European Journal of Human Genetics (2006) 14, 410–417

www.nature.com/ejhg

ARTICLE

Systematic re-examination of carriers of balanced reciprocal translocations: a strategy to search for candidate regions for common and complex diseases

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Balanced reciprocal translocations associated with genetic disorders have facilitated the identification of a variety of genes for early-onset monogenic disorders, but only rarely the genes associated with common and complex disorders. To assess the potential of chromosomal breakpoints associated with common/complex disorders, we investigated the full spectrum of diseases in 731 carriers of balanced reciprocal translocations without known early-onset disorders in a nation-wide questionnaire-based re-examination. In 42 families, one of the breakpoints at the cytogenetic level concurred with known linkage data and/or the translocation co-segregated with the reported phenotype, for example, we found a significant linkage (lod score = 2.1) of dyslexia and a co-segregating translocation with a breakpoint in a previously confirmed locus for dyslexia. Furthermore, we identified 441 instances of at least two unrelated carriers with concordant breakpoints and traits. If applied to other populations, re-examination of translocation carriers may identify additional genotype–phenotype associations, some of which may be novel and others that may coincide with and provide additional support of data presented here.
European Journal of Human Genetics (2006) **14,** 410–417. doi:10.1038/sj.ejhg.5201592; published online 22 February 2006

Keywords: reciprocal translocation; complex diseases; late-onset disorders; clinical epidemiology; questionnaire-based study

Introduction

So far, strategies for identification of genes associated with complex diseases have been based primarily on the mapping of susceptibility loci by linkage and association studies. The inherent difficulties of these approaches are due to the genetic heterogeneity associated with complex disorders, families with few affected members, incomplete penetrance, difficulties in defining the diagnostic criteria and the need for large-scale genotyping in order to detect

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✠Claes Lundsteen died on 10 November 2003.
Received 22 September 2005; revised 15 December 2005; accepted 12 January 2006; published online 22 February 2006

susceptibility loci. In monogenic disorders, an alternative and very successful approach has been to identify affected individuals with unique chromosomal rearrangements (including balanced reciprocal translocations) that have subsequently facilitated the positional cloning of the disease gene involved.[1] Previous attempts to link chromosomal breakpoints with complex and late-onset disorders have been of a sporadic nature, for example, diabetes,[2] schizophrenia,[3] dyslexia[4] and Tourette's syndrome;[5] compilations of published cases within a specific subset of disorders, for example, related to mental illness[6] or male infertility,[7] and a single register-based screen for co-occurrence of chromosome 18 abnormalities and mental illness.[8]

Approximately 0.1–0.2% of the population carries a balanced reciprocal translocation detectable in the light microscope using moderate levels of banding.[9] To asses the potential of these translocations for identification of candidate genes and loci for common and complex disorders in a population, we performed a systematic re-examination of carriers of a translocation in Denmark, where near complete, nation-wide registries for personal identification and for constitutional cytogenetic data provide an ideal setting for such a study.

Materials and methods

Ethical considerations

The National Ethics Committees, the Danish Data Protection Agency and all clinical genetic departments in Denmark approved the study, and informed written consent was obtained from all respondents in the questionnaire study.

Population

National cohort A nation-wide cohort of carriers of balanced reciprocal translocations was established by identifying carriers in The Danish Cytogenetic Registry (DCR) which was established in 1968 and collects the results of chromosome examinations from all cytogenetic laboratories in Denmark (population of ~5.4 million). DCR is believed to have a virtually complete coverage of constitutional chromosomal abnormalities diagnosed in the country since 1961.[10] The national cohort was defined as all postnatally examined carriers of a constitutional balanced reciprocal translocation who were alive and residing in Denmark at the time of the chromosome examination.

Follow-up cohort Medical files were read at the local clinical genetic department to ascertain the reason for the cytogenetic examination, family relations and previous genetic counselling. Carriers older than 18 years of age, living in Denmark and previously informed of the chromosomal rearrangement were selected for the questionnaire study. Exclusion criteria were serious, early-onset diseases (mental retardation, multiple congenital anomalies, etc), death, young age and emigration; in addition, some were excluded due to insufficient counselling or if their medical file could not be located. Non-Danish-speaking carriers were excluded as well, whereas adults examined in childhood were included when relatives stated that the carrier knew of the chromosomal rearrangement.

A sex-specific questionnaire was designed to reveal information about phenotypes, diseases, hospital admissions and medication throughout life (see the translated questionnaires in electronic supplementary information). Questions concerning reproduction was based on a questionnaire used in a Danish population-based epidemiological study.[11] An invitation to participate was posted together with the questionnaire to the home address found in the Centralized Civil Register (CCR) and a reminder letter was mailed 2 and 4 weeks after the first letter. In all letters, an offer of a consultation with an MD within the project group (IB) was given.

In order to validate and optimize the questionnaire, a pilot study involving 34 carriers was carried out on 31 respondents subsequently interviewed by telephone.

Data handling

The questionnaires were assessed by two people independently and the answers were classified according to a disease classification system used in the Mendelian Cytogenetics Network database (MCNdb, www.mcndb.org). Whenever additional information about diseases or family relations was needed, the carrier was contacted by phone and clinical information was obtained from the hospital/doctor/education authority treating the patient. For each carrier, the clinical data and the potential relation to the chromosomal breakpoints involved were compared with known data on cytogenetic localization of candidate genes and loci. Chromosomal bands were defined according to the International System for Human Cytogenetic Nomenclature (ISCN 1995),[12] using the minimum ~300 band pattern resolution (eg bands 1p22.1, 1p22.2 and 1p22.3 were compiled under 1p22). The following three criteria were used in the search for potential disease-associated breakpoints:

Criterion 1: Breakpoints localized within chromosomal bands known to harbour loci for the observed disease or trait as listed as single loci in Online Mendelian Inheritance of Man (OMIM, www.ncbi.nlm.nih.gov/omim), eg 608995; Dyslexia, DYX8; Gene map locus 1p36–p34. Additional loci identified by linkage studies registered in PubMed (http://www.ncbi.nlm.nih.gov/entrez) were also included.

Criterion 2: Families where the translocation and the disease or trait co-segregated.

Criterion 3: Unrelated cases with the same disease or trait and with a breakpoint in the same chromosomal band. Since a proportion of individuals with the same balanced reciprocal translocation are likely to be identical by descent[13] carriers involving the same chromosomal bands were considered related except for the known recurrent 11;22-translocation.

If the same trait was reported for non-carriers in a family, the trait was not considered as potentially associated with the breakpoints.

Statistical analyses

In a family with a t(1;18)(p36.1;q21) co-segregating with dyslexia, a lod score was calculated under the assumption of complete penetrance of a dominant trait. In Table 2, we quote an 'apparent lifetime penetrance fraction' (ALPF) calculated as the number of translocation carriers in a family showing a specific trait divided by the total number of family members carrying that translocation with an age equal to or older than the latest onset in the affected carriers. A test for an overall association between band-specific breakpoints and reported traits was performed by means of a log likelihood ratio statistic by analyzing the overall distribution of band-specific breakpoints against the observed traits and evaluated by permutations under the null hypothesis. Each combination of band-specific breakpoints and traits was individually calculated by Fisher's exact test (one-sided).

Results

Population

National cohort By 1 January 2003, 74 130 post-natal chromosome results were registered in DCR and among these we identified 1320 carriers of a constitutional balanced reciprocal translocation, representing 669 independently ascertained translocations according to clinical genetic files, the CCR and the questionnaires (see Appendix in electronic supplementary information). Twenty-two percent of these families were initially ascertained because of reproductive difficulties, 30% because of a prenatal examination, 16% because of an abnormal karyotype in a family member and 22% because of an abnormal phenotype (Table 1). The 669 karyotypes included 637 simple reciprocal translocations, 25 complex rearrangements and seven mosaics. More than one balanced reciprocal translocation was observed in six families (see notes in Appendix, electronic supplementary material).

In total, 448 individuals were excluded from the questionnaire study for the following reasons: serious early-onset disease ($n=149$, for phenotypic description see publication by Bugge *et al*[14]); death ($n=123$); emigration ($n=20$); unknown address ($n=2$); younger than 18

Table 1 Reason for the chromosome examination for the independently ascertained families

Ascertainment	*Nation-wide cohort n = 669 families*	*Follow-up cohort n = 454 families*
1 Reproductive difficulties	146 (22%)	128 (28%)
1.1 Infertility	38 (6%)	34 (7%)
1.2 Recurrent abortions	99 (15%)	88 (19%)
1.3 Amenorrhea	9 (1%)	6 (1%)
2 Prenatal diagnosis[a]	199 (30%)	174 (38%)
2.1 Balanced translocation	181 (27%)	157 (35%)
2.2 Unbalanced translocation	15 (2%)	14 (3%)
2.3 Other chromosomal abnormality	3 (0%)	3 (1%)
3 Relatives of abnormal karyotype	109 (16%)	89 (20%)
3.1 Balanced translocation	9 (1%)	9 (2%)
3.2 Unbalanced translocation	90 (13%)	72 (16%)
3.3 Other chromosomal abnormality	10 (1%)	8 (2%)
4 Abnormal phenotype	144 (22%)	35 (8%)
5 Research project/ fortuitous	51 (8%)	27 (6%)
5.1 Newborn screening	34 (5%)	20 (4%)
5.2 Mental retardation/behavioural disorder screening	6 (1%)	0
5.3 Other screening	9 (1%)	5 (1%)
5.4 Fortuitous	2 (0%)	2 (0%)
6 Haematological abnormality	1 (0%)	0
7 Unknown	19 (3%)	1 (0%)

[a]The probands (foetus) were only included in the cohort when a post-natal test was performed later.

years of age ($n=22$); non-Danish-speaking carrier ($n=16$); uncertainty of counselling (patient file could not be located) ($n=15$); examined as a child but no confirmation that they had been informed ($n=44$); recommendation from the local clinical genetic department ($n=57$).

Follow-up cohort Questionnaires were posted to the remaining 872 carriers representing 454 families (see Table 1 for their ascertainment). Follow-up time after the chromosome examination ranged from less than 1 year to 38 years with an average of 14.9 years. Initially, 381 carriers agreed to participate after the first letter; this increased to 731 (338 males and 393 females representing 405 families) after two reminder letters, resulting in a total response rate of 84%. Among these, 287 carriers were contacted by phone to obtain additional information about the diseases/traits and family relations. Of the 731 respondents, 36 carried *de novo* rearrangements, 214 had inherited the rearrangement from the mother and 173 from the father while 308 carried a rearrangement of unknown origin.

In total, 141 carriers (from 105 families) did not participate. The non-respondents did not differ significantly from the participants with regard to ascertainment (χ^2 sum = 5.87 (5 degrees of freedom (df), $P=0.32$) and sex (χ^2 sum = 3.54 (1 df), $P=0.06$, a larger fraction of females among respondents). When separated into age groups, we found a significant difference between non-respondents and respondents with fewer respondents among the young (18–19 years) and old age groups (>70 years) (eight age groups; χ^2 sum = 33.66 (7 df), $P<0.0001$). In addition we found a significant difference between respondents and non-respondents with regard to the number of years between chromosome examination and re-examination with more respondents with a short follow-up (<10 years) and fewer after a long follow-up time (>30 years) (four follow-up periods; χ^2 sum = 9.17 (3 df), $P=0.03$).

Disease-associated breakpoints

By focusing on cases where a breakpoint at the cytogenetic level concurred with linkage data and/or co-segregation of translocation and trait (selection criterion 1 and 2), we observed 42 potential disease-associated breakpoints (Table 2). The strongest association was a breakpoint in 1p36 in a familial t(1;18)(p36.1;q21) co-segregating with dyslexia (Figure 1), where a locus DYX8 has been confirmed by linkage analyses.[15] The lod score for linkage between this translocation and dyslexia was 2.11, which is considered significant because of the confirmed locus.[16] In addition to dyslexia, three of the translocation carriers developed colon adenomas/carcinomas at ages 33, 45 and 62 (Figure 1). Another likely association listed in Table 2 is a family with two brothers and a son carrying t(9;17)(q33;q25.3), where all carriers have bipolar disorder. The relation between 17q25.3 and bipolar disorder is supported by the observation of two other unrelated carriers with depression and a breakpoint in 17q25.3 in the follow-up cohort and by linkage data.[17,18]

The third criterion, unrelated carriers with same breakpoint and phenotype, was used when it was supported by the two first criteria or by other sources than the present cohort (Table 2). In addition we tested the third criterion separately by studying the overall distribution of unrelated carriers with the same breakpoint and trait and found a summary log likelihood ratio (LLR) statistic of 3686.50, and 399 permutations under the null hypothesis showed a mean of 3595.21 (standard deviation = 72, $P=0.12$ (95% CI: 0.09–0.15)), compatible with there being no overall significant association. However, among the 441 instances of at least two unrelated carriers with the same band-specific breakpoint and phenotype we arbitrarily selected the combinations where the one tailed χ^2-value exceeded 5.6 and found 6 (Table 3). This included four carriers with a breakpoint in 11q23 with cervical dysplasia, including three apparently unrelated women with the recurrent t(11;22) translocation.

Discussion

We describe a systematic re-examination of carriers of balanced reciprocal translocations as a strategy to search for loci involved in common and complex diseases. Based on the cytogenetically defined breakpoints, we suggest a large number of potential disease-associated translocations; some that may be matching with loci identified previously by linkage and associations studies, others that may indicate new candidate regions.

Since we asked about common diseases and traits, we can assume that many of these will not be causally related to the specific translocation. To optimize the chance of finding specific translocation-trait relationships, we focused on translocations co-segregating with a specific trait within a family and/or on breakpoints that at the cytogenetic level concurred with known linkage data. The significance of an observed co-segregation of a translocation with a common trait obviously depends on the size of the family and on the penetrance. With respect to dyslexia, the t(1;18) family illustrates a near optimal situation: it is large enough to reach significance, and there appears to be full penetrance. Most of the observed translocation families are smaller but could be important as well for example the family with bipolar disease and breakpoint in 17q25 mentioned previously. The 1;18-translocation family also exemplifies a chromosomal breakpoint associated with a disease with reduced penetrance (cancer). Since the penetrance of even major genes involved in complex diseases can be fairly low,[19] we also listed families where only some of the carriers displayed a specific phenotype, as long as there were no reports of non-carriers being

Table 2 Disease-associated translocations identified due to concurrence with a known locus (Criterion 1), co-segregation with the trait (Criterion 2) and/or because of unrelated carriers with same trait/breakpoint in the present study (PS) or in Mendelian Cytogenetic Network database (MCNdb) (Criterion 3)

Trait (*n* = *Total number of families reporting the trait*)	*Karyotype*	*Criterion 1* MIM-/PubMed-id	*Criterion 2* ALPF[a]	*Criterion 3*
Allergy (*n* = 133)	t(**3**;15)(**q21**;q22)	603165	2/3	PS: 2
Aortic stenosis (*n* = 2) and tachycardia (*n* = 7)	t(2;6)(q21;q25)		3/3	
Asthma (*n* = 50)	t(2;**12**)(q31;**q24.1**)pat	*14767694*	1/2	PS: 2
	t(**7**;12)(**p14**;q24)*de novo*	608584	1/1	
Bipolar disorder (*n* = 32)	t(4;**12**)(p15.3;**q22**)	608520	1/1	
	t(9;**17**)(q33;**q25.3**)	*12772088, 15558715*	3/3	PS: 3
Breast cancer (*n* = 6)	t(**17**;19)(**q21**;q13)	113705	1/2	
Cataract (*n* = 14)	t(7;**9**)(p15;**q22**)	605749	1/1	PS: 2
	t(X;**22**)(q13;**q11**)	601547	1/1	
Coronary heart disease (*n* = 18)	t(6;**14**)(q13;**q32**)	608318	1/1	
	t(7;**16**)(q11.2;**p13.1**)	607339	1/1	
Dyslexia (*n* = 30)	t(6;**15**)(q22;**q21**)	127700	2/2	
Dyslexia (*n* = 30) and Colon tumour (*n* = 3)	t(**1**;**18**)(**p36.1**;**q21**)	608995, 120470	5/5, 3/5	
Hypermetropia (*n* = 4)	t(11;13)(q25;q22)		3/3	
Hypertension, essential (*n* = 88)	t(**1**;6)(**q42**;q21)	106150	2/2	
	t(**4**;8)(**p16**;p23)	102680	2/10	
	t(4;**18**)(p12;**q22**)	*15054836*	1/2	PS: 3
	t(11;**21**)(q23;**q21**)mat	*15665825*	1/1	PS: 2
Hyperthyroidism (*n* = 13)	t(10;**18**)(p11.2;**q21**)	*10762555*	1/2	
Inflammatory bowel disease (*n* = 4)	t(5;**12**)(q13.2;**q21.2**)	601458	1/1	
	t(9;**19**)(q21.1;**p13.1**)mat	606674	1/9	
	t(10;**12**)(q24;**q13**)pat	601458	1/2	
Lymphoma (*n* = 2)	t(3;**18**)(p23;**q21**)	151430	2/3	
Male infertility (*n* = 64)	t(**1**;4)(**q21**;q33)mat	108420	1/1	MCNdb: 19
Migraine (*n* = 25)	t(**1**;8)(**p36.3**;p11.2)mat	*15053827*	1/2	PS: 2
Multiple sclerosis (*n* = 2)	t(**12**;13)(**p12.1**;q21)	*11823448*	1/1	
Musical perfect pitch (*n* = 46)	t(6;**18**)(q22.2;**q21.3**)		3/3	PS: 3
Myopia (*n* = 151)	t(9;**18**)(p24;**q12**)		3/3	MCNdb: 1
	t(**12**;**18**)(**q21**;**p11.2**)*de novo*	603221, 160700	1/1	PS: 2
	t(**17**;19)(**q21**;q13)mat	608474	1/3	PS: 3
Myopia and cataract	t(**18**;**20**)(**p11.2**;**p11.2**)	160700, 605387	2/7, 1/7	PS: 2 (18p11)
Obesity[b] (*n* = 75)	t(7;**20**)(q11.2;**q13.2**)	602025	2/3	PS: 2
	t(**11**;18)(**q23.3**;q21)		3/4	PS: 5, MCNdb: 2
	t(**12**;17)(**q24.1**;q25)	*15647995*	1/1	PS: 3
Osteoporosis (*n* = 17)	t(**4**;12)(**p15.3**;q22)	*14672361*	1/1	PS: 2
Parkinson disease (*n* = 1)	t(**1**;18)(**p36.2**;q21.2)	605909, 606324, 606693	1/1	
Premature menopause (*n* = 2) and vaginal septum (*n* = 2)	t(**X**;9)(**q21.3**;q31)		2/2	PS: 1 with breakpoint in Xq22.3
Tachycardia, paroxysmal (*n* = 7)	t(**3**;22)(**p21**;q13)	192605	1/1	
	t(**1**;**21**)(**q42**;**q22**)	600996, 176261	1/1	
Type 1 diabetes (*n* = 8)	t(**2**;**12**)(**q31**;**q24.1**)	600321, 222100	1/2	
	t(**10**;17)(**p11.21**;q25.1)*de novo*	601942	1/1	
Type 2 diabetes (*n* = 13)	t(X;**1**)(q27;**q24**)	*11067779*	1/2	

[a]ALPF, 'apparent lifetime penetrance fraction' is the number of translocation carriers in a family reporting a specific trait divided by the total number of family members carrying that translocation with an age equal to or older than the latest onset in the affected carriers.
[b]Obesity was defined as Body Mass Index (weight/(height $\times$ height)) $>30\,kg/m^2$ based on self-reported weight and height.
Families where non-carriers reported the trait were not included in this table. The breakpoints relating to specific disease loci are in bold.
The numbers in italics refer to PubMed-id.

affected and when there were additional evidence for an association (Table 2, Criteria 1 + 3).

It is very difficult to estimate the significance of a breakpoint within a cytogenetic band harbouring a known locus for an observed trait/disease. Each cytogenetic band is unique in size and gene content, the listed number of loci for a given trait may not reflect the real number, and some traits are more frequently reported than others. For example, there are 151 unrelated myopic translocation carriers, including 12 with a breakpoint corresponding to one of the 10 cytogenetic regions with known myopia loci. Some of these could easily be chance events, but four of these 12 translocations involved a common region, 17q21–22 (MYOPIA 5). In contrast, Parkinson's disease illustrates a rare disorder with one reported individual with a t(1;18)(p36.2;q21) (Table 2). The likelihood that one of the two breakpoints (1p36) by chance coincides with a known Parkinson locus is much smaller.

Previously, it has been assumed that two or more independent breakpoints in the same cytogenetic region

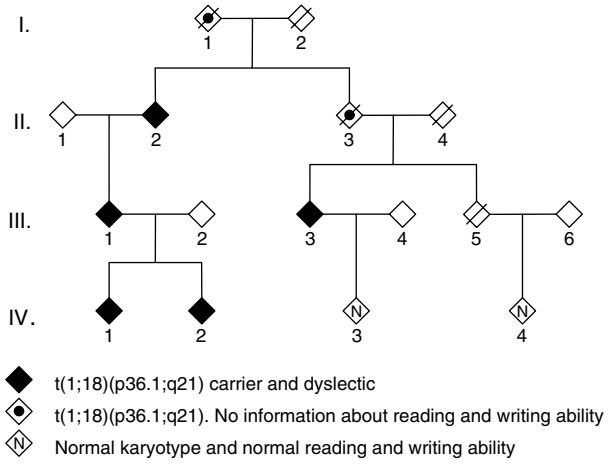

Figure 1 Co-segregation of dyslexia and colon tumours with a balanced translocation, t(1;18)(p36.1;q21). I:1 and III:3 developed colon carcinoma at the ages of 62 and 33 years, respectively, and II:3 developed several colon adenomas from the age of 45. To preserve the anonymity of the family, we omitted three non-carriers without dyslexia and colon tumour (all were siblings of carriers) from the figure.

associated with a rare disease, suggested a locus for that disease, for example, 16p13 for Rubinstien–Taybi syndrome[20] and 17q24–25 for campomelic dysplasia.[21] In the present study we have found 441 instances of such a co-occurrence, but since this includes common disorders, their significance varies. On the list of the six combinations with the highest LLR-values (Table 3) we found cervical dysplasia and 11q23 where the presence of a cervix-associated tumour suppressor gene has been suggested due to the frequent observation of loss of heterozygozity for 11q23 in cervical tumour tissues.[22] Although an increased occurrence of cervix dysplasia has so far not been described in carriers of the recurrent t(11;22) translocation, our observation of four independent carriers with breakpoints in 11q23 indicates that attention should be paid to this condition in female carriers of the recurrent t(11;22) translocation. Thus, among the 441 instances of co-occurrence there are some likely associations that may not be revealed by overall statistical analyses.

We are aware of several potential limitations of the approach taken in the present study: The traits were reported by the carriers themselves. However, in the disorders where the questionnaire led to a suspected association, we have if possible asked for confirmatory data from doctors/hospitals/educational authority. It is more likely that we have missed some genuine associations by underreporting, especially of diseases/traits not included in the questionnaire, of only minor consequences or that are poorly defined in lay terms, than we have included associations erroneously. Another potential pitfall is that the localization of the breakpoints based on the reported karyotypes may not be accurate. This may work both ways: we may incorrectly establish some false associations and we may miss some associations. The false-positive examples will likely be apparent following molecular mapping and the false-negative examples will likely be revealed by extending the cytogenetic breakpoint regions involved.

The functional relationships between the individual translocation and the common/complex trait observed may reflect simple truncation of a specific gene, in which case the mapping will be able to directly identify the candidate gene involved. Chromosomal breakpoints within

Table 3 Disease loci suggested by unrelated carriers with the same trait and breakpoint

Trait (*n* = Total number of families reporting the trait)	*Breakpoint*	*Unrelated carriers with same breakpoint and trait* *n*	*Fisher's exact test* *P-value*
Cervical dysplasia (*n* = 12)	11q23	4	0.0007
Renal stones (*n* = 6)	1p36	2	0.0011
Musical perfect pitch (*n* = 46)	7p22	3	0.0014
Hypothyroidism (*n* = 10)	18q12	2	0.0016
Inguinal hernia (*n* = 25)	1q12	2	0.0037
Hydatidiform mole (*n* = 5)	11q11	2	0.0197

The six combinations producing the highest one-sided LLR statistic are shown (exceeding 5.6).

highly conserved, regulatory landscapes of *cis*-acting regulatory elements have been shown to be associated with long-range position effects in some developmental disorders.[23] For common and/or complex traits there is a growing awareness that many predisposing mutations may not be within exons of protein-coding genes but may be located in introns[24] or in non-genic regions involving *cis*-acting mechanisms;[25] it would be logical to assume that some of these non-genic regions could be potential targets for chromosomal breakpoints as well. Indeed, this was recently shown to be the case in Tourette's syndrome (TS), where a *de novo* inversion breakpoint approximately 350 kb from *SLITRK1* pinpointed this as the first identified TS gene.[5] Furthermore, the follow-up cohort includes examples where unexplained chromosomal/epigenetic mechanisms have been suggested: females with premature ovarian failure associated with breakpoints within the 'critical q13–q26 region' on the X chromosome,[26] and infertile males with breakpoints involving virtually all of chromosome 1.[7]

In conclusion, re-examination of translocation carriers might be a valuable approach to link chromosomal breakpoints with known loci, identify new candidate loci, and reveal novel genetic mechanisms in common and complex diseases. In traits where there are no existing mapping data (eg musical perfect pitch) the associated breakpoints could guide subsequent linkage and association studies. Obviously, molecular mapping of the breakpoints is essential for providing proof of the suggested relations to the phenotypes but by publishing the strategy at the current state we hope to inspire other groups to use this approach and/or pay attention to common and complex diseases among their translocation carriers. Thereby additional genotype–phenotype associations can be identified, some of which may be novel and others that may coincide with and provide additional support of data presented here. In turn, this would facilitate the selection of potential disease-associated breakpoints for molecular mapping.

Acknowledgements

We thank the families who have participated in the questionnaire study and Jan Hansen & the Danish Cytogenetic Registry for providing data for the national cohort. We are grateful to Professor Patricia Jacobs, Wessex Region, Genetic Laboratory, UK for helpful discussion and critical reading of the manuscript and to Professor Newton Morton, Southampton University, UK for estimating lod scores. We also thank Christina Halgren Hansen for assistance with handling the questionnaires and Minna Becker, Anita Niebuhr, Ingrid Kjær for technical assistance. Wilhelm Johannsen Centre for Functional Genome Research is established by the Danish National Research Foundation who also financed this study.

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