Heterochromatin variants of chromosome 9: clinical aspects and method of molecular cytogenetic examination

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Introduction: Heterochromatin abnormalities of human chromosomes are mostly believed to be clinically insignificant variants of the human karyotype. However, several authors have studied the possible association of heterochromatin variants including those of chromosome 9, which are the most common with certain clinical diagnoses, primarily with reproduction failure (spontaneous and/or repeated abortions).

Methods I: Two special study cohorts were created from data archives of postnatal karyotype examinations (1986-2012) of Cytogenetic laboratory at the Institute of Biology and Medical Genetics. First group (Chromosome 9 variant cohort, n=465) includes all postnatal cases, where we identified heterochromatin variant of chromosome 9 (cases with coincident pathological findings were excluded).

Methods II: Second cohort (Control cohort, n=797) was created from the list of patients with no chromosomal abnormalities (no pathologies and no variants) using systematic sampling method. We have noted the clinical indication for karyotyping for each case in both study cohorts and sorted them into 12 different diagnostic groups. The frequencies of diagnostic groups in both study cohorts were compared and analyzed.

Results: Reproduction failure was the most frequent clinical indication in both study cohorts. The frequency of this indication was notably higher in the chromosome 9 variant cohort (43.46%) and this difference was statistically significant (p<0.0001; Fisher's exact test).

Conclusion: Possible association of heterochromatin variants of chromosome 9 with reproduction failure was mentioned many times and those reports continue to appear even in the 21st century. However, no explanation for this phenomenon has been widely accepted. We believe, that the more precise identification of certain subtype variants of chromosome 9 could be the key.

Molecular cytogenetic approach: - Methods: Multiprobe-FISH approach, using combination of centromeric probes and specific BAC-probe (homologous p12 and q12 sequences; we use RP11-45022 or RP1-2311-N8 probe). Similar approach was already reported in literature (Starke et al., 2004; Kehrer-Sawatzki et al., 2005).

Man (43 years), healthy, trisomy 7 in an abortion in reproductive history

46,XY (control)

Man (36 years), sterility

46,XY/inv(9)(p12q13)

Boy (2 years) with epilepsy, mental retardation and micropterygium

46,XY/inv(9)(p12q13)

Woman (33 years), sterility

46,XY/inv(9)(p12q13), t(15;22)(q26.1;p12)

Woman (56 years), healthy, mother of case 5

46,XY/inv(9)(p12q13)

Man (42 years), sterility

46,XY/inv(9)(p12q13)

Woman (28 years), sterility

46XX/inv(9)(p12q13)

Woman (28 years), sterility, IVF programme

46,XX/inv(9)(p12q13)

Woman (25 years), gamete donor

46,XY/inv(9)(p12q13)

Woman (26 years), gamete donor

46,XX/inv(9)(p12q13)

Woman (28 years), gamete donor

46,XX/inv(9)(p12q13)