Incidence and clinical significance of chromosomal abnormalities of heterochromatin area of human chromosome 9

Antonín Sipek Jr1, Ales Panczak1, Romana Mihalova1, Lenka Celbova1, Mimoza Janashia1, Nikola Kasprikova2,3, and Milada Kohoutova1

1 Institute of Biology and Medical Genetics, Charles University, 1st Faculty of Medicine and General University Hospital, Prague, Czech Republic
2 Department of biostatistics, Charles University, 1st Faculty of Medicine, Prague, Czech Republic
3 Faculty of informatics and statistics, University of economics, Prague, Czech Republic

Introduction: Cytogenetic abnormalities of the heterochromatic area of chromosome 9 are considered to be clinically insignificant variants of human karyotypes. Nevertheless, many recent studies discuss possible pathologic effect of selected variants, especially association with reproduction failure. Our objectives are to determine frequency of heterochromatitic variants of chromosome 9 among patients karyotyped because of the reproduction failure; to estimate the population frequency of these variants in the Czech population and to analyze the clinical significance of these variants, especially concerning the reproduction failure.

Reproduction failure cohort
Institute of Biology and Medical Genetics, Charles University, 1st Faculty of Medicine and General University Hospital, Prague, Czech Republic
2007 – 2010
n = 1036
- Includes cases of idiopathic reproduction failure only
- Karyotyping is the standard part of the diagnostic process
- Includes 463 pairs and 110 singles (506 females and 530 males)
- The cyto genetic examination identified chromosomal pathology (like robertsonian translocation or numerical gonosomal abnormalities) to be the possible cause of reproduction failure in 17 individuals (1.64 %)

Amniocentesis cohort
Institute of Biology and Medical Genetics, Charles University, 1st Faculty of Medicine and General University Hospital, Prague, Czech Republic
2003 – 2010
n = 995
- Includes fetuses, that were karyotyped prenatally following the amniocentesis procedure
- The only indication for the karyotyping was advanced age of the mother (35 or more years)
- Fetuses with any abnormal findings (abnormal ultrasound or abnormal screenings) were excluded
- Includes 518 females and 477 males

Methods:
Two separate patient cohorts were created especially for this analysis. All subjects were karyotyped because of a clinical indication and informed consent was obtained from all individuals. All samples (either peripheral blood or amniotic fluid) were cultured using the standard laboratory protocols. Standard G-banding method was used for the chromosome analysis. Each sample was analyzed by at least two different cytogeneticists. Statistical analysis was done using the R-software (www.R-project.org)

Results

<table>
<thead>
<tr>
<th>Heterochromatin variant</th>
<th>Reproduction failure cohort (n = 1036)</th>
<th>Amniocentesis cohort (n = 995)</th>
<th>Relative risk</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1qh+</td>
<td>15</td>
<td>8</td>
<td>1.44</td>
<td>0.4239</td>
</tr>
<tr>
<td>9qh+</td>
<td>40</td>
<td>21</td>
<td>2.11</td>
<td>1.83</td>
</tr>
<tr>
<td>9qh-</td>
<td>0</td>
<td>1</td>
<td>0.10</td>
<td>-</td>
</tr>
<tr>
<td>inv(9)(p12q13)</td>
<td>18</td>
<td>9</td>
<td>0.90</td>
<td>1.92</td>
</tr>
<tr>
<td>inv(9)(p12q21)</td>
<td>0</td>
<td>1</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>16qh+</td>
<td>26</td>
<td>17</td>
<td>2.51</td>
<td>1.71</td>
</tr>
<tr>
<td>16qh-</td>
<td>0</td>
<td>4</td>
<td>0.00</td>
<td>0.20</td>
</tr>
<tr>
<td>Yqh+</td>
<td>15</td>
<td>14</td>
<td>0.45</td>
<td>1.41</td>
</tr>
<tr>
<td>Chromosome 9 variants in total</td>
<td>62</td>
<td>39</td>
<td>5.99</td>
<td>3.92</td>
</tr>
<tr>
<td>Chromosome 16 variants in total</td>
<td>26</td>
<td>14</td>
<td>2.51</td>
<td>1.41</td>
</tr>
<tr>
<td>Chromosome Y variants in total</td>
<td>24</td>
<td>18</td>
<td>2.32</td>
<td>1.81</td>
</tr>
<tr>
<td>Total</td>
<td>127</td>
<td>86</td>
<td>12.26</td>
<td>8.64</td>
</tr>
</tbody>
</table>

Molecular cytogenetic analysis of inv(9)

- We are using 3 different FISH probes for detailed analysis of human chromosome 9 pericentric area.
- Homologous sequences on the short and long arm of chromosome 9 are detected by the specific BAC FISH (RP11-211-N8 clone)
- There are at least 6 different sub-variants of basic inv(9) that could be distinguished using multiprobe FISH method (Starkov et al., 2004)
- Potential association of reproduction failure with certain sub-variant of inv(9) wasn’t analyzed yet
- This analysis is the main goal of the next phase of our project

Conclusions and References

- We have found that the association between heterochromatin variants of human chromosome 9 and reproduction failure is statistically significant.
- Our results in the Czech population correspond to findings of other authors.
- However, the causal mechanism for these observations remains unknown for now.
- It is certain that the majority of these heterochromatin variants is benign. However, some cases could be possibly harmful.
- The distinguishing between benign and harmful variant is impossible on the standard G-banding level. Molecular cytogenetic analysis is necessary for more detail analysis.


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Contact information: Antonín Sipek, MD; National Registry of Congenital Anomalies and Institute of Biology and Medical Genetics, Charles University, 1st Faculty of Medicine and General University Hospital, Prague, Czech Republic. Email: antonin.sipek@ff1.cuni.cz http://www.vrozene-vady.cz/