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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 (sterility 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 =405) includes all postnatal cases, where we identified heterochromatin variant of chromosome 9 (cases with coincident pathological findings were excluded).

General University Hospital (1986-2012)	Chromosome 9 variant cohort		Control cohort	
Clinical indication	**Cases**	**%**	**Cases**	**%**
Children awaiting adoption	1	0.25	1	0.14
Chromosome 9 variant in family history	29	7.16	3	0.43
Gamete donors	10	2.47	13	1.86
Impaired spermatogenesis	8	1.98	15	2.14
Down syndrome in family history	9	2.22	25	3.57
Karyotype confirmation	10	2.47	38	5.43
Abnormal growth or sex development	24	5.93	48	6.86
Psychomotor and/or mental retardation	27	6.67	55	7.86
Congenital anomaly in family history	27	6.67	66	9.43
Congenital anomalies	50	12.35	107	15.29
Other diagnosis	34	8.40	98	14.00
Reproduction failure	176	43.46	231	33.00
Total	**405**	**100.00**	**700**	**100.00**

Conclusion:
Possible association of heterochromatin variants of chromosome 9 with reproduction failure was mentioned many time 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 (sub)variants of chromosome 9 could be the key.

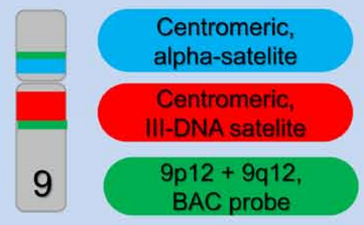
Methods II:
Second cohort (**Control cohort**, n =700) was created from the list of patients with no chromosomal abnormalities (no pathologies and no variants) using systematic sampling method. We have noted the clinical indication for karyotyping for each case in both study cohorts and sorted them into 12 different diagnostic groups. The frequencies of diagnostic groups in both study cohorts were compared and analyzed.

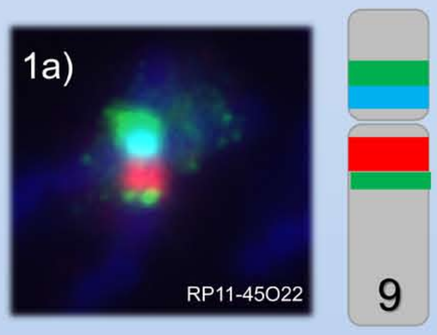
Results:
Reproduction failure was the most frequent clinical indication in both study cohorts. The frequency of this indication was notably higher in the chromosome 9 variant cohort (43.46%) and this difference was statistically significant ($p<0,0001$; Fisher's exact test).

Introduction:
Variants of the heterochromatin area of chromosome 9 in G-banding.
More detailed analysis of the variant is quite impossible.

inv(9)(p12q13) **9qh-**

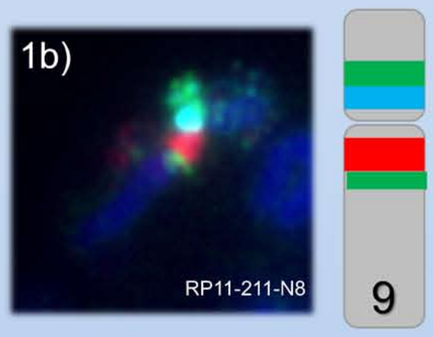
Molecular cytogenetic approach - Methods:
Multiprobe-FISH approach, using combination of centromeric probes and specific BAC-probe (homologous p12 and q12 sequences; we use RP11-45O22 or RP11-211-N8 probe). Similar approach was already reported in literature (Starke et al., 2004; Kehrer-Sawatzki et al., 2005).

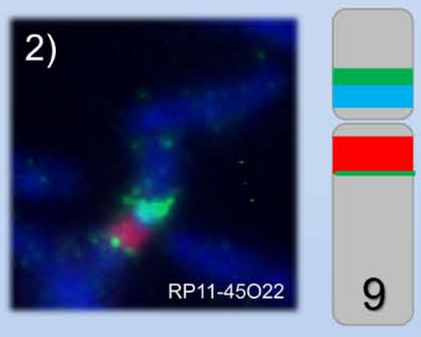




Man (43 years), healthy, trisomy 7 in an abortion in reproductive history

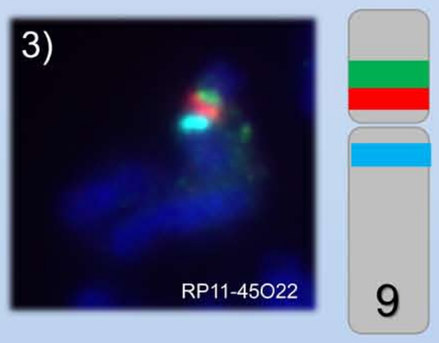
46,XY (control)





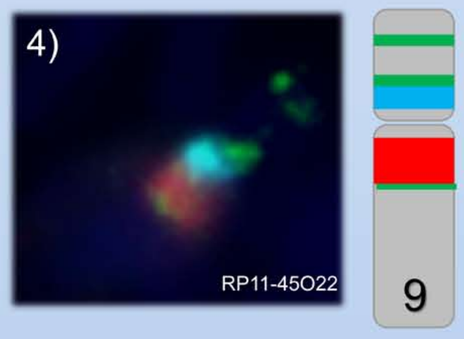
Man (36 years), sterility

46,XY,inv(9)(q21.2q34.2)



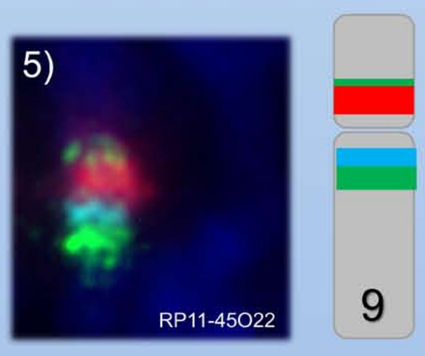
Boy (2 years) with epilepsy, mental retardation and micropenis

46,XY,inv(9)(p12q13)



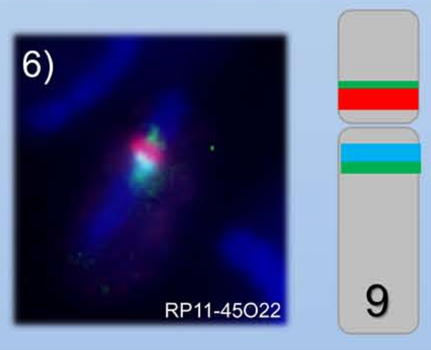
Boy (1 year) with psychomotor and mental retardation and dysmorphic features

47,XYY,inv(9)(p11.2p24)



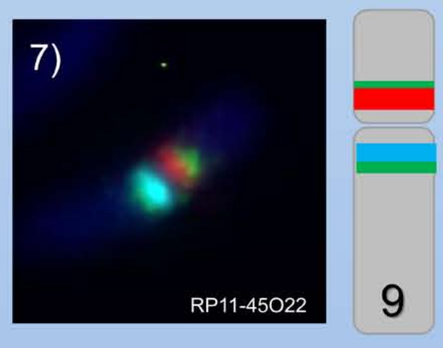
Woman (33 years), sterility

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



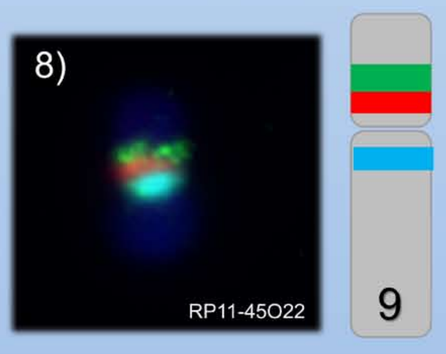
Woman (56 years), healthy, mother of case 5)

46,XY,inv(9)(p12q13)



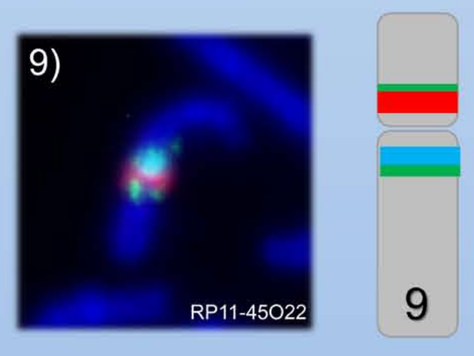
Man (42 years), sterility

46,XY,inv(9)(p12q13)



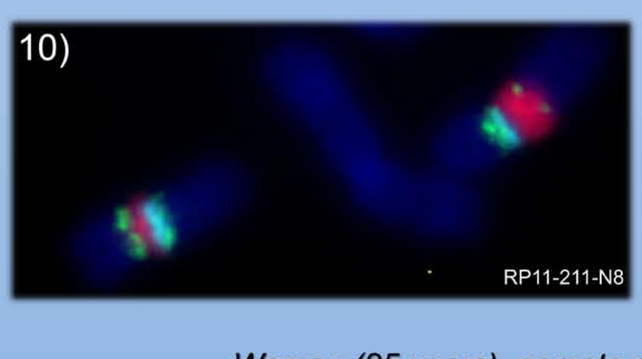
Woman (28 years), sterility

46,XX,inv(9)(p12q13)



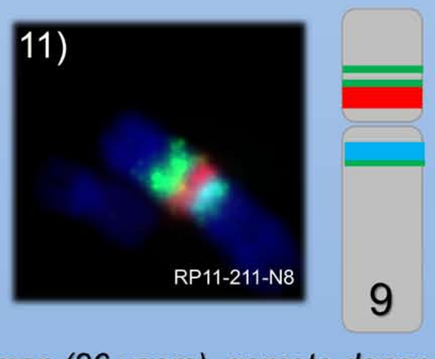
Woman (28 years), sterility, IVF programme

46,XX,inv(9)(p12q13)



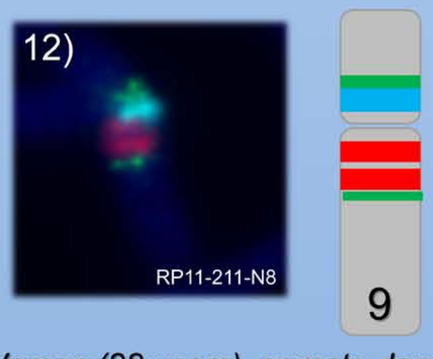
Woman (25 years), gamete donor

46,XY,9qh+,inv(9)(p12q13)



Woman (26 years), gamete donor

46,XX,der(9)dup(9)(p12)inv(9)(p12q13)



Woman (28 years), gamete donor

46,XX,der(9)dup(9)(q12q21.12)

Literature:
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