13

A dual FISH assay for detecting deletions associated with VCFS/DiGeorge syndrome I and DiGeorge syndrome II loci. SA Berend[1], RK Holmes[1], WJ Craigen[1], AS Spikes[1], CD Kashork[1], JM Wu[1], SC Daw[2], PJ Scambler[2], LG Shaffer[1]. [1]Baylor College of Medicine, Department of Molecular and Human Genetics, Houston, TX, [2]Molecular Medicine Unit, Institute of Child Health, London, UK

DiGeorge syndrome (DGS) is a developmental field defect of the 3rd and 4th pharyngeal pouches. This syndrome is characterized by dysmorphic features, hypoplasia of the thymus and parathyroid glands, and conotruncal heart defects. Over 90% of patients with the syndrome have a microdeletion at 22q11.2. This deletion occurs in about 1 in 4000 live births. Since these deletions are difficult to visualize at the light microscopic level, fluorescence *in situ* hybridization (FISH) has been instrumental in the diagnosis of this disorder. Another less frequent chromosomal abnormality associated with the DGS phenotype is a deletion at 10p13p14. Since both deletions are associated with a similar phenotype, we have developed a dual FISH assay in our laboratory for screening samples referred for DGS or velocardiofacial syndrome (VCFS). This assay includes two test probes: a cosmid (F5) located in the DGSI critical region on chromosome 22, a PAC (72-A7) that is contained within the DGSII critical region on chromosome 10, and control probes specific for chromosomes 10 and 22. Since 1996, over 400 patients have been tested with the dual FISH assay. Recently, one patient was identified who was deleted for the DGSII locus at 10p13p14. This child had facial features of VCFS, sensorineural hearing loss, and renal anomalies. Cytogenetic analysis revealed a large deletion of 10p [46,XX,del(10)(p12.2p14)] and FISH using a 10p telomere-specific probe confirmed the interstitial nature of the deletion. The identification of this case prompted us to review the results of samples submitted to our laboratory for the dual probe assay. 412 patients have been screened with the dual assay and 54 were found to be deleted for 22q11.2 (13%), whereas only one patient was found to be deleted for the locus on chromosome 10 (0.24%). Hence, the deletion on chromosome 10p may be 50 times less frequent than the deletion on chromosome 22. Based on a frequency of 22q11.2 deletions of 1 in 4000, the incidence of deletions in the DGSII critical region on chromosome 10 is estimated to be about 1 in 200,000.

14

A patient with Gorlin-Chaudhry-Moss syndrome and del(9)(q22.1q22.3)
C.H. Tsai, J.R. Roberson, D.L. Van Dyke. Henry Ford Health System, Department of Medical Genetics, Detroit, MI .

We report a patient with a rare 9q deletion and features of Gorlin-Chaudhry-Moss syndrome (GCM). At age 3, the patient presented with acrocephaly, small maxilla, low frontal hairline, two occipital hair whorls, epicanthal folds, hypotelorism and prominent eyes with strabismus and nystagmus, and oval irides. She also had synophrys, low set ears, a tuft of hair on her nose, cleft tip of the nose, thin upper lip, downturned corners of the mouth, high arched palate, webbing between the gums and buccal mucosa, wide alveolar ridge and dental anomalies including fusion of some teeth, mild pectus excavatum, 5th finger clinodactyly, left transverse palmar crease, short 4th metacarpals, overlapping toes 2-3, and thoracic scoliosis. She had persistent rhinorrhea and serous otitis media requiring PE tubes. She was not walking or talking. Karyotype was 46,XX,del(9)(q22.1q22.3). Mother's karyotype was normal and father was unavailable. CT scan identified agenesis of the corpus callosum. At age 21 she had moderate mental retardation and spoke in short phrases with unclear speech. Numerous scars on her arms were secondary to skin picking. Surgeries included spinal fusion with Harrington rod placement and removal of 5 odontogenic cysts. Right retinal detachment and cataract had occurred and she continued to have rhinorrhea and serous otitis. Acrocephaly, coarse facies, shallow orbits with prominent eyes, oval irides, synophrys, right ptosis, midface hypoplasia, prominent chin, hypodontia, short 4th metacarpals, and hypoplastic and dysplastic finger and toenails were noted.

GCM was first reported in sisters with craniofacial dysostosis, hypertrichosis, dental and eye anomalies, patent ductus arteriosus, and mental retardation. Other features included short 4th metacarpals and distal phalanges. Two other unrelated females have been identified and all four patients had hypertrichosis, low frontal hairline, conductive hearing loss, and coarsening of facial features with time. Autosomal recessive inheritance was postulated.

We are unaware of other subjects with this deletion though 9q22-q32 deletions have been reported to have mental retardation, seizures, hypotelorism, sclerocornea, duodenal atresia, malrotation, hydronephrosis, preaxial polydactyly and syndactyly of the toes. Our findings suggest that GCM may represent a contiguous gene syndrome residing within the 9q22.1-q22.3 segment. Our patient's more severe mental retardation may be secondary to deletion of other genes on 9q .

15

Chromosome abnormalities due to maternal translocations not detected with routine amniocentesis.

M.K. Kukolich[1], L.L. Estabrooks[2], S.L. Martin.[1] [1]Cook Children's Clinical Genetics Service Ft. Worth, Texas and [2]Genzyme Genetics Santa Fe, New Mexico.

Individuals carrying balanced translocations may have offspringwith unbalanced karyotypes. This may result in symptoms ranging from mild to severe mental retardation with multiple congenital defects depending, on the chromosomes involved. We are reporting two very interesting chromosomal abnormalities detected postnatally, after the infants were referred for genetic evaluation. Both mothers had amniocentesis: the first because of abnormalities detected on ultrasound and the second because of a previous child with anomalies and because of advanced maternal age. The first was interpreted as showing a balanced translocation and the second as normal. The first case involves a child whose mother carried a 3 way reciprocal translocation. The child inherited 2 of the 3 maternal derivatives resulting in an unbalanced chromosome complement, which in turn created multiple congenital anomalies that were incompatible with life. The second child's mother had a reciprocal translocation involving chromosomes 19 and 21. The child inherited an abnormal chromosome 21, a derivative secondary to the maternal translocation. This abnormality resulted in both a deletion of a part of the long arm of chromosome 21 and a duplication of a portion of the long arm of chromosome 19. Reevaluation of the chromosome analysis obtained by amniocentesis from the first pregnancy in which the child had a diaphragmatic hernia showed the same chromosome abnormality. Both abnormalities were identified postnatally with the use of FISH. This case illustrates the importance of careful genetics follow up of infants with anomalies.

16

Karyotyping miscarriage tissue in the managed care environment. E.M. Karson Columbia Hosp for Women, Washington, DC.

Various economic factors have lead to the emergence of large corporate laboratories and perishable cytogenetic specimens are directed away from in-hospital and nearby local and regional university laboratories to distant,designated sites. Most amniocentesis and blood specimens have sufficient numbers of viable cells to withstand 24 to 72 hour transport if protected from extreme heat or freezing. Specimens of miscarriage tissues, known as products of conception (POC's) autolyze rapidly and/or become contaminated by the normal vaginal flora if not placed immediately in solutions containing antibiotics and constantly refrigerated. In addition, as specimen deteriorate, it becomes increasingly difficult to cleaning separate away contaminating maternal decidua tissue.

The majority of first and early second trimester pregnancy losses are a result of abnormal karyotype in the conceptus. The major purpose for performing karyotypes on POC's is to differentiate those women whose loss (often recurrent losses) are of normal karyotype conception and who may require other evaluation and intervention, those who may be carriers of translocations who need to be counseled that future pregnancies may result in continued losses or even the birth of offspring impaired by an unbalanced chromosome complement, and finally those for whom the aneuploid event was sporadic and future pregnancies are likely to succeed without special intervention. When the POC karyotype is erroneously reported as "46, XX - normal female" because maternal rather than conceptus cells predominate in culture, the subsequent counseling will be inaccurate and medical interventions offered to the patient may be inappropriate or even harmful. Depending on the true karyotype, the treatment error may be omission or excess.

In the past 2 years, as more specimens from outpatient dilatation and curettage procedures were directed to laboratories, a distinct change in the patterns of results was observed. If one postulates that the karyotype should not be vary by the patient insurance company, one would expect a similar rate of successful culture and distribution of abnormal karyotypes in the outsourced specimens. What has been observed is a significant increase in the number of "non-viable" specimens and "normal female" karyotypes compared to specimens that were allowed to remain in the hospital cytogenetics laboratory for processing. The patterns of karyotypes seen and hypotheses for these variations will be discussed.