7q35q36.3 Deletion and Concomitant 20q13.2q13.33 Duplication in a Newborn: Familiar Case

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Case Report

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Abstract

Array-CGH is a powerful tool in identifying and characterizing complex genomic rearrangements when classical cytogenetics approaches are not sensible enough in detecting rearrangements smaller than 5-10 Mb. The use of Array-CGH has increased the detection rate of unbalanced cryptic rearrangements such as deletions and/or duplications of 10-20%

We present here the first report of a patient with 7q35q36.3 microdeletion and concomitant 20q13.2q13.33 microduplication detected by array-CGH and confirmed by reiterative FISH experiments associated with dysmorphism, delayed development, Long QT syndrome (LQTS), complex congenital heart disease, pulmonary hypertension, hypotonia, respiratory distress, cognitive deficit. We proved that this unbalanced rearrangement was due to an adjacent-1 segregation inherited by the mother carrier of a balanced translocation between chromosomes 7 and 20.

Introduction

Reciprocal translocations are commonly balanced exchanges between homologous chromosomes usually associated in carriers with normal phenotype.

Heterozygous carriers of translocations can result in abnormal meiosis, thus resulting in an increase rate of miscarriage[1]. The pregnancy lost is related to meiotic segregation since the meiosis in heterozygous for translocation may generate gametes with unbalanced rearrangements such as duplications and deletions.

Unbalanced chromosomal rearrangements can be studied by Comparative Genomic Hybridization (array-CGH) that is able to identify at high resolution (5-10 Mb) the genetics causes of complex phenotypes usually only partially detectable (9.5%) by classical cytogenetics[2-5]. When the CGH array was not discovered these genomic alterations were called "idiopathic syndromes".

Moreover, array-CGH is a technique faster than fluorescence in situ hybridization in detecting in one experiment, chromosomal unbalanced rearrangements without *a priori* knowledge. On the other hand, array-CGH has a relevant limitation in detecting balanced rearrangements where instead classical and molecular cytogenetics (Fluorescence *in situ* hybridization) are used as still elective strategies.

Here, we present the first report of a patient with 7q35q36.3 deletion and 20q13.2q13.33 duplication detected by array-CGH and deeply studied by reiterative FISH experiments, and associated with dysmorphism, delayed development, Long QT syndrome (LQTS), complex congenital heart disease, pulmonary hypertension, hypotonia, respiratory distress and cognitive deficit. The unbalanced rearrangements resulted as adjacent 1 segregation of the balanced translocation (7q;20q) carried by the mother of the patient. We detected the translocation in the mother and characterized by FISH an unbalanced rearrangement involving the same chromosomes in the mother's brother of the patient (D.A.), thus showing traces of the presence of the translocation in the grandparent's patient.

Clinical Report

The subject of this study is a girl (D.A.) six months old (Figure 1: family tree III4). The mother (L.M.) reported four pregnancies two of which terminated in the first trimester as abortion, one gave birth D.M. (Figure 1: family tree III3) and from the last pregnancy was born D.A. (index case). In addition, L.M. reported to have a 27-year-old brother L.F. (Figure 1: family tree II3) who, at the age of ten, was diagnosed with a suspicion of Dandy Walker syndrome Rubinstein Taybi syndrome by two different groups of clinicians. These syndromes have never been confirmed through the use of biomolecular investigations.

L.M. prenatal history showed no evidence of teratogen exposure or any other relevant exposures or pathologies. Ultrasound reports during weeks 14 and 25 of gestation showed no morphological alterations.

The delivery was natural, and the baby born at term (39 weeks and six days) with a weight of 2230 grams. She showed APGAR indices of 6, 7 and 8 at one minute, five and ten minutes respectively after birth. D.A. was transferred to the Neonatal Intensive Care Unit (NICU) due to the low weight (<2500 grams) and the presence of dismorphic elements (microcephaly, ears and cup, hypotelorism, squat and short neck, clenched hands with overlapping fingers, active and passive hypertonus of the limbs, absent cry, posture with extended lower limbs and tense and abducted upper limbs). Furthermore, she showed tense and not very palpable abdomen, the heart rate at 140 beats/minute, respiratory rate at 45 acts/minute and blood pressure at 53/43 mmHg.

Blood tests showed an increase in transaminases (GOT: 537 IU/L, GPT: 247 IU/L), leukocytes (36970 cells/uL), creatininemia (1.8 mg/dL), Reactive Protein C (8,9 mg/dL), creatinkinase (CK or CPK: 217 IU/L), creatine kinase MB (CK-MB: 42.9 IU/L) and a decrease in sodium levels (125 mmol/L). In addition, the newborn girl had been subjected to antibiotic therapy due to Escherichia coli detection on blood culture and pharyngeal swab.

Upon entering UTIN, continuous monitoring of tissue oxygenation (kidney and brain) was detected through the Near-Infrared Spectroscopy (NIRS), while brain electrical activity was monitored through the use of Cerebral Function Monitoring (CFM). Given the difficulty in breathing highlighted since birth, the Nasal Continuous Positive Airway Pressure (nCPAP) was applied to the small D.A. Echocardiography showed: situs solitus, levocardia; atrial septal defect (DIA) near the superior vena cava (high caval), moderate tricuspid insufficiency which indicates a high blood pressure (PAPs about 80mmHg); normal-sized left heart chambers; preserved biventricular kinesis; pulmonary artery of normal caliber and with normoconfluent branches; patent arterial duct with moderate bidirectional shunt; aortic arch and aortic isthmus of normal caliber and flowmetry; normopulsing abdominal aorta; absence of pericardial effusion. To treat pulmonary hypertension, the following therapy has been implemented: Dobutamine and Milrinone with continuous infusion.

In seventh day of life given the persistence of high lung pressure associated with an unconvincing radiographic picture, the little D.A. was intubated and treatment with High Frequency Oscillation (HFO)

with nitric oxide (No) was started. At the following echocardiographic control there was a sharp drop in lung resistance (right ventricle pressure: 25 mmHg) and the presence of two muscle interventricular defects apical (DIV). The nitric oxide dosage was reduced and suspended after about 24 hours, followed by suspension of Milrinone after a few days. On this occasion, a bronchoalveolar lavage was performed which resulted negative for Clamidya, Ureoplasma and Mycoplasma.

On the tenth day of life, an electrocardiogram (ECG) was performed detecting: presence of a QTc (QT corrected according to the frequency) lengthened by 480 msec in V5 (normal values: 350-440 msec). For this reason, D.A. started therapy with propanolol hydrochloride (beta blocker) initially at a dosage of 1mg/Kg/die and then reached a dose of 7mg/Kg/die in three administrations for the persistence of the extended QTc (values between 440 and 490 msec). In addition, the ECG detected the presence of ventricular pre-excitation (delta wave at the beginning of the QRS complex).

The abdominal ultrasound showed: liver of dimensions within the limits of norm without appreciable ecostructural alterations. Gallbladder with endoluminal biliary mud and moderate concentric thickening of the walls. Hint of ectasia of the intrahepatic biliary tract. Pancreas not explorable. Spleen within normal limits. Kidneys in size within the limits with regular eco-structure.

The magnetic resonance imaging (MRI) of the brain showed: semibrachycephalic caput. The corpus callosum was thin and incomplete, with reduced thickness of the splenium and not recognizable rostrum; a moderately squared aspect of the posterior sectors of the lateral ventricles was associated. Mild hypoplasia of the cerebellar worm and consensual megacisterna magna. No significant signal alterations of the nerve tissue, regular progression of myelination. Substantially regular the volume of the ventricular system. Regular amplitude of the pericerebral spaces. Neonatal screenings for phenylketonuria, hypothyroidism and cystic fibrosis were negative.

The girl, after two months of hospitalization, was discharged with suitable therapy. Physical examination in resignation revealed a weight of 3240 grams, pink color, good state of hydration, regular cardiorespiratory objectivity, abdomen treatable, moderate hypertonus to the four limbs. The discharge diagnosis was: newborn with dysmorphism, development delay, Long QT syndrome (LQTS), complex congenital heart disease, pulmonary hypertension, hypotonia, respiratory distress, cognitive deficit. In order to evaluate the possible presence of genomic alterations, genomic analysis was carried out using Comparative Genomic Hybridization (a-CGH) arrays, karyotype and molecular cytogenetics.

Methods

Array-CGH

Cytogenetic and a-CGH analyses were performed on peripheral blood of the patient, her parents and her brothers and sister. High resolution chromosomes were GTG banded using the standard procedure. Genomic DNA was extracted from peripheral blood leukocytes using "QIAamp® DSP DNA Blood Mini" from Qiagen (DNA IQTM System) (Qiagen S.r.l., Italy) commercial kit, in accordance with the

manufacturer's specifications. Array-CGH analysis was performed using ISCA V2, 4x180K oligo platforms (Oxford Gene Technology), with 25Kb probe spacing (higher resolution in ISCA region). Experiments were conducted according manufacturer's protocol. Commercial reference DNAs (male and female) provided by Promega G1521 were used for the analysis. The slides were scanned with Innoscan 710 Microarray Scanner; captured images were analyzed with CytoSure Interpret Software version 4.10. Genomic region analysis was performed according to the human reference sequence hg19 Genome Reference Consortium (GRC) h37. The copy number variations (CNVs) founded in the proband were compared with genomic variants present on different databases (DECIPHER: https://decipher.sanger.ac.uk - UCSC Genome Browser: https://genome.ucsc.edu – Clinical Genome Resource (Clingen) (http://clinicalgenome.org) -Troina Database of Human CNVs: (http://gvarianti.homelinux.net/gvariantib37/index.php).

Cytogenetic analysis with FISH

The array-CGH results were confirmed by fluorescence in situ hybridization (FISH). Metaphase spreads of each investigated individual (42/19, 43/19, 129/20, 145/20) were obtained from phytohaemagglutinin (PHA)-stimulated whole blood cultures. FISH experiments were performed using human BAC clones (table 1) directly labeled by nick-translation with Cy3-dUTP (Perkin-Elmer), Cy5-dUTP (Perkin-Elmer) and fluorescein-dUTP (Enzo) as described by Lichter et al. (Lichter et al. 1990), with minor modifications. Briefly, 300 ng of labeled probe were used for the FISH experiments; hybridization was performed at 37oC in 2xSSC, 50% (v/v) formamide, 10% (w/v) dextran sulphate and 3 µg sonicated salmon sperm DNA, in a volume of 10 µL. Posthybridization washing was at high stringency (60°C in 0.1xSSC, three times). Fluorescence signal intensity from DAPI, Cy3, Cy5 and fluorescein was detected with specific filters using a Leica DMRXA2 epifluorescence microscope (Leica Microsystems GmbH, Wetzlar, Hesse, Germany) equipped with a cooled CCD camera. Digital images were separately recorded as grayscale pictures and subsequently pseudocolored and merged using Adobe Photoshop software (Adobe, San Jose, California, United States).

Results

Array-CGH performed on D.A. detected a microdeletion on the long arm of chromosome 7 (7q35q36.3= ~12.55 Mb) and a microduplication on the long arm of chromosome 20 (20q13.2q13.33= ~10,28 Mb) (figures 2 and 3).

The chromosomal region 7q35q36.3 (146,581,463-159,128,155) contains the OMIM "Morbid" genes ASB10, CDK5, CNTNAP2, DNAJB6, DPP6, EZH2, KCNH2, KMT2C, LMBR1, MNX1, NCAPG2, NOS3, PRKAG60 and XHCC2DR (table 2).

The chromosomal region 20q13.2q13.33 (52,667,758-62,949,155) involves the following "Morbid" OMIM genes ATP5E, AURKA, CHRNA4, COL9A3, CYP24A1, DNAJC5, EDN3, EEF1A2, GATA5, OS, KCRNQ2, MC3, PCK1, PRPF6, RTEL1, SLC17A9, SOX18, STX16, TUBB1, VAPB (table 2). CGH-Array of the parents was found to be normal.

Furthermore, the maternal uncle of D.A. (Figure 1: family tree II3) presented a syndromic picture associated with Dandy-Walker and / or Rubinstein Taybi syndrome.

To understand if there was a connection between what was found in D.A. (family tree III4) and his uncle (family tree II3) we have extended the CGH-Array exam to L.F.

Array CGH performed on L.F. found the same genomic structure found in D.A.: del7q35q36.3 (146581463_159128155) and dup20q13.2q13.33 (52667758_62949155).

To establish if what was highlighted was the result of a balanced family reciprocal translocation we performed the study of the peripheral blood karyotype followed by Fluorescent in situ hybridization (FISH) respectively to the mother of the D.A. (L. M, family tree II2 – ID43/19) and his brother (L.F., family tree II3 – ID 42/19).

In silico analysis of the candidate regions using UCSC genome browser has allowed to choose three BAC clones as probes (table 1) to detect the supposed translocation.

FISH analyses revealed that the mother (ID 43/19) was carrier of a balanced translocation between the q terminal arm of chromosome 7 and the q terminal arm of chromosome 20 (**Figure 4b**). The aCGH negative result was due to balanced translocation. The FISH results of the uncle (ID 42/19) showed the deletion of the q terminal region of chromosome 7 and the duplication of the q terminal region of chromosome 20 (**Figure 4a**).

In order to define the breakpoints of the rearrangements, FISH experiments were performed on 42/19 metaphases. *In silico* analysis of the candidate regions using UCSC genome browser has allowed to choose two BAC clones (RP11-702N14 and RP11-368H3) as probes for FISH experiments (figure 5). The results showed a normal chromosome 7 with a red signal, a derivative chromosome 7 identified by the presence of both the red and green signals at lower intensity due to the split of the clones embedded in the breakpoints, and two normal chromosomes 20 with green signals (figure 5).

To understand the familial arrangement of the studied genomic regions, the same FISH experiment was also performed on the D.F. (III3 of the family tree, ID 129/20) and on a cousin of Mrs. L.M. (ID 145/20), both phenotypically normal and with no signs of pathologies. By FISH analyses the individuals appeared normal. All the results are summarized in figure 6.

Deep study of gene content of the unbalanced genomic regions has detected 16 deleted and 21 duplicated genes on chromosome 7 and 20 respectively (table 2).

Discussion

Translocations are balanced rearrangements can be responsible in heterozygous of missegregation of events during meiosis thus obtaining unbalanced gametes. We here documented and studied an

unbalanced rearrangement due to missegregation of a balanced translocation 7q;20q likely occurred in one of the grandparents of maternal lineage (I1 or I2 of the family tree).

Microdeletions and/or microduplications complex syndromes generally lead to the deregulation of multiple genes often associated with complex phenotypes with multisystem involvement. We reported a 7q35q36.3 microdeletion (loss of approximately 12.5 MB) resulting in the loss of a copy of 16 "Morbid" OMIM genes, including SHH, KCNH2, PRKAG2 and KMT2C.

The KCNH2 is responsible for type 2 long QT syndrome (LQT2) and encodes the α-subunits of the potassium channel protein I_{kr}[6], which is crucial for the repolarization of ventricular myocardiocytes. According to the DECIPHER database, the haploinsufficiency index for KCNH2 is 8.86%, indicating that not only the point mutations but also its deletion could lead to deleterious effect[7]. Three other patients harboring the deletion of distal 7q encompassing KCNH2 were found to have a LQTS2[8,9]. The previous literature suggests that in individuals with mutations in KCNH2 the use of chlorpheniramine, an antihistamine H1, is strongly discouraged, as this drug blocks the functionality of the hERG channels, favoring the development of arhythmogenic mechanisms[10].

The PRKAG2 gene (Protein Kinase, AMP-Activated, Non catalytic, Gamma-2) encodes an AMP-activated protein kinase (AMPK) activated by various cellular stresses that increase AMP levels and decrease ATP levels. Failure of the PRKAG2 gene is associated with Wolff-Parkinson-White syndrome (WPW). Diagnosis is often made based on the finding of heart rhythm disturbances. In our case the index case had electrocardiogram (ECG) ventricular pre-excitation (delta wave at the beginning of the QRS complex), which is typical expression of WPW syndrome[11].

The SHH (Sonic Hedgehog) gene codes for a protein called "sonic hedgehog" which represents the best example of a morphogenetic molecule: this protein spreads producing a concentration gradient, and the cells of the embryo develop in different tissues, depending on the local concentration of SHH. In particular, the protein has a role of primary importance in the modelling of the central ventral nervous system, the axis of the anterior-posterior limb and the ventral somites. An alteration of its function causes defects in the brain. D.A. presents at the MRI changes in the central nervous system (thin and incomplete corpus callosum, absence of the rostrum, hypoplasia of the cerebellar worm) that are related to the inactivation of the SHH gene[12].

The KMT2C gene encodes the enzyme lysine N-methyltransferase 2C which together with the lysine N-methyltransferase D (KMT2D) form the core of regulatory protein known as COMPASS KMT2C/D complexes. These proteins interacting with other proteins of the COMPASS complex, modulate the activity of different cell types critical for embryonic morphogenesis and the development of the central nervous system. The loss of function of the KMT2C gene is responsible for type 2 (autosomal dominant) Kleefstra syndrome[13].

20q13.2q13.33 microduplication (approximately 10.28 MB) led to the duplication of a copy of 21 OMIM "Morbid" genes, including GATA5 gene, CHRNA4 gene and GNAS gene. GATA5 gene codeing for a zinc finger transcriptional regulator with critical functions in embryonic differentiation and development. An alteration of its function causes autosomal dominant congenital heart defects (CHTD5)[14].

The CHRNA4 (Cholinergic Receptor Nicotinic Alpha 4 Subunit) gene codes for a nicotinic acetylcholine receptor, which belongs to a superfamily of ionic binding channels that plays a role in rapid signal transmission to synapses. Mutations in this gene cause type 1 nocturnal frontal lobe epilepsy. Alternative splicing produces multiple transcription variants[15].

The GNAS (GNAS Complex Locus) gene is an imprinted complex locus that produces multiple transcripts through the use of alternative promoters and alternative splicing. In particular, the GNAS gene encodes the alpha subunit of a G protein. Gs-alpha is biallelically expressed in almost all tissues and plays essential roles in a multitude of physiological processes. The G protein produced helps to stimulate the activity of adenylate cyclase. The latter is involved in the control of the production of different hormones that regulate the activity of the endocrine glands such as the thyroid gland, pituitary gland, ovaries and testes (gonads), and adrenal glands. Other transcriptions produced by GNAS are expressed exclusively by the paternal or maternal allele. it appears to be involved in McCune-Albright syndrome[16] and autosomal dominant progressive bone heteroplasia[17].

Many of the genes present in the regions 7q35q36.3 and 20q13.2q13.33 are involved in the correct neuropsychic development and their lack of function can be the basis of the neurological clinical picture present in the index case.

CGH-Array on D.A. allowed us to re-evaluate his uncle's clinic (L.F.). So LF. has the same genomic pathology found in D.A. which results from an unbalanced reciprocal translocation which led to a microdeletion of the short arm of chromosome 7 (q35q36.3 = ~ 12.55 Mb) and a microduplication of the long arm of chromosome 20 (q13.2q13.33 = ~ 10.28 Mb). Therefore, L.F. is not affected by the Dandy-Walker /Rubinstein-Taybi syndromes, diagnosed before performing the CGH array.

Conclusion

CGH-Array is useful in diagnosing subchromosomal aberrations. For this reason, its application is rapidly increasing. Furthermore, the CGH-Array allows to precisely define the genomic region involved and consequently the "OMIM Morbid" genes it contains. So we can have an exact correlation between genotype-phenotype. The CGH-Array has made us understand that the loss of several genes is expressed with clinical manifestations due to the concomitance of several syndromes, each related to the malfunction of a "specific disease gene". For these reasons the genotype-phenotype correlation in these cases is more complex. This study confirms that the CGH-Array is useful in identifying pathologies that until a few years ago were considered idiopathic. In reality, these pathologies are caused by submicroscopic chromosomal imbalances. Almost certainly, in the near future, more information on the

cause of some pathologies; may be given by the entry into clinical practice of Next Generation Sequencing (NGS) technologies.

Statement:

Declarations

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Statement of Ethics

Published research is comply with the guidelines for human studies and it's was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Authors declare under their own responsibility that the subjects studied have given their written consent to publish their case. The signed consent is kept in the Cytogenetic and Molecular Genetics unit.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

Mario Ventura, Arianna Allegretti and Domenico Dell’Edera made substantial contributions to conception and design. Ludovica Mercuri, Angela Mitidieri, Rosalba Ardea Dell’Edera, Maria Teresa Dell’Edera Francesca Simone and Annunziata Anna Epifania contributed to the acquisition, analysis and interpretation of data. Mario Ventura and Arianna Allegretti were involved in drafting the manuscript. Domenico Dell’Edera gave final approval of the version to be published. All authors read and approved the final manuscript.

References

1. Pritti K, Priya VV, Mishra P, Roy, Patel H. A Study on Balanced Chromosomal Translocations in Couples with Recurrent Pregnancy Loss. J Hum Reprod Sci. 2018 Oct-Dec; 11(4): 337–34.

2. Van Karnebeek CD, Jansweijer MC, Leenders AG, Offringa M, Hennekam RC. Diagnostic investigations in individuals with mental retardation: a systematic literature review of their usefulness. Eur J Hum Genet. 2005;13:6–25.
3. Hochstenbach R, Buizer-Voskamp JE, Vorstman JAS, Ophoff RA. Genome arrays for the detection of copy number variations in idiopathic mental retardation, idiopathic generalized epilepsy and neuropsychiatric disorders: lessons for diagnostic workflow and research. Cytogenet Genome Res. 2011;135:174–202.
4. Rosenberg C, Knijnenburg J, Bakker E, Vianna-Morgante AM, Sloos W, Otto PA, et al. Array-CGH detection of micro rearrangements in mentally retarded individuals: clinical significance of imbalances present both in affected children and normal parents. J Med Genet. 2006;43:180–6.
5. Kashevarova AA, Nazarenko LP, Skryabin NA, Salyukova OA, Chechetkina NN, Tolmacheva EN, et al. Array CGH analysis of a cohort of Russian patients with intellectual disability. Gene. 2014;536(1):145–50.
6. Anderson CL, Delisle BP, Anson BD. Most LQT2 mutations reduce Kv11.1 (hERG) current by a class 2 (trafficking-deficient) mechanism. Circulation. 2006;113:365–73.
7. Ni Huang I, Lee EM, Marcotte. and Matthew E. Hurles. haracterising and Predicting Haploinsufficiency in the Human Genome. PLoS Genet. 2010 Oct;6(10):e1001154.
8. Bisgaard A-M, Rackauskaite G, Thelle T. Maria Kirchhoff and Thue Bryndorf. Twins with mental retardation and an interstitial deletion 7q34q36.2 leading to the diagnosis of long QT syndrome. March 2006; American Journal of Medical Genetics Part A 140(6):644–8.
9. Di Stolfo G, Accadia M, Mastroianno S, Leone MP, Palumbo O, Palumbo P, Potenza D, Maccarone P, Sacco M, Russo A, Carella M. Long QT syndrome in chromosome 7q35q36.3 deletion involving KCNH2 gene: Warning for chlorpheniramine prescription. Mol Genet Genomic Med. 2019 Sep;7(9):e855. doi:10.1002/mgg3.855.
10. Hee-Kyung Hong and Su-Hyun Jo. Block of hERG K^+ Channel by Classic Histamine H_1 Receptor Antagonist Chlorpheniramine. Korean J Physiol Pharmacol. 2009 Jun;13(3):215–20.
11. Gollob MH, Seger JJ, Gollob TN, Tapscott T, Gonzales O, Bachinski L, Roberts R. Novel PRKAG2 mutation responsible for the genetic syndrome of ventricular preexcitation and conduction system disease with childhood onset and absence of cardiac hypertrophy. Circulation. 2001 Dec;18(25):3030–3. 104(.
12. Britto J, Tannahill D, Keynes R. A critical role for sonic hedgehog signaling in the early expansion of the developing brain. Nat Neurosci. 2002 Feb;5(2):103–10.
13. William J, Lavery A, Barski S, Wiley EK, Schorry, Andrew W. Lindsley. KMT2C/D COMPASS complex-associated diseases [K_{CD}COM-ADs]: an emerging class of congenital regulopathies. Clin Epigenetics. 2020;12:10.
14. Yang YQ, Wang J, Wang XH, Wang Q, Tan HW, Zhang M, Shen FF, Jiang JQ, Fang WY, Liu X. Mutational spectrum of the GATA5 gene associated with familial atrial fibrillation. Int J Cardiol. 2012 May 31;157(2):305-7.

15. Neng X, Xiao M, Yuanlu C, Qinyan L, Li S, Zhanyi S. Novel variant in CHRNA4 with benign childhood epilepsy with centrotemporal spikes and contribution to precise medicine. Mol Genet Genomic Med. 2020 Apr;28:e1264.
16. Gaujoux S, Pasmant E, Silve C, Mehsen-Cetre N, Coriat R, Rouquette A, Douset B, Prat F. Leroy K.McCune Albright syndrome is a genetic predisposition to intraductal papillary and mucinous neoplasms of the pancreas associated pancreatic cancer in relation with GNAS somatic mutation - a case report. Medicine. 2019 Dec;98(50):e18102.
17. Happle R. Progressive osseous heteroplasia is not a Mendelian trait but a type 2 segmental manifestation of GNAS inactivation disorders: A hypothesis. Eur J Med Genet. 2016 May;59(5):290–4.

Tables

Table1. BAC clones labelled with specific fluorophores, their genomic position on GRCh37 human release and the followed strategies.

BAC clone	Fluorescent dye	Mapping (GRCh37/hg19)	Strategy
RP11-648P19	CY3	chr7:151,029,463-151,180,365	Probe mapping into the deleted region
RP11-959A2	FITC	chr20:55,845,790-56,022,780	Probe mapping into the duplicated region
RP11-696D4	CY5	chr7:62,003,599-62,160,915	Probe mapping downstream with respect to the centromere in order to identify chr7

Table 2. Reference of 34 affected genes by RefSeq database for altered regions on chromosomes 7 and 20

CHROMOSOME	Start hg19	Stop hg19	GENES INVOLVED (OMIM Morbid)
7q35q36.3del	146,581,463	159,128,155	ASB10, CDK5, CNTNAP2, DNAJB6, DPP6, EZH2, KCNH2, LMBR1, MNX1, NOS3, PRKAG2, SHH, WDR60, XRCC2, KMT2C, NCAPG2.
20q13.2q13.33dupl.	52,667,758	62,949,155	ATP5E, AURKA, CHRNA4, COL9A3, CYP24A1, DNAJC5, EDN3, EEF1A2, GNAS, KCNQ2, MC3R, OSBPL2, PCK1, PRPF6, RTEL1, SLC17A9, SOX18, STX16, TUBB1, VAPB, GATA5.

Figures

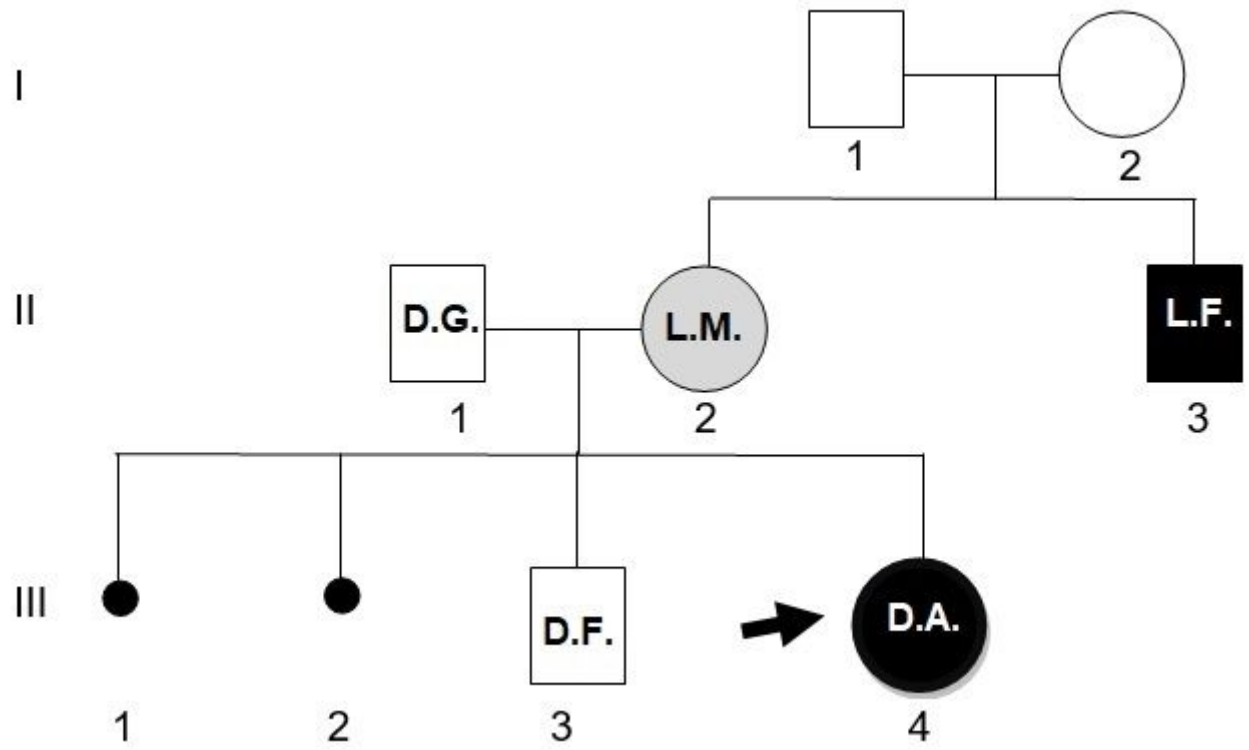

Figure 1

Figure 1

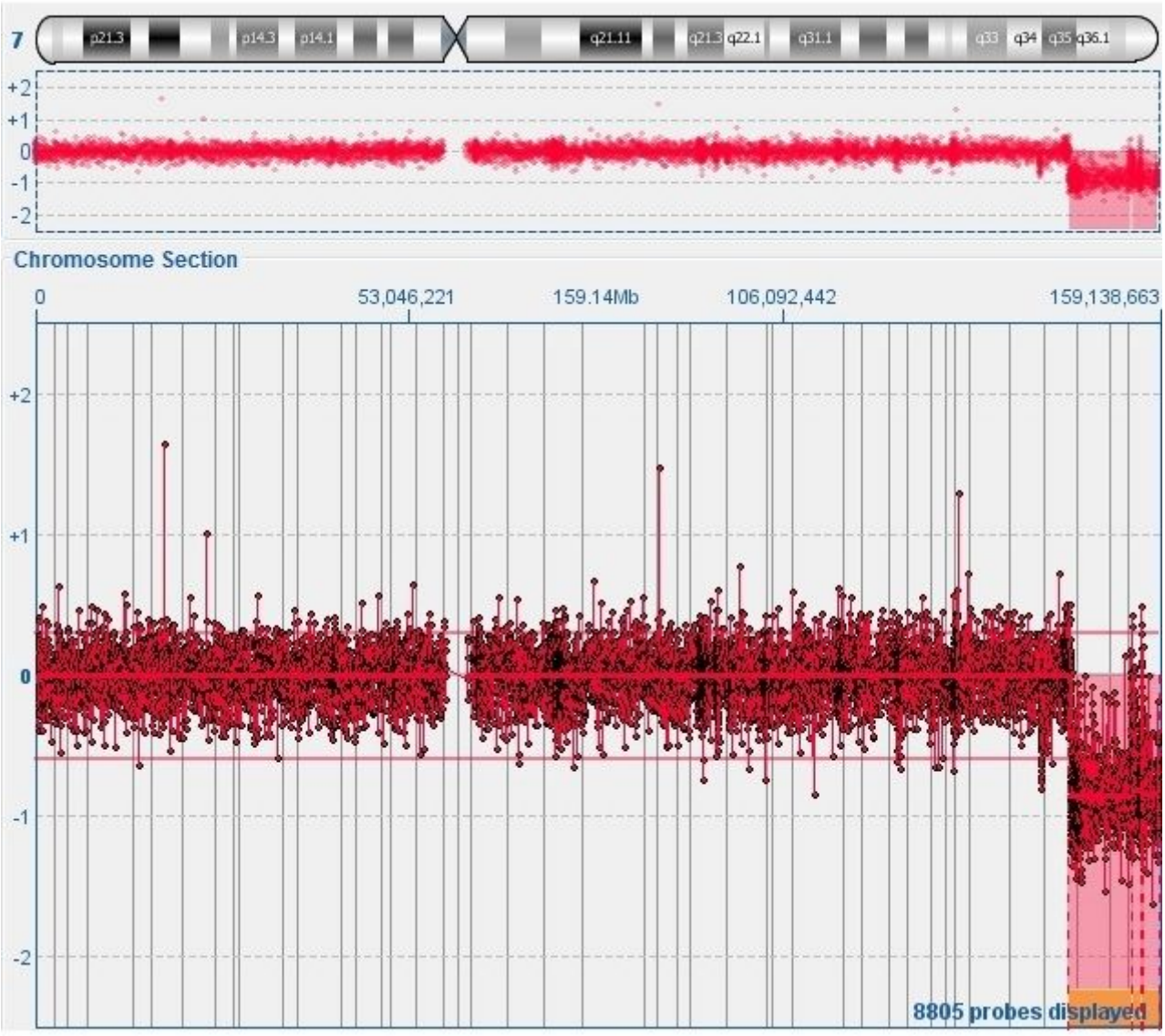

Figure 2

Figure 2

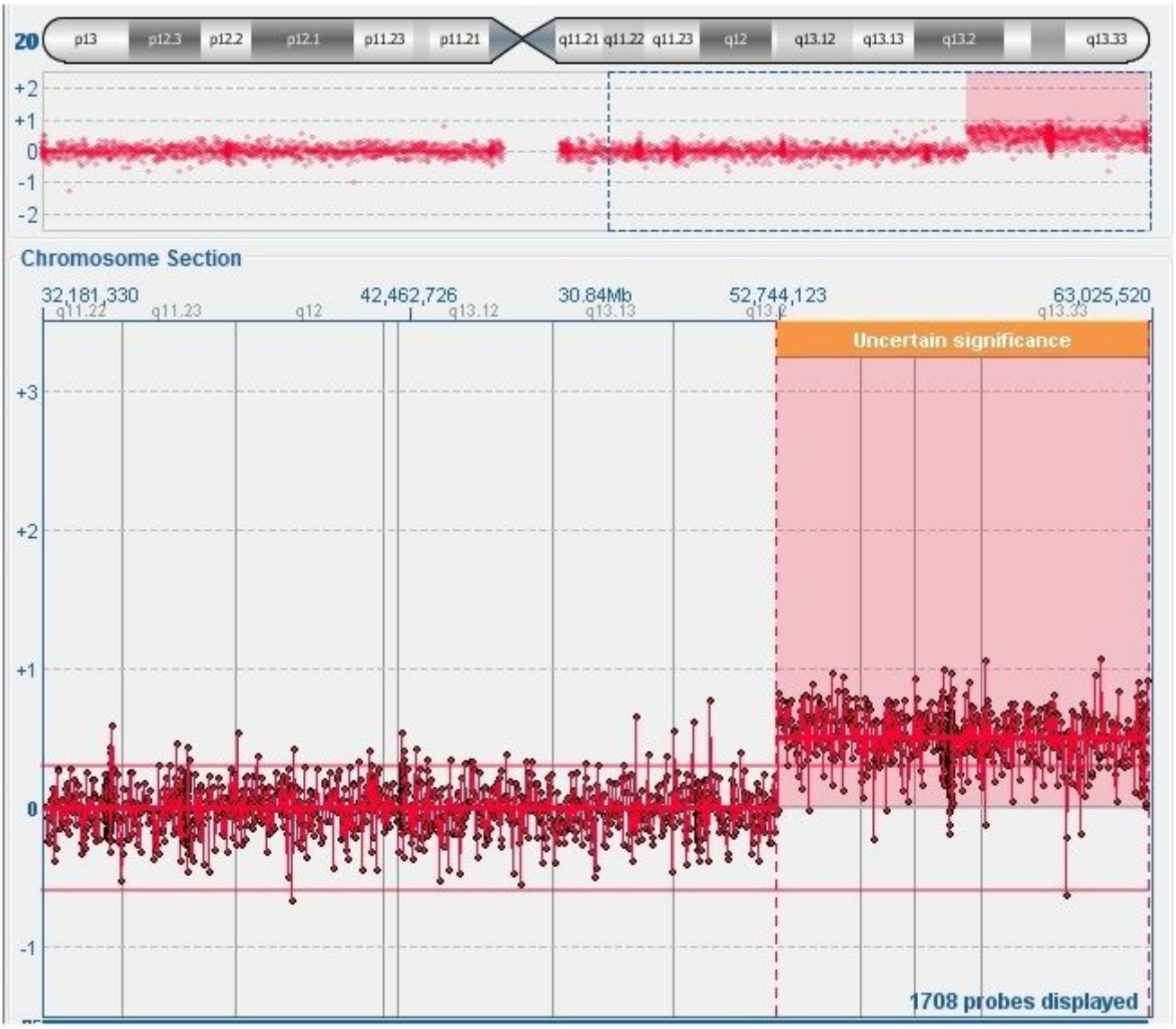

Figure 3

Figure 3

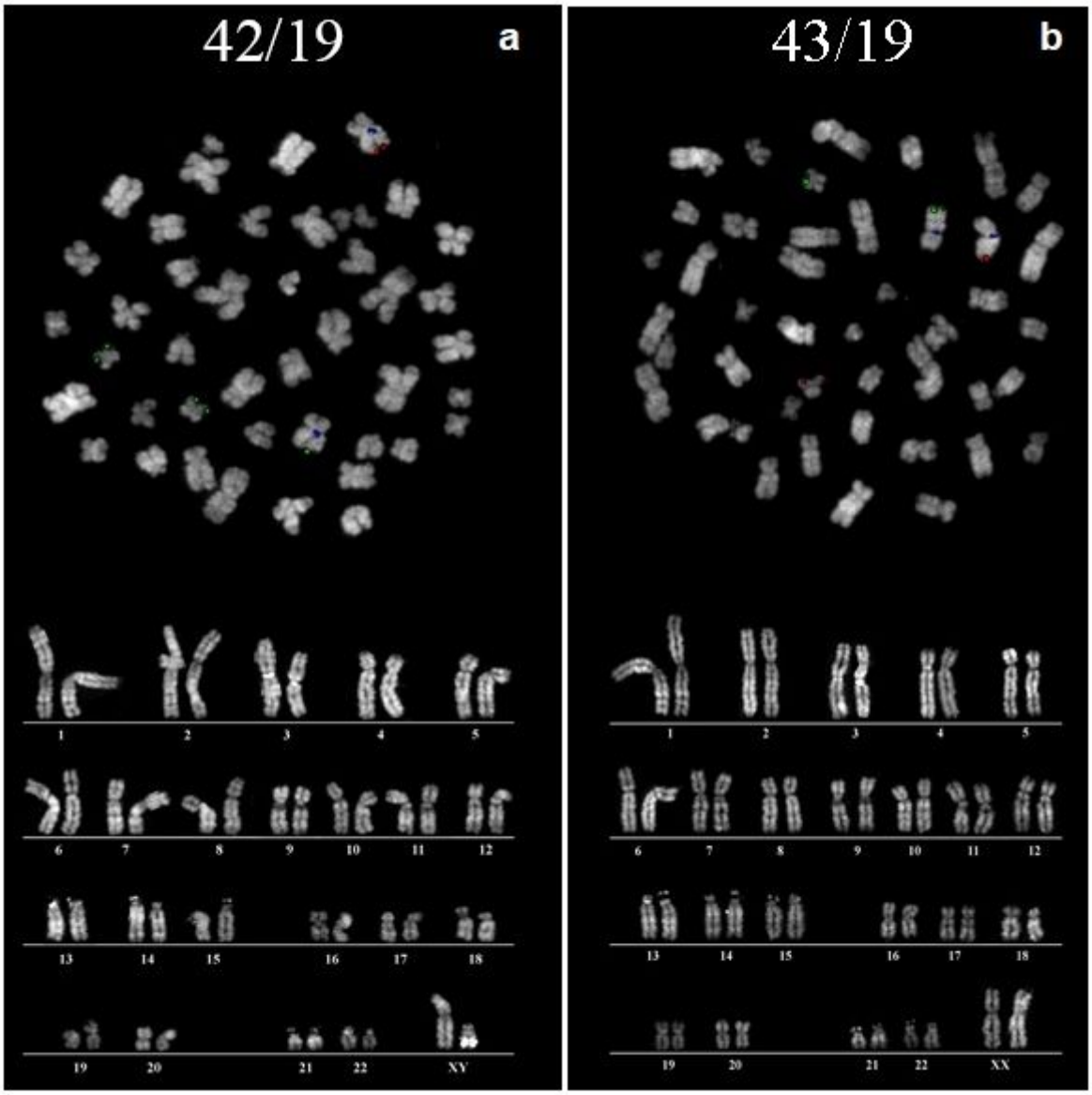

Figure 4

Figure 4

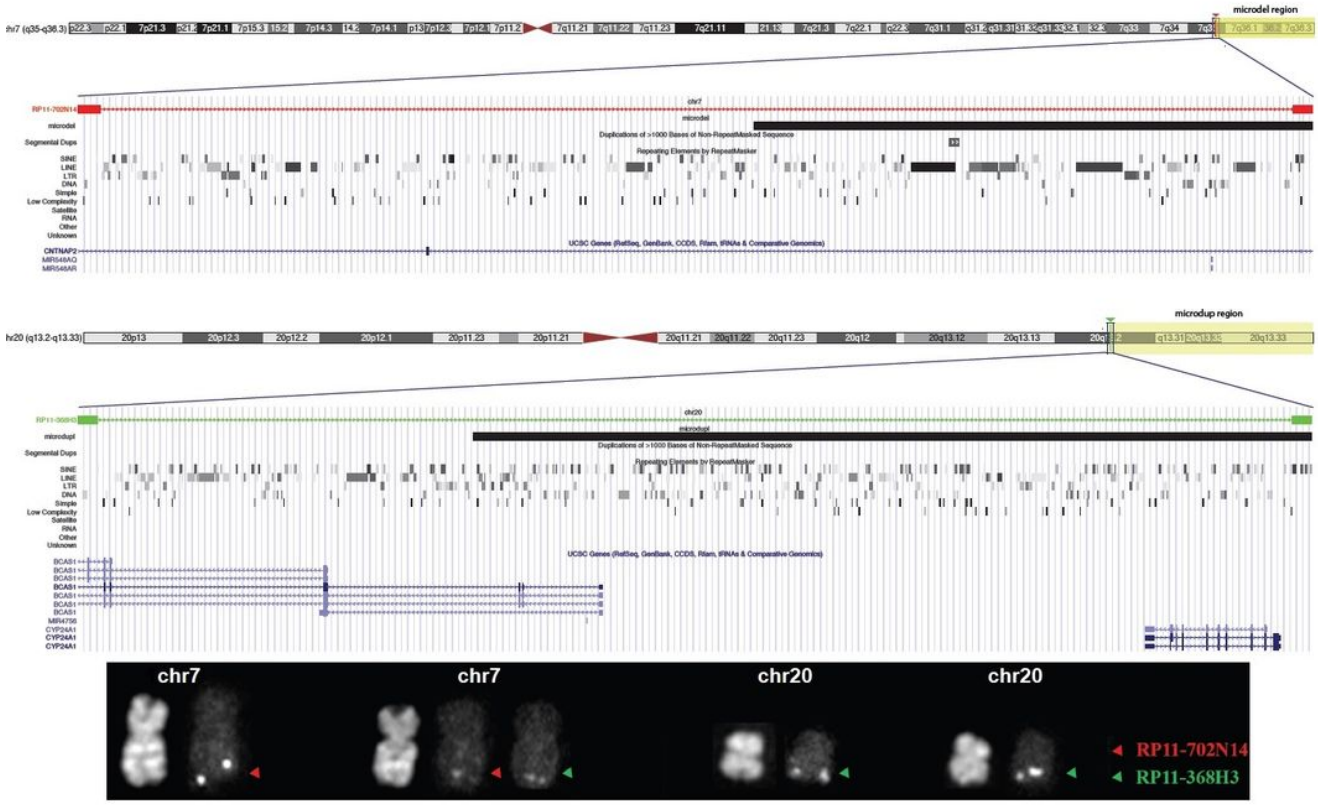

Figure 5

Figure 5

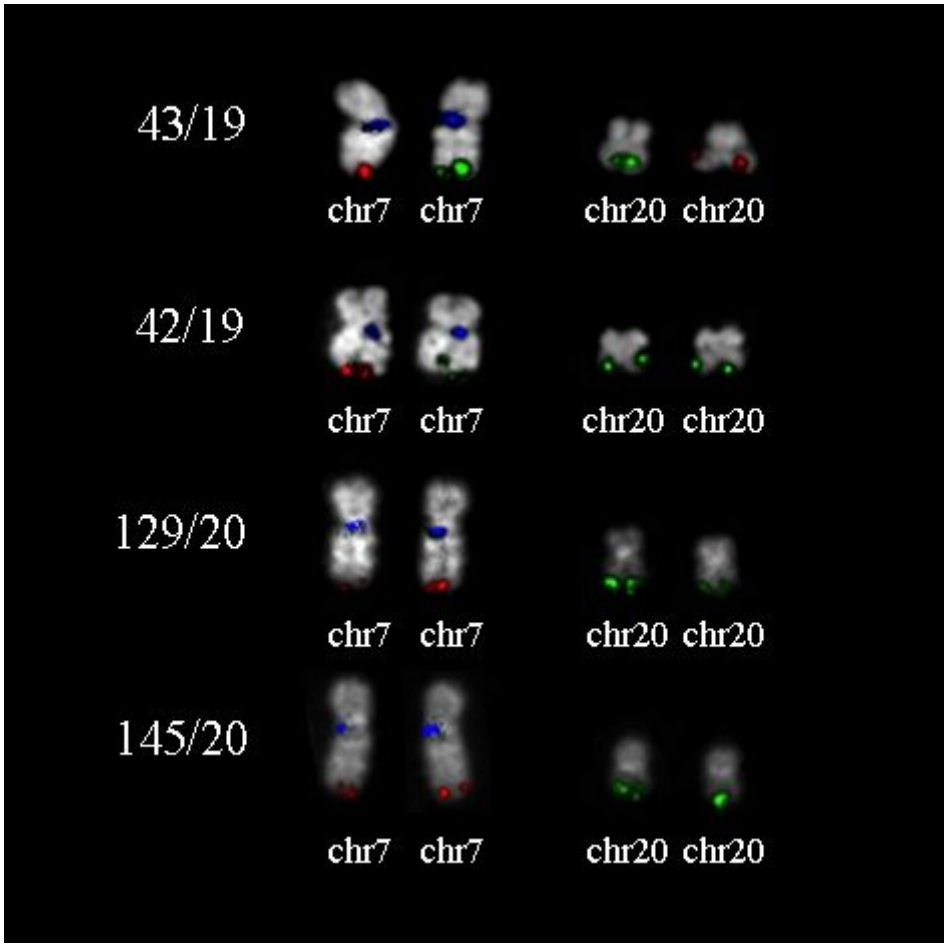

Figure 6

Figure 6

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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