Search for late onset diseases among carriers of 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 on the localisation 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 cases that suffer from the same disease have breakpoints in the same chromosomal region.
- When the breakpoint is localised in a chromosomal region known to harbour a disease locus for the observed disease.

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.*

Disease	Karyotype	Disease-associated Breakpoint?
Dyslexia	46,XX,t(**1**;18)(**p36.1**;q21)	Disease and translocation co-segregate in the family (Fig. 1). Known dyslexia locus: 1p36.1
Male infertility	46,XY,t(**1**;4)(**q21**;q33)mat	In the Mendelian Cytogenetics Network (4) 21 infertile males with breakpoint in 1q21 are observed
Male subfertility	46,XY,t(7;16)(q11.2;p13.1)	Disease and translocation co-segregate in the family
Preeclampsia	46,XX,t(**7**;15)(**q35**;q26)pat	Candidate gene of preeclampsia, NOS3 localised in 7q35
Parkinson Disease	46,XY,t(**1**;18)(**p36.2**;q21.2)	Two Parkinson disease loci in 1p36.2
Rheumatoid arthritis	46,XY,t(4;8)(p16;p23)	Disease and translocation co-segregate in the family
Thyroid adenoma	46,XX,t(**1**;4)(**q21**;q33)	Known thyroid neoplasm locus in 1q21
Otosclerose	46,XY,t(12;**15**)(p13;**q25**)pat	Known otosclerose locus in 15q25-26
IDDM	46,XX,t(**10**;17)(**p11.21**;q25.1)de novo	Known IDDM locus in 10p11
NIDDM	46,XY,t(18;20)(p11.1;p11.1)	Disease and translocation co-segregate in the family
Bipolar affective disorder	46;XX,t(4;**12**)(p15.3;**q22**?)	Known bipolar disorder locus in 12q24
Bipolar affective disorder	46,XX,t(16;**17**)(q13;**q25.3**) 46,XY,t(9;**17**)(q33;**q25.3**)	Same disease and breakpoint in a number of individuals

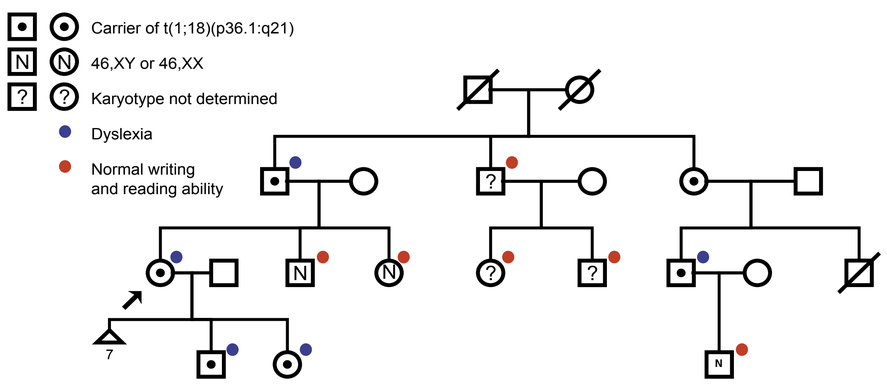

Fig. 1. *Example of a phenotype (dyslexia) co-segregating with a balanced translocation.*

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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