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Influence of heterochromatin on fetal loss: Clinical and counseling aspects. T.V. Shklovskaya[1], S.M. Kleyman[1], M.J.Macera[1], R.S.Verma[1,2]. [1]Institute of Molecular Biology and Genetics, Brooklyn, NY -[2] SUNY Health Science Center at Brooklyn, NY.

Morphological variations of human chromosomes due to heterochromatic DNA have been the subject of numerous speculations for a quarter of century. Chromosomal variations or heteromorphisms have been correlated to a number of clinical parameters and a barrage of conflicting views have emerged. An enlarged secondary constriction region [qh] of chromosome 9 and the heterochromatin of the Y chromosome are frequent examples that have been correlated with increased risk of abortions. Recently, we were referred two couples for cytogenetic evaluation, each having three consecutive fetal losses. Both males had very large heterochromatic segments on their Yq chromosomes, while the male of the second couple also had an enlarged qh region on chromosome 16. To the best of our knowledge, such an enlarged qh region on chromosome 16 has not been reported before in combination with a large Y chromosome. A chromosome 16 specific alphoid probe [Oncor] was used to evaluate centromeric size by the FISH technique. A normal size centromere was noted, suggesting that the morphological variation of the long arm of chromosome 16 [16q] was due to the enlarged qh region. Does the male have double trouble or is this a fortuitous finding? Utmost caution should be exercised during counseling of such couples as there are no convincing evidence suggesting heterochromatin plays a role in fetal loss.

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Prenatal diagnosis of a non-fluorescent Y chromosome as characterized by FISH-technique.M.N. Silverman[1,2], T. Shklovskaya[3], M.J. Macera[3], R.S.Verma[2,3]. [1]Maimonides Medical Center/ [2] SUNY Health Science Center at Brooklyn, [3]Institute of Molecular Biology and Genetics, Brooklyn, NY.

Currently, Y chromosomal DNA is being used to trace back the origin of our common ancestors. Cytogenetically, the structural variation [polymorphisms] of the Y-chromosome has been classified into three groups. Variation of the long arm is being contributed by fluorescence [Y^{qf}] and non-fluorescent segments [Y^{qnf}] by QFQ staining. The rarest form is a pericentric inversion that is a 'third type'of variation. Here, we report a *'fourth type'* where fluorescent heterochromatic DNA is apparently deleted and could no be detected by QFQ-technique. A 28 years old female was referred for genetic amniocentesis because of her high MSAFP. Her first pregnancy ended in fetal loss after 9-10 weeks of gestation. The cytogenetic findings with QFQ-technique revealed a marker chromosome which was found in his biological father. By FISH-technique using WCP probe [Vysis], it was a Y-chromosome. A small amount of heterochromatic DNA was detected in the fetal Y and the father by the Y cocktail probe [DYZ1\DYZ3, Oncor] which is specific for heterochromatin suggesting that it is not a Y^{qnf}. In addition the presence of telomere on Yq was also noted by the all human telomere probe [Oncor]. Utmost caution should be exercised during post-amniocentesis counseling as earlier claims of dire consequences are unfounded. However, Y^{qnf} chromosome may serve as a phylogenetic treat for molecular anthropologists who are in search of human lineage.

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Discordant detection of monosomy 7 by GTG banding and FISH in a patient with Schwachman-Diamond syndrome. R.A. Sokolic[1], W. Ferguson[2] and H.F.L. Mark[3]. [1]Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, [2]Department of Pediatrics, Rhode Island Hospital and Brown University School Medicine, Providence, RI. [3]Lifespan Academic Medical Center Cytogenetics Laboratory, Rhode Island Hospital and Brown University School of Medicine, Providence, RI

Schwachman-Diamond Syndrome (SDS) is an inherited illness characterized by exocrine pancreatic insufficiency and by congenital neutropenia. Patients with SDS are at increased risk of developing myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). Bone marrow aspiration and biopsy can be used to detect MDS in a presymptomatic state. Monosomy 7 is a poor prognostic sign in MDS and AML, and therefore establishing its presence is important. However, different methods of detection may lead to different results in some patients.

A three month old girl was referred to Rhode Island Hospital in 1988 with failure to thrive. White blood cell count was mildly depressed at 4 x 10^9 cells/L and pancreatic insufficiency was demonstrated. The diagnosis of SDS was made. In February of 1998, surveillance bone marrow cytogenetic analysis of a suboptimal specimen demonstrated the following karyotype by GTG banding: 45,XX,-C[3]/46,XX[45]/47,XX+C[1]. Fluorescent in Situ Hybridization (FISH) was performed with a chromosome 7 specific alpha-satellite probe (D7Z1). 373 of 376 cells exhibited only one chromosome 7 signal. A further marrow aspiration in August of 1998 showed an essentially normal karyotype by GTG-banding. FISH with the same chromosome 7 probe showed 230 of 250 cells to be monosomic for chromosome 7. A whole chromosome 7 painting probe demonstrated disomy for chromosome 7 in 90 out of 90 cells, but subtle heteromorphism in the centromeric regions of the two copies of chromosome 7 was noted in some cells.

This case demonstrates that FISH can give results discordant with those of other methodologies and should not be used as a stand-alone cytogenetic test. The chromosome 7 variant detected in this patient may or may not be related to MDS. The relationship of the patient's karyotype to SDS is also not known. Thus, further investigation with repeated bone marrow examination in this patient and further characterization of the abnormalities in other SDS patients are warranted.

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An unusual case of pseudodicentric Xq and one possible mechanism. J Sullivan, M Murray, A Ratti, T Marini, R Naeem. Baystate Medical Center and the Western Campus of Tufts University School of Medicine.

Structural abnormalities of the X chromosome are relatively common with isochromosome Xq being the most common. While isochromosome for Xp has been reported, its existence is questionable since true isochromosome Xp lacks the inactivation center and thus is presumed to be non-viable. Most of these cases are in fact believed to be pseudodicentric (having one active and one inactive centromere) and contain at least one inactivation center. We report an 18 year old female referred for primary gonadal failure (elevated FSH and LH; decreased estradiol). Cytogenetics revealed a 46,X,psu dic(X)(q24) karyotype suggesting trisomy for Xp and proximal Xq and monosomy for Xq distal to band q24. Fluorescent in situ hybridization (FISH) analysis using whole chromosome paint and XIST probes confirmed a structurally abnormal dicentric X chromosome containing two inactivation centers. Additional clinical history included oligoammenorrhea with menarche at age 12 and insulin dependent diabetes mellitus with onset at 14-15 years of age. No significant Turner stigmata were noted which may be attributable, in part, to an indeterminate X inactivation pattern. Mechanisms for the formation of pseudodicentric X chromosomes have been hypothetical thus far. One proposed mechanism is a U-type exchange between two chromatids or chromosomes following a break in each at a homologous site. This repair process would result in a dicentric inverted duplication or dicentric X chromosome. We propose another mechanism and suggest that the genetic constitution may have begun as trisomy X. Breaks in two of the X chromosomes at band q24 with subsequent fusion of the centric fragments would result in a pseudodicentric X chromosome. The remaining acentric fragments would be lost in continued cell division. Further investigation by microdissecting the dicentric X chromosome may help in understanding other atypical cytogenetic mechanisms for dicentric chromosome formation. These studies could determine whether the dicentric centromeres originated from homologous X chromosomes or are identical via duplication.