemical reactivity for the amino and carboxy termini were similar to the controls.

We conclude that this immunohistochemical assay using buccal cells may serve as a minimally invasive, clinical tool to detect germline BRCA 1 gene mutations.

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Limb deformations in oligohydramnios sequence: effects of gestational age and duration of oligohydramnios. C. Christianson[1], D. Huff[2], and E. McPherson[1] [1]Magee-Womens Hosp., Pittsburgh PA and [2]Childrens Hosp. of Philadelphia, PA.

Oligohydramnios, regardless of cause, results in a sequence of anomalies including characteristic facies, contractures and lung hypoplasia, but the timing and duration of of oligohydramnios required to produce different features of the sequence, especially limb defects, are not well defined. Other causes of restricted fetal movement such as fetal neuromuscular disorders also result in limb contractures and lung hypoplasia. Because such neuromuscular disorders often cause polyhydramnios which in turn predisposes to premature rupture of membranes, such fetuses may present with ruptured membranes and oligohydramnios. Additional data regarding the type and incidence of limb contractures in fetuses with differing onset and duration of oligohydramnios is needed to provide accurate counseling regarding the underlying cause and recurrence risks .

We have reviewed maternal histories, delivery records, pathology reports, radiographs and photographs of 90 fetuses with gestational ages from 14 weeks to term with >24 hrs documented oligohydramnios. The causes of oligohydramnios included premature rupture of membranes (44 cases), fetal renal insufficiency (25 cases), idiopathic (15 cases) and twin-twin transfusion (6 cases). The fetuses were grouped according to gestational age at delivery and duration of oligohydramnios. As expected, contractures were more frequent with earlier onset and longer duration of oligohydramnios. During the second trimester, the frequency of contractures in fetuses with oligohydramnios was 77% compared to 52% in the third trimester($p=.02$). Considering all gestational ages together, 57% of fetuses had contractures after less than 2 weeks of oligohydramnios compared to 81% of fetuses with a longer duration of oligohydramnios ($p<.02$). The type of contracture varied with gestational age. Club foot was the most frequent at all ages, but hand contractures such as camptodactyly were common only in the second trimester while the broad flat hand originally described in Potter sequence was found almost exclusively in the third trimester. Of the 59 fetuses with oligohydramnios and contractures, 25 (42%) had either additional malformations or family history that could explain contractures independent of oligohydramnios.

Oligohydramnios sequence is common in the second trimester, but presents differently compared to the third trimester and is more easily confused with other birth defects. Fetuses with oligohydramnios and contractures require a detailed examination and review of history before the contractures can be attributed to oligohydramnios sequence.

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Mixoploidy with a Proteus syndrome phenotype. J.A. Claus, H.A. Farag, B.G. Kousseff. University of South Florida Genetics Program, Tampa, Florida.

We report a 22-month-old female patient with diploid-triploid mixoploidy (46,XX/69,XXX) and asymmetric overgrowth of the limbs; the legs being more affected, macrodactyly and a subcutaneous lipoma. The patient, A.J., was the 4th child of a 28-year-old para 3-0-0-3 mother. Family history was unremarkable. Pregnancy was complicated by polyhydramnios in the third trimester and there was small abruptio placentae. Normal spontaneous vertex delivery was at 34 weeks gestation. Apgar scores were 4/8; birth weight was 2280 g (50th percentile), and OFC was 29 cm (15th percentile). The large placenta, weight 1310 g, demonstrated triploidy: 69,XXX. Peripheral lymphocyte culture: 21/22 cells were 46,XX and 1 cell was 69,XXX. A higher percentage of mosaicism was present in skin fibroblast culture: 15/6 (46,XX/69,XXX). Recently a macrodactyl toe was removed and cytogenetic studies indicated 3/17 mosaicism (46,XX/69,XXX). Echocardiogram revealed a moderate-sized PDA which closed with Indocin, a trace of tricuspid regurgitation, and moderate pulmonary hypertension. Renal sonogram was normal. At birth, asymmetric macrodactyly of the 2nd, 3rd, and 4th toes and partial 2, 3 toe syndactyly were noted. Palpebral fissures were narrow. At 10.5 months, height was 73.3 cm (60th percentile), weight was 11.12 kg (above 95th percentile) and OFC was 46.5 cm (75th percentile). The lower limbs had grown disproportionately large with increasing asymmetry of all limbs. As a new finding, there was macrodactyly of the 4th left finger. There was left pes cavovarus. A small subcutaneous lipoma-like mass was present in the right axilla. A developmental assessment at 10.5 months indicated slight motor delay. Due to the limb overgrowth, macrodactyly and subcutaneous lipoma, Proteus syndrome was diagnosed. Somatic mosaicisim has been previously reported with this syndrome, but to our knowledge, this is the first case with mixoploidy; the latter is usually associated with developmental delay, asymmetric growth deficiency (Russell-Silver-like phenotype), cutaneous syndactyly, and facial dysmorphy. Since the mixoploidy may be a causative factor, karyotyping appears warranted for patients with Proteus syndrome.

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Caudal regression and holoprosencephaly in a fetus of a diabetic mother. R. Einy[1], J.C. Ferreira[1], G.S. Sachs[1], A. Orda[2], N.M. Allen[2], S.J.Gross[1]. [1]Montefiore Medical Center-Albert Einstein College of Medicine, Bronx, NY, [2]Bronx Lebanon Hospital, Bronx,NY.

It is well established that the risk of malformations in children born to women with overt diabetes is two to three times greater than the general population. Caudal regression (combining sacral agenesis and hypoplastic femurs) is a rare usually sporadic disorder that is most commonly associated with maternal diabetes. Holoprosencephaly is the abnormal formation and separation of the developing brain and is also known to be associated with maternal diabetes. Both anomalies have been mapped to 7q36 (Huggins,1998, Strachan,1998).

Case report: We describe a fetus with caudal regression and holoprosencephaly in a 30-year-old diabetic woman who was well controlled on insulin therapy. Ultrasound examination at 31.8 weeks revealed multiple anomalies including holoprosencephaly, hypotelorism, an abnormal nasal structure suggestive of a single nostril, abnormal sacrum, undetectable femurs, severe clubbing of the feet which appeared rocker-bottom, clinodactyly and clenched fingers. The 2150 g male fetus was stillborn at 34 weeks. Post-mortem examination revealed cardiomegaly and an absent left kidney, and confirmed the ultrasound findings of craniofacial and skeletal anomalies. Chromosome analysis on the tissue culture revealed a normal 46,XY male complement in all cells analyzed.

Conclusion: Although diabetic embryopathy cannot be excluded as the causative factor for these malformations, the presence of two rare anomalies which map to the same chromosome region is suggestive of a specific genetic defect. The human Sonic Hedgehog gene (SHH), which maps to 7q36, has recently been reported to be expressed not only in the CNS but also in human limb buds (Odent, 98). The possibility that an alteration in the SHH gene may be the cause of this combination of anomalies in this fetus is currently under investigation.