Search for late onset diseases among balanced chromosomal rearrangements

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Aim
Information on diseases among carriers of balanced reciprocal translocation in Denmark will be obtained in order to identify potential late-onset disorders associated with chromosomal breakpoints.

Background
Although chromosomal breakpoints which truncate specific disease genes have been instrumental for the identification of genes associated with a variety of mostly early onset disorder (1), most carriers of balanced reciprocal translocations are believed to be phenotypically normal.

However, the mutational target of chromosomal breakpoints (exons + introns) account for ~30% of the total genome. Thus, assuming that chromosomal breakpoints are distributed equally in the genome, ~30 % of the chromosomal breakpoints may actually result in inactivation of genes. Since ~0.5% of the normal population carry a balanced chromosomal rearrangement (2), there might be thousands of genes inactivated by chromosomal breakpoints. Some of these individuals show no sign of disease, i.e. if the breakpoint is in a recessive gene. If a chromosomal breakpoint inactivates a gene coding for a late onset disease, then some of these healthy carriers might develop symptoms later in life. Thus, a systematic re-examination of individuals with balanced translocations might be a strategy to identify disease genes associated with late onset disorders.

Systematic re-examination of carriers of structural constitutional chromosomal aberrations is possible in Denmark, with near complete, nationwide registries for personal identification (Civil Personal Number) and cytogenetic results (The Danish Cytogenetic Registry). In addition, the Danish population usually have a high compliance when asked to participate in research projects.

Study design
Participants: all individuals in Denmark with a diagnosed balanced reciprocal translocation: 1297 individuals to date.

a) Carriers of translocations, older than 18 years of age and who have been examined because of spontaneous abortions, infertility, and family history of chromosomal rearrangements etc. will be asked to answer a questionnaire in order to obtain knowledge about a broad spectrum of diseases. Also, the carrier may be contacted by telephone. In addition, any clinical information from the hospital or doctor treating the patient will be obtained.

b) Carriers of translocations suffering from a serious disease which was the reason for the cytogenetic examination e.g. mental retardation, will be re-examined by medical files and registries. We know from previous studies that this accounts for about 200 individuals (3).

Methods
For each person the clinical data and the chromosomal breakpoints involved will be compared with known data of the phenotype of candidate genes and loci for the observed disease. The following criteria will be used to support that a disease may be potentially associated with a breakpoint:
- Co-segregation of the translocation with the phenotype in the family.
- When a number of patients that suffer from the same disease have breakpoints in the same chromosomal region.

The carrier will be asked to donate a blood sample, if a disease-associated breakpoint is suspected for future CGH analysis and FISH mapping

Results
The medical files of 554 of the 1298 carriers have been reviewed before inclusion in the questionnaire study:

- 238 individuals were excluded:
  - 49 are dead
  - 12 have emigrated to another country
  - 128 have a serious disease which was the indication of the cytogenetic examination, e.g. mental retardation
  - 41 due to advice from the local clinical genetic department (e.g. language difficulties).
- 8 are younger than 18 years
- 316 individuals were included in the questionnaire study
  - 250 have agreed to participate
  - 14 do not want to participate
  - 52 have not yet answered

Table 1. Potential disease associated breakpoints identified in the study:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Karyotype</th>
<th>Disease-associated Breakpoint?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslexia</td>
<td>46,XX,t(18;21)(p11.21;q21.1)</td>
<td></td>
</tr>
<tr>
<td>Mental retardation</td>
<td>46,XY,t(16;17)(p11.2;q21.1)</td>
<td>Yes</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>46,XY,t(16;21)(q12;q21.31)</td>
<td>Yes</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>46,XY,t(18;21)(p11.2;q21.1)</td>
<td>Yes</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>46,XY,t(18;21)(q11.21;q21.1)</td>
<td>Yes</td>
</tr>
<tr>
<td>Thyroid adenoma</td>
<td>46,XX,t(4q;14q)</td>
<td>Yes</td>
</tr>
<tr>
<td>Otosclerose</td>
<td>46,XX,t(15p12;q25)</td>
<td>Yes</td>
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<tr>
<td>Thyroid adenoma</td>
<td>46,XX,t(10p13;q26)</td>
<td>Yes</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>46,XX,t(7q36;17q21)</td>
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<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>46,XX,t(15q21;22q11)</td>
<td>Yes</td>
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<tr>
<td>Bipolar affective disorder</td>
<td>46,XX,t(13q14;21q22)</td>
<td>Yes</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>46,XX,t(18;23)(p11.1;q25.1)</td>
<td>Yes</td>
</tr>
<tr>
<td>Bipolar affective disorder</td>
<td>46,XX,t(15q26;22q13)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Fig. 1. Example of a phenotype (dyslexia) co-segregating with a balanced translocation.

Conclusion
By this systematic approach we expect to find breakpoints associated with a variety of late onset diseases. An expansion of these investigations to the Berlin population is underway.

References

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This poster can be obtained as a PDF file at www.wjc.ku.dk

1297 individuals to date.