A balanced translocation truncates Neurotrimin in a family with intracranial and thoracic aortic aneurysm

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Abstract

Background—Balanced chromosomal rearrangements occasionally have strong phenotypic effects, which may be useful in understanding pathobiology. However, conventional strategies for characterizing breakpoints are laborious and inaccurate. We present here a proband with a thoracic aortic aneurysm and a balanced translocation t(10;11)(q23.2;q24.2). Our purpose was to sequence the chromosomal breaks in this family to reveal a novel candidate gene for aneurysm.

Methods and results—Intracranial and thoracic aortic aneurysms appear to run in the family in an autosomal dominant manner: After exploring the family history, we observed that the proband's two siblings both died from cerebral hemorrhage, and the proband's parent and parent's sibling died from aortic rupture. After application of a genome-wide paired-end DNA sequencing method for breakpoint mapping, we demonstrate that this translocation breaks intron 1 of a

splicing isoform of Neurotrimin (*NTM*) at 11q25 in a previously implicated candidate region for intracranial (IAs) and aortic aneurysms (AAs) (OMIM 612161).

Conclusions—Our results demonstrate the feasibility of genome-wide paired-end sequencing for the characterization of balanced rearrangements and identification of candidate genes in patients with potentially disease-associated chromosome rearrangements. The family samples were gathered as a part of our recently launched National Registry of Reciprocal Balanced Translocations and Inversions in Finland (n=2575), and we believe that such a registry will be a powerful resource for the localization of chromosomal aberrations, which can bring insight into the etiology of related phenotypes.

Keywords

Molecular genetics; Cardiovascular Medicine; Chromosomal; Clinical Genetics; Genome-wide

INTRODUCTION

Intracranial aneurysms (IA), thoracic aortic aneurysms (TAA), and abdominal aortic aneurysms (AAA) contribute significantly to morbidity, mortality, and medical expenditure despite continued improvement in diagnostic and surgical techniques [1–4]. Aneurysms usually result from accumulated degenerative changes, and over the course of time, medial degeneration in the artery wall can progress to rupture *i.e.* sudden subarachnoid hemorrhage (SAH), or acute aortic dissection or rupture.

Aneurysms are typically multifactorial, with both genetic and environmental risk factors such as hypertension, atherosclerosis, bicuspid aortic valve, alcohol consumption, smoking, and sex influencing the risk of subsequent aneurysm [5–12]. Pedigree analysis examining the familial forms of TAA suggest that the primary mode of inheritance is autosomal dominant with reduced penetrance and variable expression, whereas in IA and AAA families, autosomal recessive and X-linked modes are also observed [1,13–25]. Clinicians have historically regarded IA, TAA, and AAA as distinct diseases, but recent studies suggest commonalities in some families [26]. Estimation of co-occurrence of IA and aortic aneurysms (AA) within a family is 10.5%, and, in these families, patients often share not only aneurysm morphology but also a susceptibility locus [26–32]. Researchers have applied multiple genetic approaches including candidate gene approaches [33], linkage analysis [27,34–45], and GWAS [11,46–50], and revealed multiple loci predisposing to aneurysm [27]. Identification of the causative genes has important clinical implications - not only allowing identification of individuals at risk, but also optimizing the timing for surgical repair of such aneurysms.

Interestingly, the chromosome 11q25 region has been implicated in both IA and AA in several independent linkage studies. First, a Japanese study of affected sib pairs with IA revealed significant linkage to 11q25 [36]. Ozturk et al. subsequently reported an analysis of two multigenerational families with IA replicating this susceptibility locus [42]. Mounting evidence came from Worrall et al. who studied families with both IA and AA, and managed to verify the 11q25 region [51].

To date, six genes are known to be associated with familial TAA: *TGFBR1* at 9q22 [52], *TGFBR2* at 3p24-25 [28], *MYH11* at 16p13.13-13.12 [53], *ACTA2* at 10q23-24 [54], *MYLK* at 3q21 [55], and *SMAD3* at 15q21-q22 [56]. In addition, the gene implicated in Marfan syndrome, *FBN1* at 15q24-26, has variants, which, on rare occasions, can lead to TAA without comorbid Marfan syndrome [48,57,58]. One of these genes, *ACTA2* (OMIM 102620) locates near our 10q translocation breakpoint, and is implicated in 14% of TAA cases. Also, two recent studies have identified mutations in *TGFB2* at 1q41 associated with TAA and propose haploinsufficiency as the relevant mechanism [59,60]. Family studies have suggested two additional loci: TAAD1 (AAT2) at 5q13-14 [44], and FAA1 (AAT1) at 11q23-24 [27]. FAA1 (OMIM 607086) [27,61] was identified near our 11q translocation breakpoint through genome-wide linkage analysis (Z_{max} = 4.4, 1.1 cM telomeric to D11S1356). However, candidate gene analysis has thus-far failed to identify any causative variants on 11q. Together all these known genes and loci explain less than 20% of familial TAA cases [13,14].

In this pilot study, we identified the exact breakpoint on 11q25 on a prior strong positional candidate locus for IA and AA (OMIM 612161) through the application of genome-wide paired-end sequencing. Our study demonstrates the potential power and utility of comprehensive national ascertainment of balanced translocations and inversions for gene identification.

MATERIALS AND METHODS

National Registry of Reciprocal Balanced Translocations and Inversions in Finland

We have created a comprehensive National Registry of Reciprocal Balanced Translocations and Inversions in Finland by ascertaining all known carriers (n=2575) from every Medical Genetics Department and Clinical Genetics Laboratory in the country. This is feasible because the Finnish health care system retains comprehensive lifelong medical records of every individual. One physician (TV) has examined all the rearrangement carriers' medical records, summarized their medical histories, and photocopied the specific medical records containing clinically relevant phenotypic information. Where multiple family members were known to carry the same rearrangement, we recorded the pedigree structure (n=584) together with the aforementioned clinical information. Our database allows for examination of all clinical aspects of all cases, such that we can use the information for diagnostic purposes, for genetic counseling, and also for subsequent follow-up.

Our main scientific objective is to identify the specific chromosomal breakpoints for each translocation, and then to link this information with both data from the medical records as well as clinical data available from Finland's extensive collection of population health registries. This facilitates the process of determining the specific effects of chromosomal rearrangements on various traits and diseases. Finland's extensive collection of registries includes the Finnish Cancer Registry, the Social Insurance Institution of Finland registries (listing for all citizens e.g. all compensable prescription medications and all diagnoses which led to >9 sick days away from work), and the National Institute for Health and Welfare registries (nationwide registry of all hospitalized patients and all congenital malformations).

All familial relationships back to the 1600s are likewise known and searchable at the Finnish population registries [62].

Permission for sampling and analyzing the genetic material was granted by the Ethical Committees of the Joint Authority for the Hospital District of Helsinki and Uusimaa, and the Office of the Data Protection Ombudsman in connection of the Ministry of Justice is appropriately notified. The Ministry of Social Affairs and Health has approved our search for additional clinical information from the national health registries described above.

Sample collection

In August 2010 we launched nationwide sampling from the Department of Medical Genetics, Väestöliitto, The Family Federation of Finland. To date, we have collected blood samples from 91 carriers of balanced translocations or inversions. Extracted DNA, RNA and established lymphoblastoid cell lines are stored at −20°C, −80°C, and −150°C respectively.

Case report

Cytogenetic analysis—We performed standard cytogenetic analyses to verify earlier karyotyping (figure 1). Blood samples and informed consent were obtained from the proband and proband's child. Peripheral-blood lymphocytes were isolated from whole blood and primed *in vitro* with phytohemagglutinin. Lymphocytes were harvested and chromosomes were prepared and stained using standard techniques. G-banding karyotype analysis was performed at an approximately 650 band resolution according to established protocols. Chromosomal aberrations were described according to the ISCN 2009 guidelines [63].

Copy number analysis—To study submicroscopic deletions or duplications associated with the translocation breakpoints, genotyping was performed with the HumanHap300 BeadChip platform developed by Illumina Inc. (San Diego, CA, USA) according to the manufacturer's protocol. The data were normalized using a commercially available proprietary algorithm implemented in the BeadStudio 3.1.0 software provided by Illumina Inc. [64]. Genotype clusters were created with BeadStudio 3.1.0. from a large panel of normal population-based samples. A genotype success rate of >95% was required for SNPs and for samples in each study set. The B allele frequency and log R ratio were visualized with Illumina BeadStudio 3.1.0. Illumina Genome Viewer (IGV) was utilized to inspect each breakpoint region for CNVs.

ACTA2 sequencing—We sequenced *ACTA2* using the conventional Sanger sequencing method. Primer sequences were designed using UCSC Genome Browser (http://www.genome.ucsc.edu) and Primer 3 version 0.4.0 (http://frodo.wi.mit.edu) and their map locations were verified with UCSC In-Silico PCR, Fast PCR software (PrimerDigital Ltd., Helsinki, Finland) and Sequencer 4.8 software (Gene Codes Corporation, Ann Arbor, MI, USA). Primers and PCR conditions are available on request. Coding exons, intron-exon boundaries, introns, and 5′ and 3′ regulatory regions flanking 3 kb up- and downstream from *ACTA2* gene were PCR-amplified and cyclic bidirectional sequencing reactions were carried out using BigDye 3.1 terminator technology (Applied Biosystems, CA, USA).

Electrophoresis of the sequenced products was conducted with ABI3730 x1 capillary DNA Analyzer (Applied Biosystems), and base calling was performed using Sequencing Analysis 5.2 software (Applied Biosystems). The alignment between sequenced individuals and reference obtained from UCSC Genome Browser database was performed using Sequencher 4.8 software. Sequencing results were checked against dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/).

Genome-wide paired-end sequencing—To characterize the chromosomal breakpoints in the proband and proband's child, we applied a paired-end sequencing strategy. We randomly sheared 3 μg of genomic DNA using a Covaris-S2 focused sonicator (Covaris, Inc., Woburn, MA, USA) with the following parameters: duty cycle 10%, intensity 5 and 200 cycles per burst. Genomic paired-end libraries were prepared using NEBNext® DNA Sample Prep Master Mix Set 2 (New England BioLabs, Ipswich, MA, USA) according to the manufacturer's protocol with minor modifications. We generated three libraries with distinct target fragment sizes of ~200 bp, ~500 bp, and ~1 kb with the Caliper LabChip XT –instrument (Caliper Life Sciences, Hopkinton, MA, USA) to increase the genomic coverage and optimize the insert size for translocation detection. We assessed whether the insert size could be increased up to 1 kb without compromising sequence yield, mapping, or evenness of the genomic coverage. The 500 bp library was the most effective of the insert sizes we targeted, yielding the best coverage. Illumina GAII and HiSeq2000 analyzers were used for cluster amplification and to generate three lanes of short sequencing reads from both ends of these DNA fragments using the manufacturer's protocol. The images were processed using the manufacturer's software.

Data processing—An in-house developed SAMtools-based variant calling pipeline version 1.0 (VCP 1.0), described in detail by Sulonen et al., was used to align the sequence reads (GRCh37) [65]. We generated a total of ~354 million paired-end reads mapping back to the reference yielding 91% coverage of the reference. The overall mean depth of coverage was 8.7 X, and for *NTM* gene the average coverage was 6.04 X. We excluded 3.4 million reads as PCR duplicates, 0.8 million read pairs where only one end mapped to the genome, and 6.3 million read pairs because neither end mapped. We used the Integrative Genomics Viewer visualization program (Broad Institute, Cambridge, MA, USA) to identify rearrangements as discordant reads aligning to different chromosomes. Only when 2 read pairs spanned the same junction fragment were they used in further analysis. We subsequently targeted our search to paired-end anomalies mapping to chromosome 10 at one end and chromosome 11 at the other.

Confirmatory screening of the junction fragments—We designed primers for capillary sequencing of both derivative chromosomes to encompass the junction fragments. We used different combinations of primer sets located 1 kb outside the paired-end reads, for a maximum product size of 1 kb. Phusion High Fidelity PCR kit (Finnzymes, Vantaa, Finland) and a gradient of 56–65°C for primer annealing were used on patient and normal genomic DNA for each set of primers at least twice. Primers and PCR conditions are available on request. We assessed products from each primer set using gel electrophoresis. Rearrangements were defined as those PCR reactions giving a convincing band in the

patient DNA with no matching band in the control, detected in 2 separate reactions, together with ambiguously mapping sequence data. PCR products were used as templates for sequencing in both directions using BigDye Terminator 3.1 chemistry (Applied Biosystems) on 3730xl DNA Analyzer (Applied Biosystems). The sequences of the junction fragments were aligned to the human genome reference sequence (GRCh37) using Sequencher 4.8 software (Gene Codes Corporation) to define the breakpoints at base-pair resolution.

RESULTS

Karyotype and exclusion of copy number variation

Conventional G-banding karyotype analysis refined the preexisting translocation breakpoint from t(10;11)(q22;q23) to t(10;11)(q23.2;q24.2) (figure 1). To assess whether the translocation is truly balanced, we performed SNP genotyping of the two translocation carriers to detect CNVs. The raw intensity plots of the breakpoint regions (several megabases up- and downstream) revealed no detectable aberrations, submicroscopic, or large-scale CNVs.

Clinical summary

While building up our comprehensive National Registry, we observed that a proband with translocation t(10;11)(q23.2;q24.2) had suffered from a TAA. This comorbidity was previously not recognized by the clinical geneticists, and only came to light as a byproduct of this project. The pedigree is given in figure 2. The patient first had shortness of breath after exertion after the age of 50. Echocardiography and angiography revealed a TAA: dilatation of the ascending aorta to 68 mm as well as aortic insufficiency grade III – IV. At the age of 55 the proband received a prosthesis of the ascending aorta and valve. Based on death certificates, the proband's two siblings both died of cerebral hemorrhage at the ages of 69 and 50, respectively. The first sibling's forensic autopsy confirmed a ruptured aneurysm in the left carotid artery as the cause of death. The second sibling died in hospital care. The cause of death was based on anamnesis, clinical examination and laboratory results. According to the family history, the index case's parent and parent's sibling both had the same kind of symptoms and disease as the proband, and very likely had an aortic dilatation: their causes of death were aortic ruptures at the ages of 65 and 69, respectively. Unfortunately, autopsies were not routinely performed in the 1950's at the time of their death. We excluded Marfan syndrome in the family based on family history and detailed medical records. The index case's child is now followed regularly every three years with magnetic resonance imaging (MRI) or echocardiography, which have thus-far revealed nothing abnormal by the age of 45.

The translocation in this family was initially observed a decade ago, when the proband's child's family had a routine prenatal screening of their first pregnancy. An otherwise normal ultrasonography repeatedly failed to reveal an air bubble in the ventricle of the fetus. Being suspicious of an esophageal atresia, the gynecologist referred the family to prenatal genetic counseling. After counseling, the parents opted for examination of the fetal chromosomes from a chorionic villi sample, which revealed an unbalanced translocation with a large

excess of chromosome 11. The parents chose to terminate the pregnancy. Autopsy of the fetus confirmed the diagnosis of esophageal atresia and esophagotracheal fistula, and revealed dysmorphic features: broad back of the nose, micrognathia, narrow palpebral fissures, and single palmar creases in both hands.

ACTA2 sequencing

We chose *ACTA2* located near our 10q breakpoint for systematic bidirectional mutation screening. The coding sequence revealed no previously uncharacterized variants, and no splice mutations. The only detected variants were two single base substitutions verified as common SNPs (rs72809344 and rs72809340) in intron 1. The paired-end sequencing data confirmed these variants as heterozygous SNPs.

Breakpoint mapping

From the ~354 million uniquely mapping paired-end read pairs, we searched for those spanning the breakpoints. We identified five pairs that mapped consistently to chromosomes 10 and 11, suggesting they might cross the translocation breakpoint (figures 3A–B). In addition, we identified one orphan read with only one end mapping to chromosome 10, whereas the other unpaired end was complementary to chromosome 11. The minimal intervals containing the breakpoints defined by these overlapping reads were ~750 bp on chromosome 11 between nucleotides 131778051 and 131778904, and ~40 bp on chromosome 10 between nucleotides 90973021 and 90973118. The junction fragments crossing the translocation were subsequently amplified by PCR and Sanger sequenced. The exact breakpoint positions were finally identified on chr10: 90,973,081-90,973,082 and chr11: 131,778,234-131,778,235 (GRCh37) (figures 4A and 4C). The chromosome 11 breakpoint is in intron 1 of a splicing isoform of the *NTM* gene and the 5′ regulatory region of another *NTM* splicing isoform (http://genome.ucsc.edu/, NM_001048209) (figure 4A). In contrast, the breakpoint on chromosome 10q maps to an intergenic region flanked by the 3′ end of *LIPA* and the 5′ end of *CH25H* (figure 4C) within a simple tandem repeat consisting of a tract of 'AAAGA' (figures 4B and 4D). This repeat structure is not present in the chromosome 11 region, which shares no apparent regional microhomology with the chromosome 10 breakpoint region. We detected no gain or loss of chromosomal material near the translocation breakpoint on the derivative chromosome 11 region. On the derivative chromosome 10 region, we identified three breakpoint flanking microdeletions. Two were 1-bp deletions at 90,973,081 and 90,973,078, and one a 5-bp deletion between nucleotides 90,973,049 and 90,973,055 (GRCh37) (figure 5). To identify interspersed repetitive elements near the breakpoints, we referred to the UCSC Genome Browser (GRCh37), but identified no repeats within 1 kb upstream or downstream. No significantly homologous sequences were observed to flank the two breakpoints.

National Registry of Reciprocal Balanced Translocations and Inversions in Finland

We are currently constructing the National Registry of Reciprocal Balanced Translocations and Inversions in Finland. We have ascertained all known Finnish cases (n=2575), of which 2104 are balanced translocations and 471 balanced inversions. To date 584 are known to be familial cases and 102 to carry a *de novo* mutation. We are currently harmonizing the data

and performing the relevant quality control steps and aim to have the Registry accessible to the scientific and clinical community in the near future. An epidemiological study of all known Finnish cases is in progress.

DISCUSSION

Discovery of this translocation described above is a byproduct of a larger project to collect all known balanced translocations and inversions in Finland, giving us momentum towards our goal of characterizing more generally the molecular basis of all translocations in Finland and their associated phenotypic effects. The opportunity in the Nordic countries to link the data to national health registers provides additional openings for future studies. Such a database will benefit not only those of us interested in research, but more importantly will be a useful resource for clinical geneticists and genetic counselors.

We systematically examined and analyzed the medical records from all translocation carriers in our database, and as the first clinical fruit of this endeavor, we were able to identify a translocation carrier with TAA, who had a strong family history of both TAA and IA. Both conditions can lead to sudden death without follow-up examination, therefore we paid immediate clinical attention to this family. For first-degree family members, it will be essential to schedule an angiography to diagnose future IAs and echocardiography or MRI to follow the aortic dilatation expansion rate so that surgical intervention can be correctly timed before a fatal aneurysm occurs. Based on previous reports that the region at chromosome 11q25 was involved in both IA and AA [51], we focused on the translocation breakpoint to search for a novel genetic disruption potentially underlying the risk of these aneurysms. As shown here, sequencing the breakpoint regions in a patient with an aneurysm and reciprocal translocation has facilitated the identification of one potential positional candidate gene, which had not been previously associated with TAA or IA. However, our preliminary finding requires extensive validation, hence follow-up studies will be essential to establish conclusively whether this gene-disruption is itself causative of aneurysm, and to exclude other potential genetic factors nearby.

Balanced chromosomal rearrangements occasionally have strong phenotypic effects, which may be useful in understanding pathobiology. To delineate translocation breakpoints in a timely and cost-effective fashion, we employed next-generation sequencing. Genome-wide paired-end sequencing enabled us to map the chromosomal breakpoints to a <1000 bp region, pointing to a single PCR primer pair: The identified translocation disrupts intron 1 of a splicing isoform of Neurotrimin (*NTM*) at 11q25 in a strong candidate region for IA and AA (OMIM 612161). This susceptibility locus has previously emerged in three independent linkage studies suggesting a susceptibility gene for IA somewhere between 125.8 and 133.7 Mb on 11q [36,42,51].

The *NTM* gene encodes a member of the IgLON cell adhesion molecule family. The encoded protein has been previously implicated in the promotion of neurite outgrowth and adhesion. *NTM* is mainly expressed in the central nervous system, but also in lung and heart. Studies have confirmed that it can mediate cell-cell interactions, indicating that it may have additional functions in the human cardiovascular system [66]. Our study suggests that the

disrupted *NTM* gene is one potential positional candidate gene for the IA/TAA phenotype in this family. Unfortunately, we lacked biological samples from the deceased relatives, which would be needed to confirm that they carry the translocation.

The reciprocal breakpoint on chromosome 10q is located in an intergenic region flanked by the 5′ end of *CH25H* and the 3′ end of *LIPA*. The *LIPA* gene encodes lipase A, the lysosomal acid lipase, which catalyzes the hydrolysis of cholesteryl esters and triglycerides in the lysosomes. Mutations in *LIPA* cause Wolman disease and cholesteryl ester storage disease (OMIM 278000). *CH25H* is also involved in cholesterol and lipid metabolism. Without further insight we are reluctant to speculate that either of these genes on 10q are plausible functional candidates for IA or TAA. A novel gene for familial TAA, *ACTA2* also lies at 10q23-24 (49). However, early on in our study, we sequenced this candidate gene, and excluded its causative mutations.

Repetitive elements have been implicated as one cause of chromosomal instability. However, in this case, we detected no interspersed repeats or common overlapping microhomology flanking our breakpoints, other than a simple tandem repeat of 'AAAGA' within the der(10) breakpoint. Small cryptic submicroscopic changes (microdeletions and duplications) have also been associated with balanced translocations (56). While the SNP array revealed no suspicious CNVs in our patients, the subsequent Sanger sequencing identified three microdeletions on der(10) regions: a 1-bp deletion located precisely at the genomic breakpoint at position 90,973,082, a 1-bp deletion at 90,973,079, and a 5-bp deletion ('AAAGA') between 90,973,049 and 90,973,055 (GRCh37). The microdeletions identified are consistent with previous studies indicating that small cryptic submicroscopic changes, which may also lead to phenotypic abnormalities in dosage-sensitive genomic regions, can be associated with balanced translocations [67,68]

Previous studies suggest that balanced rearrangements might be risk factors for many complex and late-onset diseases like diabetes, schizophrenia, and dyslexia [69–72]. Our comprehensive National Registry of Reciprocal Balanced Translocations and Inversions in Finland will, in the future, link translocations and inversions with all lifelong registry diagnoses from all Finnish national health registries, and it will therefore become a powerful resource for complex disease research as well as clinical practice.

Acknowledgments

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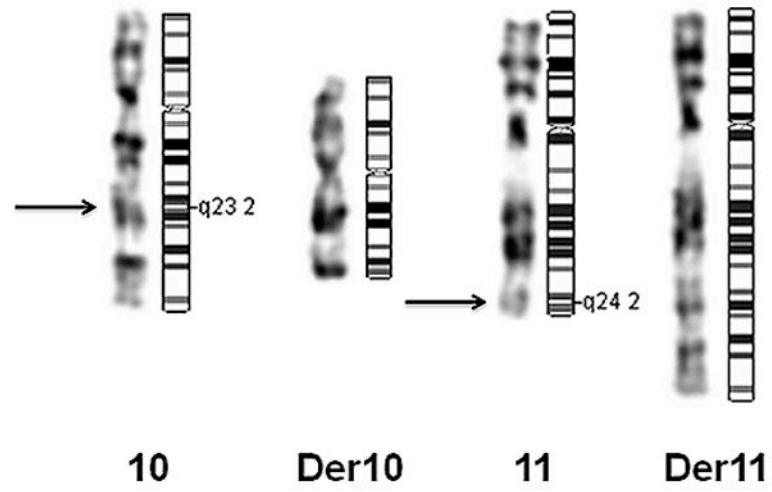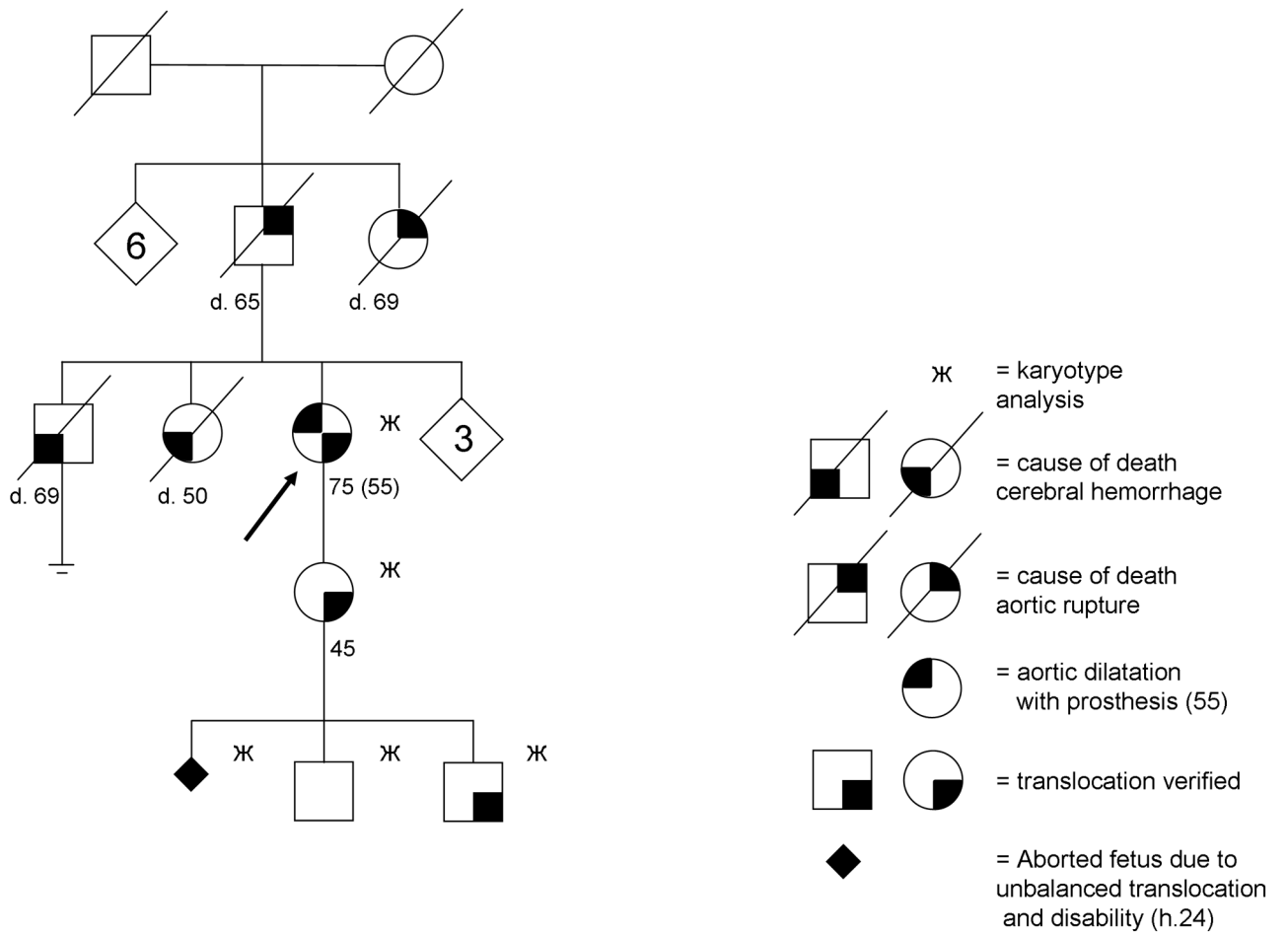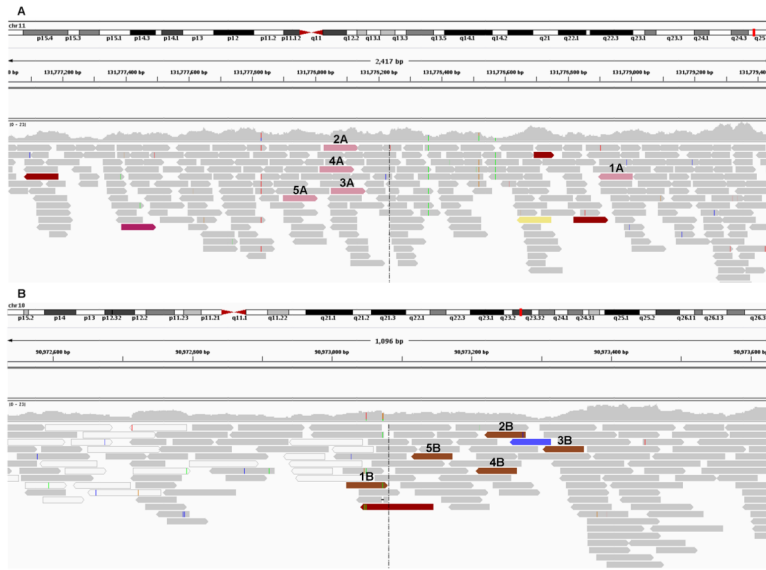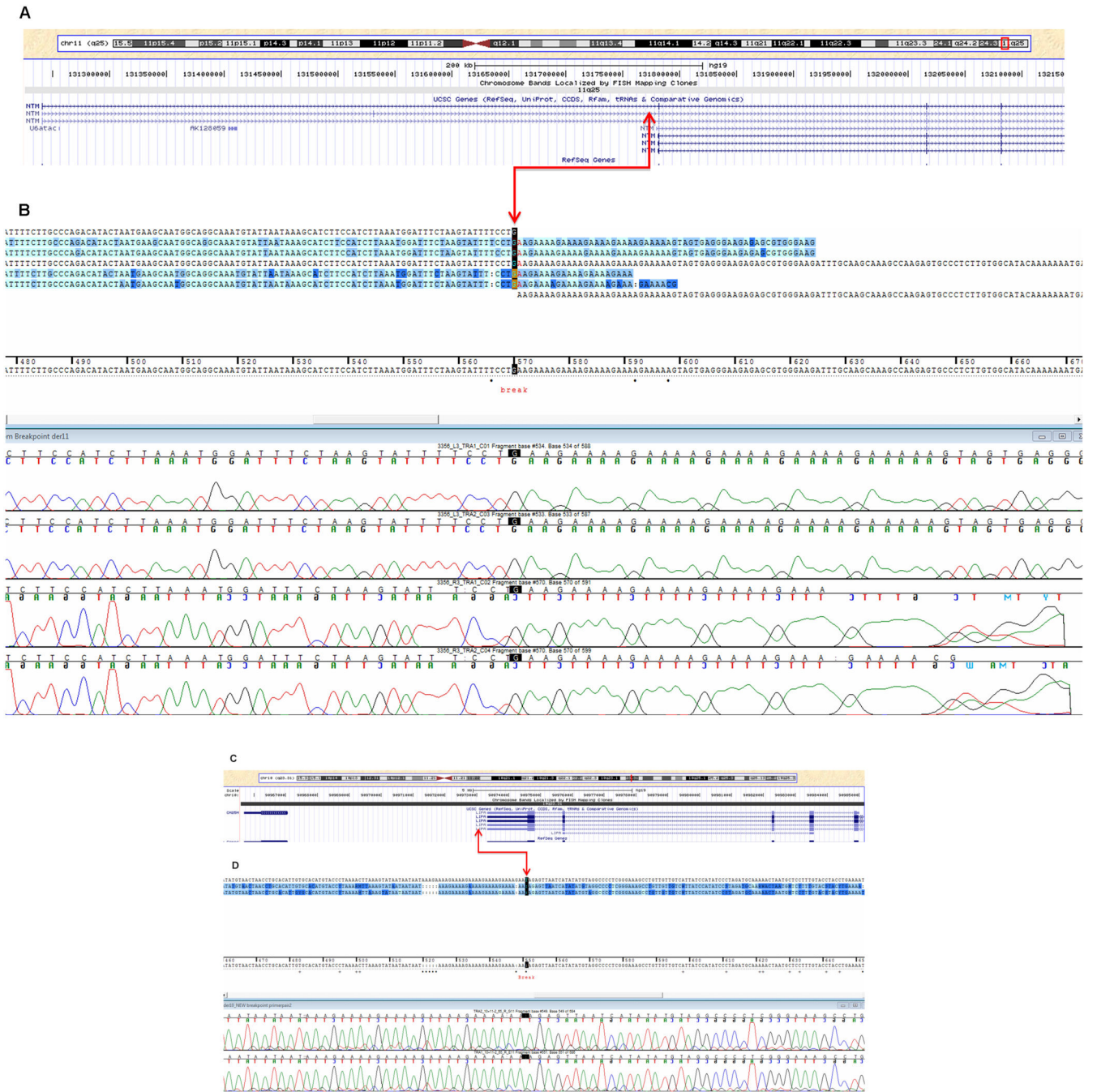
Figure 1.

Figure 2.

Figure 3.

Figure 4.