Population screening for 15q11-q13 duplications : corroboration of the difference in impact between maternally and paternally inherited alleles

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Authors

Ilse Parijs[1], Nathalie Brison[1], Leen Vancoillie[1], Machteld Baetens[3], Bettina Blaumeiser[2], Sébastien Boulanger[5], Julie Désir[5], Boyan Dimitrov[4], Nathalie Fieremans[4], Katrien Janssens[2], Sandra Janssens[3], Axel Marichal[5], Björn Menten[3], Colombine Meunier[5], Kim Van Berkel[4], Ann Van Den Bogaert[4], Koenraad Devriendt[1], Kris Van Den Bogaert[1] and Joris Robert Vermeesch[1]

1 Center for Human Genetics, University Hospitals Leuven–KU Leuven, Leuven, Belgium.

2 Center of Medical Genetics, University and University Hospital Antwerp, Antwerp, Belgium

3 Center of Medical Genetics, University Hospital Ghent, Ghent, Belgium

4 Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Clinical Sciences, research group Reproduction and Genetics, Center for Medical Genetics, Brussels, Belgium

5 Center for Medical Genetics, Institut de Pathologie et de Génétique Gosselies, Charleroi, Belgium.

Corresponding author email: Joris.Vermeesch@uzleuven.be

Abstract

Maternally inherited 15q11-q13 duplications are generally found to cause more severe neurodevelopmental anomalies compared to paternally inherited duplications. However, this assessment is mainly inferred from the study of patient populations, causing an ascertainment bias towards patients at the more severe end of the phenotypic spectrum. Here, we analyze the low coverage genome-wide cell-free DNA sequencing data obtained from pregnant women during non-invasive prenatal screening (NIPS). We detect 23 15q11-q13 duplications in 333,187 pregnant women (0.0069%), with an approximately equal distribution between maternal and paternal duplications. Maternally inherited duplications are always associated with a clinical phenotype (ranging from learning difficulties to intellectual impairment, epilepsy and psychiatric disorders), while paternal duplications are normal or associated with milder phenotypes (mild learning difficulties and dyslexia). This data corroborates the difference in impact between paternally and maternally inherited 15q11-q13 duplications, contributing to the improvement of genetic counselling. We recommend reporting 15q11-q13 duplications identified during genome-wide NIPS with appropriate genetic counselling for these pregnant women in the interest of both mothers and future children.

Key words: genomic disorders, neurodevelopment, 15q11, 15q11-q13 duplications, NIPS

Introduction

Noninvasive prenatal screening (NIPS) is commonly used as a sensitive and specific method for the detection of fetal aneuploidies, typically trisomy 13, 18 and 21. The test is based on the analysis of cell-free DNA (cfDNA) in the maternal serum using either targeted sequencing or shallow whole genome sequencing (1,2). The latter method also enables the detection of other fetal aneuploidies, segmental imbalances, and copy-number variations (CNVs) (3–6). Moreover, since the cfDNA is largely of maternal origin, not only fetal, but also maternal CNVs can be detected, the latter at a much higher resolution than fetal CNVs (7–10).

Copy number gains and losses of the 15q11-q13 region are associated with various imprinting disorders. Loss of the paternal allele leads to Prader-Willi syndrome (OMIM 176270), while loss of the maternal allele causes Angelman syndrome (OMIM 105830) (11,12). The phenotypic consequences of maternal or paternal duplications remain less defined (13,14). Maternal duplications give rise to the 15q duplication syndrome (OMIM 608636), which is characterized by hypotonia and motor delay, feeding difficulties, intellectual disability, autism spectrum disorder and epilepsy. Symptoms differ between patients with an interstitial duplication and those with an isodicentric supernumerary marker chromosome, idic(15), probably due to dosage effects. However, even in patients with the same duplication, the phenotype can be highly variable (11,15–17). Paternal 15q11-q13 duplications are associated with developmental delay, increased risk for epilepsy, sleeping problems and autistic features. The phenotype is however more variable and in many cases even absent, suggesting incomplete penetrance (18–20).

The consequences of 15q11-q13 duplications have mainly been studied via ascertainment of patients with developmental anomalies (13,18,20,21). Since the phenotype shows considerable variability and reduced penetrance, those studies will be biased, as they often only describe patients at the more severe end of the phenotypic spectrum. The easily available detection of maternal 15q11-q13 duplications during routine NIPS provides an opportunity for population screening of pregnant women. Here we present 23 cases in which 15q11-q13 duplications were detected as maternal

secondary findings with NIPS. As part of the routine clinical follow-up, we determined the parental origin for 18 of these duplications and analyzed the clinical phenotype of the women. Our data support the hypothesis that carriers of paternal duplications often lack phenotypic abnormalities. In contrast, maternal duplication carriers always present with developmental anomalies, with varying severity.

Materials and methods

Sample collection and NIPS analysis

All pregnant women undergoing NIPS in some of the Belgian genetic centers between July 1, 2017 and December 1, 2021 were included in the study. Phenotypic characterization of the pregnant women was performed during genetic counselling. A blood sample was collected in a cell-free DNA BCT tube (Streck, Omaha, NE, USA), a cell-free DNA collection tube (Roche Diagnostics, Mannheim, Germany), or a PAXgene blood ccfDNA tube (Qiagen, Hilden, Germany) from 12 weeks of gestation onwards and written informed consent for reporting secondary findings was obtained. NIPS analysis was performed as described previously (6,7,10,22,23). Briefly, plasma from the maternal blood samples was isolated by means of centrifugation. CfDNA was extracted using the QIAamp Circulating Nucleic Acid Kit (Qiagen), the Maxwell HT cfDNA kit (Promega, Leiden, The Netherlands) or the VeriSeq NIPS solution v2 (Illumina, San Diego, CA, USA) according to the manufacturer's recommendations. Libraries were prepared using the Kapa HyperPlus preparation kit (Kapa Biosystems, Wilmington, MA, USA); the TruSeq ChIP, TruSeq DNA Nano library preparation kit or the VeriSeq NIPS Solution v2 (Illumina); the NEXTflex Cell-free DNA-seq kit or NEXTflex Rapid DNA-Seq kit 2.0 (PerkinElmer, Waltham, MA, USA). Genome-wide shallow genome sequencing was performed with either the Ion Proton system (ThermoFisher scientific, Waltham, MA USA) or the HiSeq1500, HiSeq2500, HiSeq3000, HiSeq4000, Novaseq6000, NextSeq500 or NextSeq550 sequencer (Illumina). Genome-wide genomic representation profiling and interpretation was performed using the VeriSeq NIPS Assay Control Software v2.0.0 (Illumina) or as previously described (6,7,22–24). Maternal CNVs were identified by WISECONDOR (25) or by visual inspection of the genomic representation profiles, visualization in BrightCNV NIPS visualization tool and SeqCBS analysis (23). The data were filtered by fold change and region. Specifically, only duplications with 1.3 > fold change > 1.7 that overlapped with the Prader-Willi/Angelman Critical Region on chromosome 15 were included.

Follow-up analysis

Maternal CNVs were confirmed on DNA extracted from maternal white blood cells, obtained from the stored buffy coats of the NIPS blood samples or from additional maternal blood samples. Fetal CNVs were confirmed on DNA extracted from amniotic fluid. The CNV confirmation was performed using the Agilent ISCA 60 K or 44 K array (Agilent, Santa Clara, CA, USA), Cytoscan 750 K array (Affymetrix, Santa Clara, CA, USA), HumanCytoSNP-12 v2.1 BeadChip kit (Illumina) or by shallow genome sequencing (CNVSeq). Fluorescent *in situ* hybridization (FISH) and conventional karyotyping were performed according to standard procedures. To determine maternal or paternal inheritance of the duplication, the methylation status of the CNVs was investigated by Methylation-Specific Multiplex Ligation-Dependent Probe Amplification using the SALSA MLPA kit P140 probe mix HBA (MRC- Holland, Amsterdam, the Netherlands) or by an alternative methylation specific method in which bisulfite treatment was used following a specific PCR and migration on the ABI 3130 genetics analyzer.

Results

Incidence of 15q11-q13 duplications

Copy number analysis of 333,187 NIPS profiles predicted 23 15q11-q13 duplications in the maternal cfDNA (Table 1), which results in a population incidence of 0.0069%. All duplications were confirmed using DNA extracted from maternal white blood cells in the NIPS sample or from an independent blood sample of the pregnant women, except for case 21 for which no follow-up data was available. Hence, the positive predictive value to detect this CNV by NIPS is 100%.

NIPS is unable to determine whether or not a CNV detected in a pregnant woman was passed on to the fetus. Hence, an amniocentesis was performed for 14 out of 23 cases. For the remaining 10 cases we have no follow up data. Seven fetuses (cases 3, 7, 10, 12, 13, 17, 23) inherited the duplication and were thus at high risk to develop the 15q duplication syndrome. In two cases (12 and 23), the pregnancy was terminated, while for cases 10, 13 and 17 the pregnancy was carried to term. There is no follow-up for the remaining two cases. No information on the clinical phenotype of the fetuses was collected.

Parental origin and phenotypes in the pregnant women

To investigate the parental origin of the duplications, the methylation status of specific imprinted loci was analyzed. Ten duplications were of maternal origin (cases 1-10) and all women showed a (variable) clinical phenotype (Table 1). Eight duplications were of paternal origin (cases 11-18) and five women were clinically normal, while three showed (mild) clinical symptoms. For the remaining five duplication carriers (cases 19-23), the parental origin was not available. All of these women were reportedly clinically normal.

Type of duplications

The proximal 15q region consists of five blocks of segmental duplications or low copy repeats, which have been identified as recurrent breakpoints (BPs), termed BP1 to BP5. The Prader-Willi/Angelman

Critical Region is located between BP2 and BP3 at position 23651570-28664979 (NCBI Build GRCh37/hg19) (ref. 14). The 23 15q11-q13 duplications vary in size and different BPs are involved. The size and location of all duplications is shown in Figure 1. For seven cases (2-5, 12, 13, 21), the duplication encompasses the BP1-BP3 interval, while for twelve (cases 6-10, 14-18, 22, 23), it involves the smaller BP2-BP3 region. Two cases (1 and 19) were larger in size and had breakpoints in BP1 proximally and BP5 and BP4 distally, respectively. All cases contain the Prader-Willi/Angelman Critical Region. Finally, two cases (11, 20) were smaller, atypical duplications not resulting from recombination in the BP regions and did not include the entire Prader-Willi/Angelman Critical Region.

Two main mechanisms that lead to the increase in copy number of the 15q11-q13 region have been previously described (26). The first is formation of an isodicentric or pseudodicentric 15q11-q13 supernumerary chromosome – idic(15) – that comprises two extra copies of 15q11-q13, thus resulting in tetrasomy for 15q11-q13. The second is non-allelic homologous recombination leading to a 15q11-q13 duplication that includes one extra copy of 15q11-q13, adjacent with the original region, resulting in trisomy for 15q11-q13 (ref. 14). These are referred to as interstitial duplications. The presence of more than one additional copy was excluded for all independently confirmed cases, which also excludes the presence of an idic(15) marker chromosome. Notably, one marker chromosome that only contained one additional copy of the 15q11-q13 region was detected (case 1). In another case (11), a derivative chromosome originating from a balanced translocation between chromosome 15 and the Y-chromosome in the father of the pregnant woman was present. Two duplications were confirmed to be interstitial and in tandem (cases 4 and 12). For the remaining duplications, no detailed structural information was available.

Discussion

Based on a population screening of over 300,000 pregnant women, the incidence of the 15q11-q13 duplications is 0.0069%. We observe an approximately equal number of duplications of the maternal and paternal allele. Our data show that maternal duplications are invariably associated with a clinical phenotype, ranging from learning difficulties to intellectual impairment, epilepsy and psychiatric disorders. The majority of paternal duplication carriers are phenotypically normal, although for three cases mildly affected phenotypes such as mild learning difficulties and dyslexia have been observed. Notably, two of the paternal duplications with a normal phenotype (case 11 and 20) do not include the entire Prader-Willi/Angelman Critical Region, which could also contribute to the lack of phenotypic features. Both maternal and paternal duplication carriers have been associated with learning difficulties and the difference in severity is not always clear. However, for most cases, maternal duplication carriers are more severely affected. These results are in line with previous reports, which collected data from 15q11 patient support groups, a general database of patients with a variety of phenotypic abnormalities, family members and a assumedly normal control population (13,14,17–19,21,27).

Previously, Isles *et al.* (2016) compiled the largest dataset of interstitial 15q11-q13 duplications to date, composed of both patients with a clinical phenotype (schizophrenia, developmental delay, autism spectrum disorder or multiple congenital anomalies) and assumingly normal controls (13,19–21). In 79,139 patients and 149,780 controls, they reported maternal duplications in 0.0069% and paternal duplications in 0.0033%. Interestingly, in the control population alone, the incidence of maternal and paternal duplications was equal (each 0.0027%). This is consistent with our findings in a population without bias towards patients with a known clinical phenotype. We acknowledge the limitation that only pregnant females were included in our dataset, which excludes infertile and severely intellectually impaired women as well as all men. In addition females with known 15q11-q13 duplications (or other clinically significant aberrations) may be more likely to opt for pre-implantation

genetic testing or invasive testing instead of NIPS. In contrast, the dataset of Isles et al. (2016) is likely to have an overrepresentation of patients and consequently a higher number of maternal duplications. Therefore, it remains difficult to the determine the true incidence and distribution of maternal and paternal duplications in the general population.

The Belgian Advisory Committee on Bioethics states that secondary findings of clinical relevance detected during NIPS should be reported ('Belgian Advisory Committee on Bioethics. Opinion no. 66—noninvasive prenatal testing (NIPS)', (28)). To standardize the findings that are to be reported, the Belgian Society for Human Genetics developed guidelines regarding clinically significant secondary findings detected by NIPS (29). The guidelines indicate that CNVs that have no consequence for the mother but, if inherited, are potentially harmful for the fetus in the current or in a future pregnancy should be reported. Following these guidelines, 15q11-q13 duplications should be reported as maternal secondary findings since there is a 50% risk of transmitting the duplication and hence, having a child with the 15q duplication syndrome. Invasive testing preceded by genetic counseling is recommended. Notably, the counselling is challenging because the difference between maternal and paternal duplications needs to be explained, while the available information in the literature is still limited. Conveying all information is nevertheless essential to enable informed decision making by the pregnant women and their partners. Women that carry a maternal duplication might be more likely to decline invasive testing and continue the pregnancy if they experience their own quality of life to be high. It is important to stress during counseling that symptoms are known to vary, even within a family with the same type of duplication. As such, the affected child might have a more or less severe phenotype in comparison to the mother (17).

In seven cases the fetus was found to carry the duplication and at least in two the pregnancy was terminated. The women who opted for termination carried a paternal or unknown duplication and were both clinically normal. One of the women who continued the pregnancy had a duplication on the maternal allele, while two other had a duplication on the paternal allele. In our cohort, there are

no known cases of termination when the pregnant women had a maternal duplication, however the number of cases is very limited and also women with paternal duplications chose not to terminate the pregnancy.

None of the 23 women were previously aware of being carriers of this duplication, and for some of them this finding offered an explanation for their medical condition. An important part of genetic counselling also involves looking at the family history: if the 15q11-q13 duplication is inherited from one of the parents, testing of additional family members is warranted (14).

Two classes of 15q duplications have been previously described, depending on size and breakpoints (27). We report seven class 1 (BP1-BP3) and twelve class 2 (BP2-BP3) cases. Some duplications also contained the region between the centromere and BP1; however, this region is considered to be polymorphic (19) and was not taken into account in the classification. Interestingly, we observed one case (11) that was not flanked by any of the breakpoints and was found to be a derivative chromosome that originated from a balanced translocation between chromosome 15 and Y in the father of the pregnant woman. To our knowledge, this type of 15q11-q13 duplication has not been reported previously. No correlation could be observed between the size of the maternal duplication and the severity of the clinical phenotype, which is consistent with previous reports (18). The severity of the symptoms is known to be higher in people with idic(15) due to a dosage effect (30), but none of the women carried an idic(15) nor four copies of the region. A possible reason for the lack of idic(15) cases in our dataset of pregnant women is that idic(15) patients have a more severe phenotype and therefore are less likely to reproduce.

In conclusion, we show that routine NIPS is a valuable tool to detect maternal 15q11-q13 duplications that are of importance for the health of the fetus and for future pregnancies. Our data will aid the genetic counselling of prenatally detected 15q11-q13 duplications and emphasizes the importance of reporting these duplications as a maternal secondary finding with NIPS. We recommend follow-up and appropriate genetic counselling for these pregnant women.

Data availability statement

The datasets generated during the current study are available from the corresponding author on reasonable request and within ethical constraints.

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Author contributions

Conceptualization: IP, KVDB, KD, JRV. Investigation & methodology : IP, KVDB, KD, JRV. Formal analysis: IP Visualization: IP Data curation: IP, NB, LV, KJ, BB, MB, SJ, BM, BD, NF, KVB, AVDB, CM, JD, SB, AM. Supervision: KVDB, KD, JRV. Writing—original draft, review, and editing: IP, KJ, MB, BM, NF, KVDB, KJ, KD, JRV.

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Ethical approval

This study is approved by the Ethics Committee Research of University Hospitals Leuven (S66428).

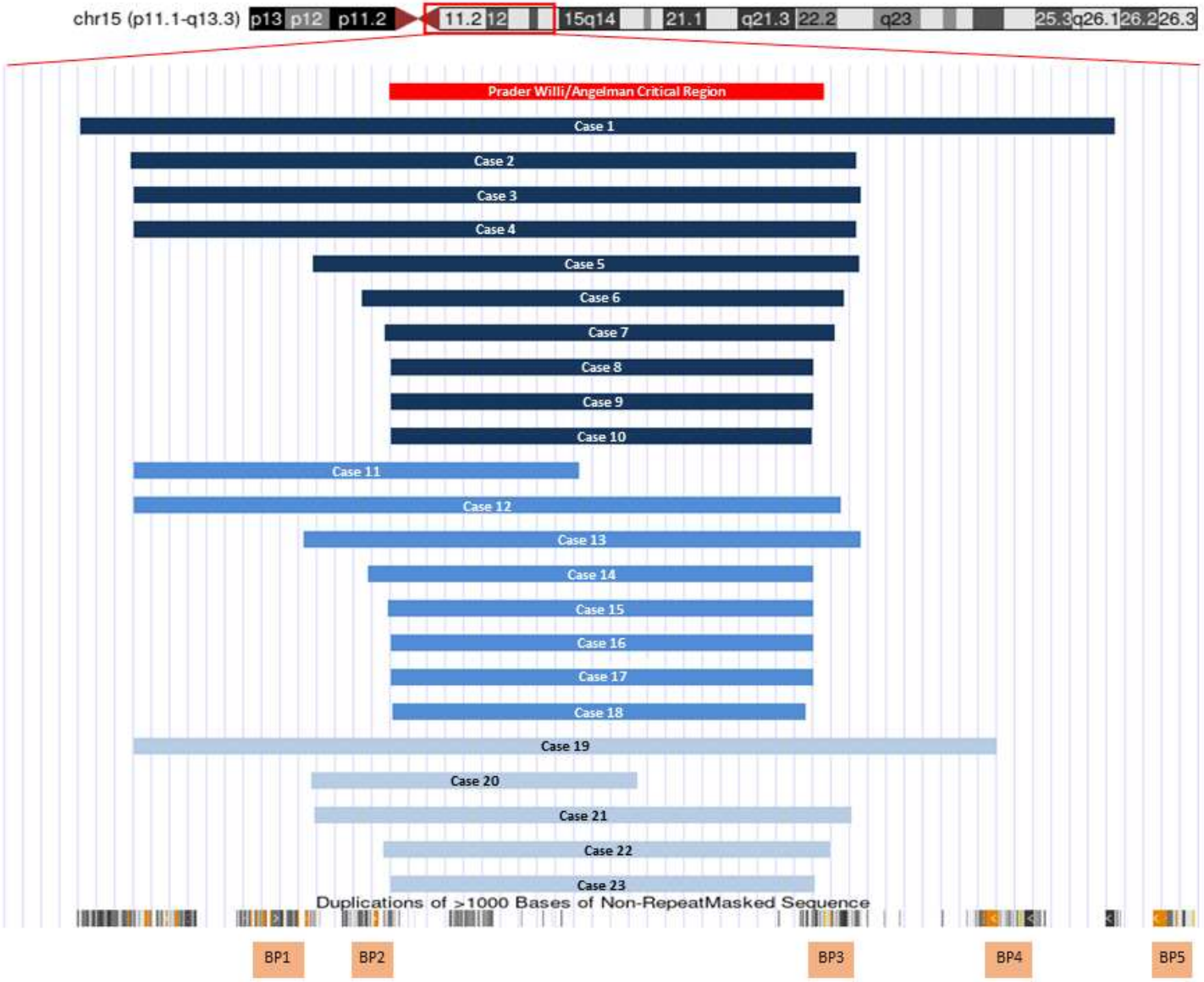
Competing interests

The authors declare no competing interests.

Figure and table legends

Figure 1: Genomic representation of the 15q11-q13 region. The 23 duplications detected with NIPS are sorted by parental origin and size and are shown in blue (maternal origin), light blue (paternal origin) and grey (unknown origin). The Prader-Willi/Angelman critical region is shown in red. At the bottom is a track of segmental duplication regions, with the different breakpoints (BP1-BP5) shown in orange.

Table 1: Overview of all 15q11-q13 duplications detected with NIPS, with parental origin and clinical phenotype of the mother and fetal follow-up. Additional information is listed when available.



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334 Figure 1

335 Table 1

Case	Start [Hg19]	Stop [Hg19]	Origin	Clinical phenotype of mother	Additional information on the maternal duplication	Duplication present in fetus?	Pregnancy terminated?
1	20079558	32011200	Maternal	Learning difficulties	Conventional karyotyping: marker chromosome FISH: 47,XX,+mar.ish der(15)(SNRPN+) --> not idic(15)		
2	20661527	29031749	Maternal	Intellectual deficit and psychiatric disorders			No
3	20686196	29085896	Maternal	Depressive episodes since the age of 18 leading to several hospitalizations in psychiatry		Yes	
4	20686203	29031767	Maternal	Intellectual difficulties compared to family	Conventional karyotyping and FISH: duplication in tandem		
5	22754322	29071810	Maternal	Borderline personality disorder with postpartum depression and psychosis		No	
6	23318052	28894685	Maternal	Learning difficulties - professional education (until age of 18)			No
7	23597805	28780204	Maternal	Intellectual difficulties, epilepsy, irritability and dysmorphia		Yes	
8	23656064	28526437	Maternal	Professional education (until age of 18)	De novo duplication	No	No
9	23656936	28542124	Maternal	Learning difficulties - unemployed (can read and write but did not finish professional education)		No	
10	23656936	28520313	Maternal	Special education, memory impairment		Yes	No

11	20686203	25838141	Paternal	Clinically normal	Conventional karyotyping: 47,XX,+der(15)t(Y;15)(q11;q12) FISH: 47,XX,+der(15)t(Y;15)(q11;q12).ish der(15)(D15Z1+,SNRPN+,PML-,DYZ1+,TelVysion Yq +) Conventional karyotyping maternal grandfather: 46,XY,t(Y;15)(q11;q12)	No	
12	20686203	28859765	Paternal	Clinically normal	FISH: Duplication in tandem De novo duplication	Yes	Yes
13	22652061	29085896	Paternal	Clinically normal		Yes	No
14	23403580	28526437	Paternal	Learning difficulties only at a young age, short follow up for Gilles de la tourette			No
15	23630074	28532327	Paternal	Dyslexia, learning difficulties - lots of support needed but obtained bachelor diploma (beyond age of 18)		No	
16	23656064	28526437	Paternal	Clinically normal			
17	23656936	28542124	Paternal	Learning difficulties. Current job: teacher in special education.		Yes	No
18	23684655	28446757	Paternal	Clinically normal	De novo duplication	No	
19	20686203	30653918	Not tested	Clinically normal (reportedly)			
20	22750001	26500000	Not tested	Clinically normal	Conventional karyotyping: no marker chromosome	No	
21	22778664	28967177	Not tested	Clinically normal			
22	23569400	28726651	Not tested	Clinically normal (reportedly)			No
23	23656064	28559437	Not tested	Clinically normal		Yes	Yes