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A Chromosome 10 Variant With a 12 Mb Inversion [inv(10)(q11.22q21.1)] Identical by Descent and Frequent in the Swedish Population

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We identified a paracentric inversion of chromosome 10 [inv(10)(q11.22q21.1)] in 0.20% of Swedish individuals (15/7,439) referred for cytogenetic analysis. A retrospective analysis of 8,896 karyotypes from amniocenteses in Sweden revealed a carrier frequency of 0.079% (7/8,896) for the inversion. Cloning and detailed analysis of the inversion breakpoint regions show enrichment for interspersed repeat elements and AT-stretches. The centromeric breakpoint coincides with that of a predicted inversion from HapMap data, which suggests that this region is involved in several chromosome 10 variants. No known gene or predicted transcript are disrupted by the inversion which spans approximately 12 Mb. Carriers from four non-related Swedish families have identical inversion breakpoints and haplotype analysis confirmed that the rearrangement is identical by descent. Diagnosis was retrieved in 6 out of the 15 carriers referred for cytogenetic analysis. No consistent phenotype was found to be associated with the inversion. Our study demonstrates that the inv(10)(q11.22q21.1) is a rare and inherited chromosome variant with a broad geographical distribution in Sweden.

Key words: paracentric inversion; chromosome 10q; breakpoint cloning; founder effect

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INTRODUCTION

Inversions are the most common human constitutional karyotype aberration detected in cytogenetic laboratories [Schmidt et al., 2005; Thomas et al., 2008]. Many specific chromosome inversions are rare or unique presenting a dilemma for the genetic counselor and requiring family follow-up. Several prevalent autosomal pericentric inversions are considered to be polymorphic variants since they are stably transmitted and without phenotypic or developmental consequences [Hysert et al., 2006]. Examples are pericentric inversions of chromosomes 2, 9, and 10. The variant inv(2)(p11q13) has a frequency of 0.1% in North Europeans [Djalali et al., 1986; Fickelscher et al., 2007] and the inv(9)(p11q13) has an overall carrier frequency of 1.98% with slight ethnical variations [Ait-Allah et al., 1997]. Both inv(2)(p11.2q13) and inv(9)(p11q13) inversions appear cytogenetically homogeneous in non-related individuals but a detailed molecular analysis indicate breakpoint heterogeneity [Schmidt et al., 2005; Fickelscher et al., 2007]. It is assumed that such independent and similar inversions have accumulated amongst different populations [Thomas et al., 2008]. On the other hand, the phenotypically silent and widely spread variant chromosome inv(10)(p11.2q21.2) has a single ancestral origin

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[Gilling et al., 2006]. This inversion is rare with an estimated carrier frequency of 1 in 3,600 to 1 in 12,800 among northern Europeans [Gilling et al., 2006]. The paracentric cytogenetic inversions have an overall estimated frequency between 0.009% and 0.049% in the general population [Balicek, 2004], and they are considerably more rare than pericentric inversions.

Many larger inversions repeatedly identified in cytogenetic laboratories are usually considered as polymorphic variants without association to any obvious or detectable phenotype. Yet, a specific but subtle effect mediated by an inversion may become clear only in a longer perspective and detected from the analysis of large and ethnically diverse populations [Stefansson et al., 2005]. In a broader context, inversions are thought to be key players in evolution and account for much of the genomic differences between humans and other primates [Iafrate et al., 2004; Sebat et al., 2004]. Detailed structural analysis of submicroscopic inversion variants indicates that they frequently origin from non-allelic homologous rearrangements between repeated and re-iterated sequences or duplicons [Shaw and Lupski, 2004; Bansal et al., 2007]. Recent progress in genomics indicates that most polymorphic inversions span minor regions down to a few kilobases of DNA [Feuk et al., 2005; Tuzun et al., 2005]. These inversions constitute a large part of the normal genomic variation among humans and may occur frequently as somatic events [Flores et al., 2007].

In this report we present a novel 12 Mb paracentric chromosome variant, inv(10)(q11.22q21.1) identified in karyotypes from both leukocytes and amniocytes. We present here our clinical, cytogenetic and molecular analysis of this rearrangement.

PATIENTS AND METHODS

Patients

A paracentric inversion of chromosome 10 inv(10)(q11.22q21.1) was identified in four non-related individuals referred to a clinical cytogenetic laboratory. The four subjects were karyotyped at a young age because of Feingold syndrome (1), neuropsychiatric symptoms (1) and/or unspecific developmental delay (2). There were no family history for the disorders and parents are healthy. The patients and five available parents were re-sampled for a detailed analysis of the rearrangement. In parallel, we re-examined karyotypes from altogether 8,896 amniocenteses and 7,439 blood specimens performed between 1996 and 2007 at two cytogenetic laboratories in Sweden (University Hospitals of Umeå and Gothenburg, respectively. DNA from 454 patients with non-specific psychomotor delay and various degree of mental retardation were also screened for the inv(10)(q11.22;q21.1) with the PCR assay. The 454 patients were previously screened and found negative for fragile X by DNA analysis. In addition, DNA from 2,400 Icelandic blood donors were screened for the inv(10)(q11.22;q21.1) with a PCR assay detecting the breakpoints. The study complies with the declaration of Helsinki and performed according to a protocol approved by the regional ethical committee in Uppsala.

Cytogenetic and FISH Studies

Standard G-banding at a resolution of approximately 400 bands was performed for the identification of inv(10)(q11.22q21.1). EBV-transformed B-lymphocytes from three subjects with the rearrangement were used to prepare metaphase spreads for FISH analysis [Henegariu et al., 2001]. We performed FISH analysis with chromosome 10 derived bacterial artificial chromosomes (BACs) obtained from RZPD-Germany. Refined mapping using mini FISH was performed essentially as previously described [Rauch et al., 2001; Mansouri et al., 2005]. Probes of approximately 6 kb were generated by long-range PCR from the BAC clones RP11-203B22 and RP11-550A9, with the Advantage 2 PCR enzyme systems (BD Biosciences, Franklin Lakes, NJ and Clontech, Mountain View, CA). The probes were digested to 100–500 bp fragments using nick-translation and hybridized to metaphase chromosomes.

Genotyping Using Microsatellite Markers

Each PCR reaction was performed in a total volume of 10 µl containing 25 ng genomic DNA, 1.5 mM $MgCl_2$, 1× PCR Reaction Buffer (Invitrogen, Carlsbad, CA), 187.5 µM of each dNTP (Amersham Biosciences, Uppsala, Sweden), 2.5 pmol of each primer, and 0.15 U Platinum *Taq* DNA Polymerase (Invitrogen). The PCR amplification consisted of an initial polymerase activation step at 95°C for 10 min; (95°C, 30 sec; 55°C, 30 sec; 72°C, 30 sec) cycled 35 times and a final step at 72°C for 7 min. The microsatellite primers were labeled with one of the fluorophores FAM, HEX, or NED. PCR products were separated by electrophoresis on an ABI 3700 DNA Analyzer (Applied Biosystems, Foster City, CA) and analyzed with Genescan v 3.1.3 and Genotyper v 3.7 softwares (Applied Biosystems).

Southern Blot Analysis

Genomic DNA was isolated from peripheral blood lymphocytes with the salt precipitation method according to standard procedures. Ten micrograms of genomic DNA was digested overnight with 30 U restriction endonuclease (*Sph*I, *Nco*I, *Nde*I, or *Nhe*I). The probe derived from 10q21.1 used for Southern blot analysis was amplified by standard PCR and labeled with ^{32}[P]dCTP using the Megaprime DNA labeling system (Amersham Biosciences).

Breakpoint Cloning and Inverse PCR

Genomic DNA (0.5 µg) was digested with 5 U *Rsa*I in a 50 µl reaction volume overnight, followed by heat inactivation of the restriction endonuclease at 65°C for 20 min. We ligated 50 ng of the cleaved DNA with 12 Weiss units T4 DNA ligase (Fermentas, Glen Burnie, Maryland) in a reaction volume of 40 µl for 2 hr at 16°C followed by ethanol precipitation. The ligation products were amplified with long-range inverse PCR for the identification of unknown DNA sequences at the proximal breakpoint [Ochman et al., 1988]. The PCR products were separated on a 1% agarose gel and visualized by ethidium bromide staining.

Sequencing

The PCR products were purified with the GFX PCR DNA and Gel Band Purification Kit (Amersham Biosciences). The sequencing was performed with an ABI 3700 DNA Analyzer (Applied Biosystems) using Big Dye Terminator v 3.1 Cycle Sequencing

chemistry (Applied Biosystems) according to manufacturer's recommendations.

Multiplex PCR

A multiplex PCR was performed with a forward primer located in 10q11.22 and two different reverse primers (sequences available upon request), one in 10q11.22 (PCR product of 391 bp) and one in 10q21.1 (PCR product of 340 bp). The PCR reactions were performed in a total volume of 20 µl containing 50 ng genomic DNA, 1.5 mM $MgCl_2$, 1× PCR Reaction Buffer (Invitrogen), 200 µM of each dNTP (Amersham Biosciences), 8 pmol of the 10q11.22 forward primer, 4 pmol of the 10q11.22 reverse primer, 8 pmol of the 10q21.1 reverse primer, and 0.5 U Platinum *Taq* DNA Polymerase (Invitrogen). The PCR amplification consisted of an initial polymerase activation step at 95°C for 5 min; (95°C, 30 sec; 60°C, 30 sec; 72°C, 45 sec) cycled 35 times and a final step at 72°C for 7 min. The PCR products were separated on a 1.5% agarose gel and visualized by ethidium bromide staining. Screening of 2,400 individuals in the Icelandic population was performed using the multiplex PCR on pools of DNA from 30 individuals in each pool. Wells spiked with DNA from a known carrier for the inversion were used as a positive control.

Sequence Analysis

The RepeatMasker program (http://www.repeatmasker.org/) was used to screen DNA sequences for interspersed repeats and low complexity DNA sequences. Primer 3 (http://frodo.wi.mit.edu/) was used for primer design.

All primer sequences used for PCR and sequencing are available upon request.

RESULTS

Mapping of the Inversion Breakpoints

Cytogenetic investigation revealed an apparently identical paracentric inversion of chromosome 10 in blood samples from four non-related subjects (Fig. 1). FISH analysis using BAC clones revealed that the distal breakpoint is located telomeric to BAC RP11-203B22, which was found inverted, and centromeric to the BAC RP11-550A9, which was not inverted (Fig. 2). These two BAC clones overlap by 60,074 bp and mini FISH analysis allowed us to further restrict the 10q21.1 breakpoint to a 36 kb region. In order to more precisely map the location of the breakpoint we designed a probe in this interval for Southern blot analysis. The probe corresponds to bp 58,880,515–58,880,815 on chromosome 10: Ensembl v42-Dec 2006 (supporting information Fig. 1 may be found in the online version of this article). Aberrant restriction fragments were observed with the restriction endonucleases *Sph*I, *Nco*I, and *Nde*I in carriers for the inversion when compared to control subjects (supporting information Fig. 2 may be found in the online version of this article). The combined results from the different restriction endonuclease patterns allowed us to position the breakpoint to within a 3 kb region.

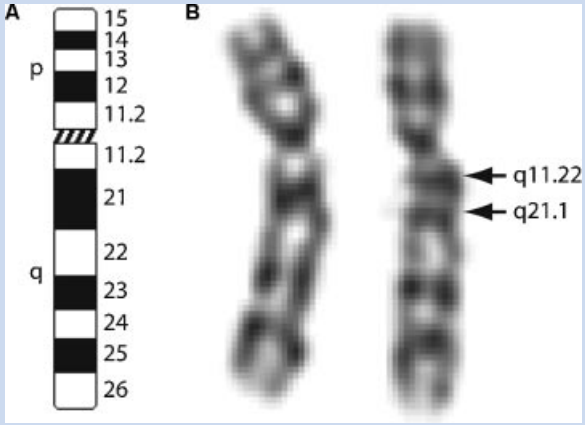

FIG. 1. Idiogram of chromosome 10 (left) and the corresponding G-banded chromosomes from a carrier of the inv(10)(q11.22;q21.1) (right). The inversion is indicated with arrows.

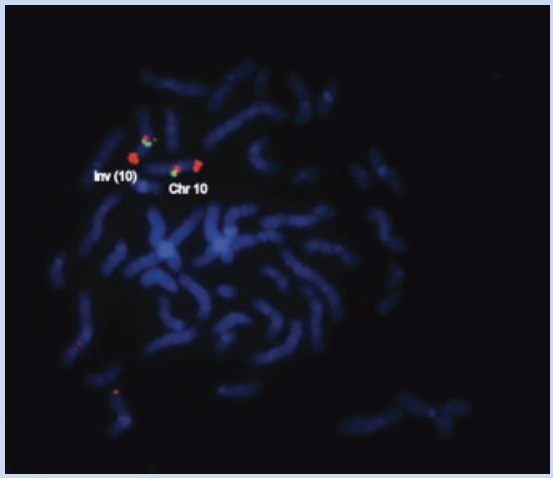

FIG. 2. FISH analysis to metaphase chromosomes from an index case with inv(10)(q11.22;q21.1) with the two BAC clones RP11-358K2 (red signal) and RP11-203B22 (green). The BAC clones are derived from chromosome 10q11 and chromosome 10q21, respectively, and separated by approximately 10 Mb of DNA. Signals from the common chromosome 10 variant (Chr 10) shows that RP11-358K2 is positioned centromeric to RP11-203B22. Signals from chromosome 10 with the inversion (Inv10) shows the opposite order of the two BAC clones along 10q which indicates that both clones are located within the inversion. A control BAC, RP11-145I2 (red signal), hybridizes to the chromosome 10p telomere. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Cloning and Sequence Analysis of the Inversion Breakpoint Regions

Due to the presence of sequence gaps in the databases and large intrachromosomal duplications on 10q11.22 (UCSC genome browser March 2006) we used inverse PCR to clone the proximal breakpoint. This was done with outward facing primers in the 3 kb region containing the 10q21.1 breakpoint. Inverse PCR on circularized *Rsa*I fragments followed by gel electrophoresis revealed an aberrant 2 kb fragment together with the expected 1 kb fragment in subjects with the inversion. Sequence analysis of the 2 kb fragment showed homologies to both 10q11.22 and 10q21.1, which confirmed this to be a junction fragment. Sequence homology allowed us to position the 10q21.1 breakpoint at 58,884 kb on chromosome 10 according to the Ensembl database (Ensembl v42-Dec 2006). A 359 bp stretch of the junction fragment corresponding to the proximal breakpoint at 10q11.22 showed homology to four regions. BLAST search (NCBI build 36) revealed 100% identity to only one of these regions at position 48,514 kb. From these findings we concluded that the size of the inverted region is approximately 12 Mb. Sequence analysis of the two breakpoints revealed a gain of four nucleotides (GGGT) at the 10q11.22 breakpoint (Fig. 3). This sequence motif is also present at the 10q21.1 junction where it flanks the inverted segment. No other genomic modifications were found associated with the inversion and no known genes or predicted transcripts were disrupted by the two breakpoints.

Using the RepeatMasker program we analyzed 10 kb of DNA spanning each breakpoint. A short interspersed nuclear element (SINE) is located 900 bp centromeric to the distal breakpoint. The results showed that the breakpoint sequences are AT-rich and enriched for interspersed repeats. The 10q11.22 breakpoint contained 66% repetitive sequence (21% SINEs, 8% long interspersed nuclear elements [LINEs], and 28% LTRs) and had an AT level of 54%. The 10q21.1 breakpoint consisted of 35% repetitive sequence (5% SINEs, 24% LINEs, and 6% LTRs) with an AT content of 67%.

Haplotype Analysis of the Inverted Region

With a single origin of the inversion the carriers were assumed to have a shared haplotype across the 12 Mb inversion. Genotyping was performed using 15 microsatellite markers along the inversion on DNA from four subjects and five available parents. Haplotype analysis established that the chromosome 10 inversion is identical by descent (Fig. 4A). A single microsatellite marker (D10S596) within the inverted segment showed an aberrant pattern in subject 3 and his carrier father when compared the other three cases with the inv(10)(q11.22;q21.1). The reason is probably a mutation at this repeat in the paternal lineage [Lai and Sun, 2003].

PCR Assay for Detection of inv(10)(q11.22;q21.1)

The multiplex PCR assay confirmed heterozygosity for the inv(10)(q11.22;q21.1) on DNA from the four subjects (Fig. 4B). Samples from five parents were available and three of these were identified as carriers by PCR, which is consistent with the cytogenetic findings. The PCR assay was also used to screen for the inversion in a non-Swedish population consisting of samples from 2,400 Icelandic individuals. All pools turned out negative for the rearrangement. In addition, the 10q inversion was excluded in DNA from 154 healthy Swedish blood donors and 454 patients with unspecific mental retardation or developmental delay negative on fragile X screening.

Retrospective Study of Karyotypes

G-banding karyotypes from altogether 8,896 amniocenteses and 7,439 blood specimens were re-examined in two Swedish cytogenetic laboratories. In total, we identified the inv(10)(q11.22;q21.1) in seven amniotic samples and 11 blood samples (the four initially identified subjects excluded). This gave an overall carrier frequency of 1 in 907 making the rearrangement the most common paracentric inversion in the Swedish population. The blood samples positive for the inversion were derived from individuals referred for karyotyping because of various clinical manifestations. One patient was analyzed because of truncus arteriosus, one because of pulmonary artery atresia and ventral septal defect, one was diagnosed with Feingold syndrome, one patient had neuropsychiatric (attention deficit) disease, and two patients were analyzed because of mild developmental delay. In nine individuals

FIG. 3. Sequence analysis of the inv(10)(q11.22;q21.1) junction fragments. The upper panel shows sequence comparison between normal chromosome 10q11.22 and the centromeric junction. Inverted sequences are boxed and the grey box illustrates a gain of four nucleotides (GGGT). The lower panel shows sequence comparison between normal chromosome 10q21.1 and the telomeric junction. Inverted sequences are boxed. The sequence ACCC (bold) flanking the breakpoint is homologous to the 4-nucleotide insertion at the centromeric junction.

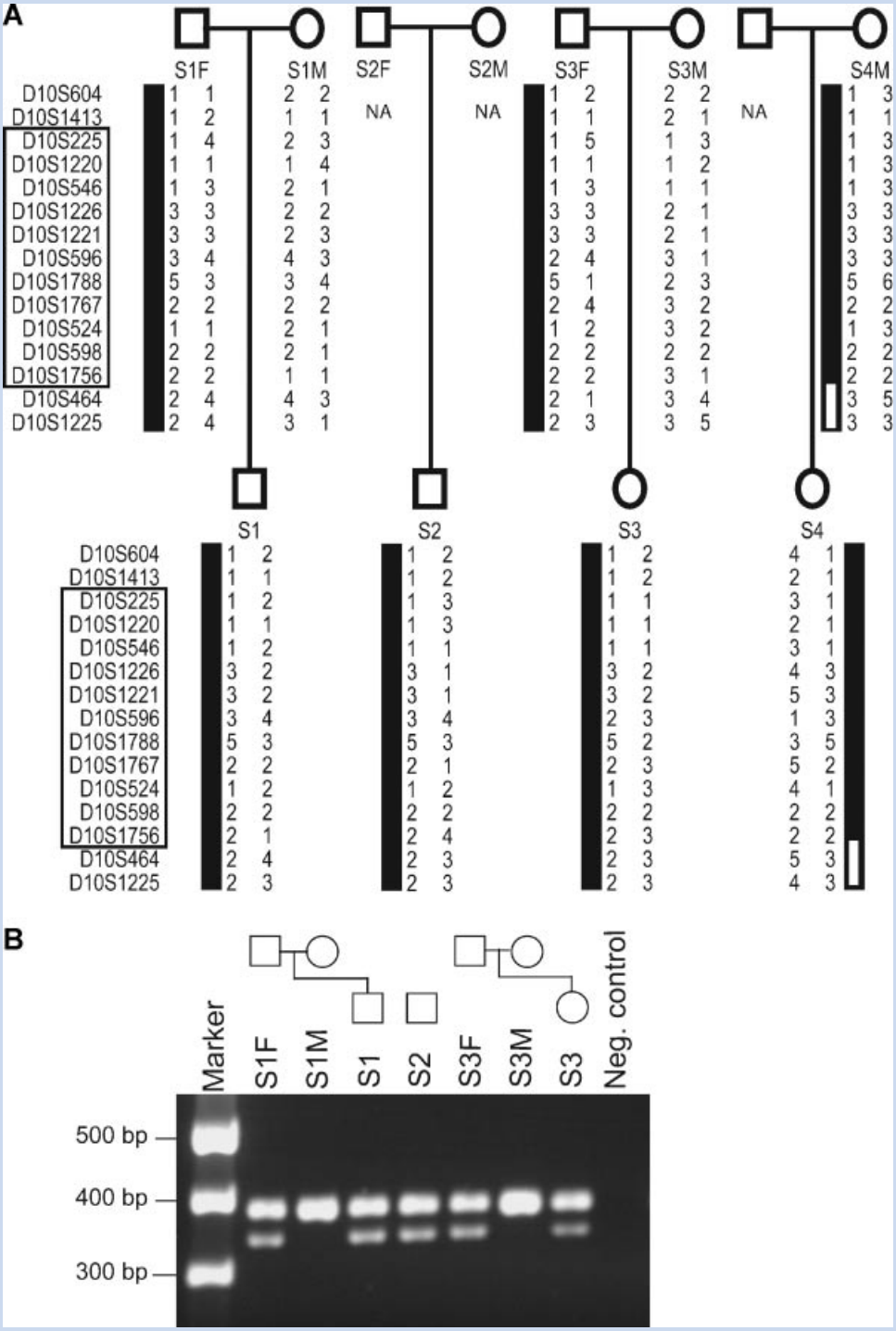

FIG. 4. A: Haplotype analysis of the inverted region on chromosome 10 in four subjects and five available parents. The boxed microsatellite markers are located within the inverted segment. The black bars below the symbols indicate the conserved haplotype associated with the inversion. A recombination close to the telomeric breakpoint has occurred in the maternal lineage of case S4. NA = not analyzed. B: PCR assay for detection of inv(10)(q11.22;q21.1). Two primers in 10q11.22 and one primer in 10q21.1 are used for a simultaneous generation of distinct fragments from both chromosome variants. A normal chromosome 10 produces a PCR product of 391 bp, whereas the inv(10)(q11.22;q21.1) produces a PCR product of 344 bp. S1F, father of subject 1; S1M, mother of subject 1; S1, subject 1; S2, subject 2; S3F, father of subject 3; S3M, mother of subject 3; S3, subject 3.

with the inversion the indication for analysis could not be retrieved in retrospective.

Statistical Analysis

The incidence of the chromosome 10 inversion is not significantly different between our patient group (11/7,428 blood samples) and the normal population (7/8,889), here represented by the amniocenteses. A significance test for differences in pattern frequencies between the two groups with a chi-square of 1.762 on 1 df corresponds to a two-tailed significance level of $P = 0.1844$. The inversion was not found in the Icelandic population group consisting of 2,400 blood donors. This suggests a higher prevalence for the rearrangement in the Swedish population but without significant differences between the two groups of normal individuals (chi-square of 2.646 on 1 df; $P = 0.1038$ compared to a total of 16,317 Swedish samples).

DISCUSSION

In this study we report on a yet un-described paracentric inversion of chromosome 10q [inv(10)(q11.22q21.1)] found in 18 independent samples in a Swedish cohort of altogether 16,335 karyotypes. This corresponds to a carrier frequency of 1 in 907 (0.11%), which makes the rearrangement the most prevalent paracentric inversion in the Swedish population. The inversion was initially found in four individuals referred for cytogenetic investigations. A retrospective analysis of karyotypes revealed seven amniotic samples and 11 peripheral blood samples positive for the inversion. Inheritance of the inversion from one healthy parent was confirmed in all 22 index cases, respectively. The reasons for cytogenetic analysis from peripheral blood samples were retrieved in six out of the 15 cases without association to any consistent phenotype. Out of six index cases, three were analyzed because of neuropsychiatric disease or mental retardation, two patients suffered from distinct cardiovascular malformations and one was diagnosed with Feingold syndrome. The predominant indication for prenatal screening of fetuses positive for the inversion was maternal age. We did not find any consistent clinical features, fetal loss, or other phenotype associated to the inv(10)(q11.22q21.1) and the inversion was also excluded in a cohort of 454 cases with unspecific neuro-developmental delay. Moreover, we found similar frequencies of the inversion in blood samples and amniocytes, which indicates that this is a silent variant. Most of the paracentric inversions identified in cytogenetic laboratories are not associated with any specific phenotypic abnormalities and the risk of heterozygotes having offspring with an unbalanced karyotype is expected to be small [Madan, 1995; Thomas et al., 2008]. Our results are also consistent with previous findings of cytogenetic paracentric inversions, which suggest that the majority (66%) is inherited [Pettenati et al., 1995]. Subtle effects of the inversion may, however, have escaped detection. A notable example is the 900 kb submicroscopic inversion polymorphism of chromosome 17q21.31 recently analyzed in different populations [Stefansson et al., 2005]. Epidemiological studies suggest that this inversion is under positive selection. Further genotype–phenotype correlations on the inversion presented here and in larger populations are required to clarify such subtle effects on carriers.

The frequencies of the inv(10)(q11.22q21.1) in non-Swedish populations are yet unknown. We screened 2,400 healthy Icelandic individuals all of whom turned out to be negative for the inversion. The frequency in the Icelandic cohort did not differ significantly from the frequency in Swedes (1/907; *P*-value 0.10) possibly due to the limited number of Icelandic samples available. Still, the absence of the inversion in the Icelandic cohort may suggest a tendency for a variation in frequency among Europeans.

We performed haplotype analysis using 15 microsatellite markers in the chromosome 10q11-q21 region and we confirmed a single origin for the inversion in four independent index cases. These four carriers originate from distinct geographical regions in Sweden. This suggests the inversion to be an ancient founder allele likely to be present also in other European populations.

Characterization of the breakpoint junction fragment by sequencing revealed that the inversion is identical in four non-related subjects. A gain of four nucleotides (GGGT) was identified at the centromeric junction and no gene or transcribed sequence was found disrupted by the breakpoints. The telomeric breakpoint was unambiguously assigned by sequence homology without a direct involvement of repetitive sequences albeit 0.9 kb telomeric to a SINE. The proximal breakpoint is located in a long terminal repeat. Previous analysis of cytogenetic and submicroscopic inversion breakpoint regions show that repetitive elements, high sequence similarity to the opposite breakpoint, pseudogenes, gene desserts, segmental duplications and co-localization with fragile sites are over-represented [Feuk et al., 2005; Schmidt et al., 2005; Tuzun et al., 2005]. Although both breakpoints identified in our study are located within or adjacent to repeats, they showed no strong homologies to each other from sequence analysis. Thus, we could not identify any obvious structural background to the origin of the inversion, for example, by a non-homologous recombination event. Still, the duplications and repeats identified at the proximal breakpoint region are consistent with findings from chromosomal rearrangements, which result from predisposing elements or sequence motifs [Shaw and Lupski, 2004]. Interestingly, the centromeric breakpoint on 10q11 in our study was recently predicted as an inversion breakpoint by in silico analysis. Submicroscopic inversions at sizes >1 Mb were identified by statistical methods applied on the HapMap data [Bansal et al., 2007]. Thus, the region around the 10q11 breakpoint identified here may predispose to different large inversions by yet unclear mechanisms.

In conclusion, this study demonstrate that a previously undescribed cytogenetic inv(10)(q11.22q21.1) is widely distributed in Sweden with an estimated overall carrier frequency of 0.11%. Breakpoint cloning and haplotype analysis across the inversion in non-related carriers indicate the inversion to be derived from one or a few founders. No known gene is directly disrupted by the inversion and it is not found to be associated with any consistent phenotype. Further studies are required to define the prevalence for the inv(10)(q11.22q21.1) in different populations and to clarify any subtle genotype-phenotype correlations for this rearrangement.

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