Pronounced maternal parent-of-origin bias for type-1 *NF1* microdeletions

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Abstract

Neurofibromatosis type 1 (NF1) is caused, in 4.7–11% of cases, by large deletions encompassing the *NF1* gene and its flanking regions within 17q11.2. Different types of large *NF1* deletion occur which are distinguishable by their breakpoint location and underlying mutational mechanism. Most common are the type-1 *NF1* deletions of 1.4-Mb which exhibit recurrent breakpoints caused by non-allelic homologous recombination (NAHR), also termed unequal crossover. Here, we analysed 37 unrelated families of patients with *de novo* type-1 *NF1* deletions by means of short tandem repeat (STR) profiling to determine the parental origin of the deletions. We observed that 33 of the 37 type-1 deletions were of maternal origin (89.2% of cases; $p < 0.0001$). Analysis of the patients' siblings indicated that, in 14 informative cases, ten (71.4%) deletions resulted from interchromosomal unequal crossover during meiosis I. Our findings indicate a strong maternal parent-of-origin bias for type-1 *NF1* deletions. A similarly pronounced maternal transmission bias has been reported for recurrent copy number variants (CNVs) within 16p11.2 associated with autism, but not so far for any other NAHR-mediated pathogenic CNVs. Region-specific genomic features are likely to be responsible for the maternal bias in the origin of both the 16p11.2 CNVs and type-1 *NF1* deletions.

Key words

Neurofibromatosis type 1 (NF1), *NF1* microdeletions, non-allelic homologous recombination (NAHR), short tandem repeat (STR) profiling, meiosis, interchromosomal unequal crossover, copy number variants (CNVs), recurrent genomic rearrangements, parent-of-origin bias

Introduction

Large deletions encompassing the *NF1* gene region at 17q11.2 (also termed *NF1* microdeletions) are detected in 4.7–11% of patients with neurofibromatosis type 1 (NF1; MIM #162200) (Cnossen et al. 1997; Rasmussen et al. 1998; Kluwe et al. 2004; Zhang et al. 2015). Frequently, these deletions exhibit recurrent breakpoints and are mediated by non-allelic homologous recombination (NAHR), also referred to as unequal crossover. However, different types of large *NF1* deletion have been identified which are distinguishable by the size and locations of their breakpoints. Most frequent are type-1 *NF1* deletions of 1.4-Mb accounting for 70-80% of all large *NF1* deletions (Pasmant et al. 2010; Messiaen et al. 2011). Type-1 *NF1* deletions are caused by NAHR between highly homologous low-copy repeats (LCRs) termed NF1-REPa and NF1-REPc (Dorschner et al. 2000; Jenne et al. 2001; López-Correa et al. 2001). Type-1 *NF1* deletions are characterized by breakpoint recurrence since most of the breakpoints are located within the NAHR hotspots referred to as paralogous recombination sites 1 and 2 (PRS1 and PRS2) (Forbes et al. 2004; De Raedt et al. 2006; Bengesser et al. 2014; Hillmer et al. 2016, 2017). Type-2 *NF1* deletions encompass only 1.2-Mb and are mediated by NAHR between the *SUZ12* gene and its pseudogene *SUZ12P* (Roehl et al. 2010; Vogt et al. 2012). Type-2 *NF1* deletions comprise 10-20% of all large *NF1* deletions (Kehrer-Sawatzki et al. 2004; Messiaen et al. 2011). Type-3 *NF1* deletions are characterized by breakpoints located within NF1-REPb and NF1-REPc and are also mediated by NAHR (Bengesser et al. 2010; Pasmant et al. 2010; Zickler et al., 2012). However, type-3 deletions are rare, accounting for only 1.4–4% of all large *NF1* deletions (Pasmant et al. 2010; Messiaen et al. 2011).

In addition to large *NF1* deletions with recurrent breakpoints, atypical *NF1* deletions have been identified which exhibit non-recurrent breakpoints. These atypical *NF1* deletions are not mediated by NAHR but instead ~~by~~ occur via DNA double strand break repair or replication-associated mechanisms (Vogt et al. 2014 and references therein). At least 10% of all large *NF1* deletions are atypical (Pasmant et al. 2010; Messiaen et al. 2011). They are heterogeneous in terms of breakpoint location, size and the number of genes located within the deleted region (reviewed by Kehrer-Sawatzki et al. 2017).

The various types of *NF1* microdeletion are distinguishable not only by breakpoint position and underlying mechanism but also by the frequency of somatic mosaicism with normal cells not harbouring the deletion. Type-2 *NF1* deletions, caused by NAHR between *SUZ12* and *SUZ12P1*, are frequently of postzygotic origin (Kehrer-Sawatzki et al. 2004; Steinmann et al. 2007); thus, at least 63% of all type-2 *NF1* deletions are associated with somatic mosaicism (Vogt et al. 2012). Atypical *NF1* deletions are also frequently mosaic; among the 17 atypical *NF1* deletion patients investigated by Vogt et al. (2014), 10 patients (59%) exhibited somatic mosaicism with normal cells. By contrast, only a small proportion (2–4%) of type-1 *NF1* microdeletions are of postzygotic origin and associated with somatic mosaicism (Messiaen et al. 2011).

Early studies reported that large *NF1* deletions are often of maternal origin but the deletions analysed were not characterized with regard to their size, type and underlying mutational mechanism (Lazaro et al. 1996; Upadhyaya et al. 1998). López-Correa et al. (2000) analysed six *NF1* deletions that had been shown to be of type-1, and all six of them were of maternal origin. The study of López-Correa at al. (2000) also included a smaller *NF1* deletion, not of

type-1, but this deletion was of paternal origin. Although these findings hinted at a maternal bias for type-1 *NF1* deletions, the number of deletions analysed by López-Correa et al. (2000) was still small. In the study presented here, we investigated a rather larger number of confirmed type-1 *NF1* deletions (N=37) and successfully identified their parental origin. Further, we determined the chromosomal origin of 14 of these type-1 *NF1* deletions, in particular ascertaining whether they were mediated by interchromosomal or intrachromosomal NAHR. We observed a strong maternal parent-of-origin bias for type-1 *NF1* deletions which might be attributable to gender-specific differences in recombination rates or chromatin conformations.

Patient data, Materials and Methods

We analysed 37 patients with *de novo* type-1 *NF1* deletions and their unaffected relatives who were collected at the Department of Neurology, University Hospital Hamburg Eppendorf, Germany. The deletions of these patients had ~~exhibiting~~ breakpoints located within the highly homologous low-copy repeats NF1-REPa and NF1-REPc as determined by MLPA and long-range breakpoint-spanning PCRs (Supplementary Table S1). The primers used for the breakpoint-spanning PCRs have been reported previously (Hillmer et al. 2017). Genomic DNA from the patients and their relatives was extracted from blood cells or saliva using Oragene•DNA (OG-250) DNA collection tubes (Genotek). The DNA extracted from saliva samples is derived from a mixture of buccal epithelial cells and blood cells (up to 74% of the DNA isolated from saliva is derived from white blood cells; Thiede et al. 2000). The patients and their family members provided written informed consent. This study was approved by the insititutional review boards of the University of Ulm and the University Medical Center Hamburg-Eppendorf.

STR profiling

Short tandem repeats (STRs), also termed microsatellite markers, were investigated by PCR and fragment analysis of the PCR products in order to determine the parental and chromosomal origin of the deletions. The primers used for these assays are listed in Supplementary Table S2. The primers were either labelled at their 5'ends with 6-FAM (Fluorescein) or HEX (Hexachloro-Fluorescein). PCR products were amplified using the AmpliTaq Gold™ 360 DNA polymerase (Applied Biosystems) and separated by capillary gel electrophoresis on an ABI 3130*xl* genetic analyzer (Applied Biosystems). The GeneScan™ 500 ROX™ size standard was used to determine the size of the allele peaks.

Recombination rate analysis

Male and female recombination rates across the type-1 *NF1* deletions region were taken from Kong et al. (2010) and visualized by means of the UCSC Genome Browser (https://genome.ucsc.edu/).

Results

Microsatellite marker analysis of DNA derived from the NF1 patients and their parents revealed that 33 of the 37 type-1 *NF1* deletions analysed were of maternal origin (89.2%) whereas only four were of paternal origin (10.8%) (Table 1). Hence, our findings indicate a

strong maternal bias for the origin of type-1 *NF1* deletions ($p < 0.0001$, two-tailed binomial test).

The chromosomal origin of 14 of the 37 type-1 deletions was identified by means of marker analysis of the unaffected siblings of the patients harbouring the deletion~~s~~ in question. The chromosomal origin of a deletion indicates whether it has been caused by inter- or intra-chromosomal NAHR. If NAHR occurs between homologous chromosomes, it is referred to as interchromosomal NAHR which occurs during meiosis I, schematically indicated in Supplementary Figure S1. Alternatively, if NAHR takes place between sister chromatids of one chromosome or within one chromatid of a single chromosome, it is referred to as intrachromosomal NAHR which most likely occurs during meiosis II (Supplementary Figures S2 and S3). The analysis of unaffected siblings indicated the phase of the markers and hence the haplotypes of the transmitting parents. If the patient exhibited an exchange of markers flanking the deletion region as compared with the haplotypes of the transmitting parent, then the deletion must have been caused by interchromosomal NAHR as exemplified in Figure 1. By contrast, no change of the haplotype phase of markers flanking the deletion is indicative of intrachromosomal NAHR (Figure 1). We noted that interchromosomal NAHR was responsible for ten (71.4%) of the 14 type-1 *NF1* deletions in which the chromosomal origin of the deletion had been identified. By contrast, four deletions (28.6%) were caused by intrachromosomal NAHR (Table 1). If only the deletions of maternal origin are considered, then nine of the 11 maternal deletions (81.8%) were mediated by interchromosomal NAHR. In the study of López-Correa et al. (2000), marker analysis of unaffected siblings of type-1 *NF1* deletion patients was informative in five of the six families investigated and all five deletions were mediated by maternal interchromosomal NAHR. If our results and those of López-Correa et al. (2000) are taken together, 14 of the 16 type-1 *NF1* deletions analysed were of maternal, interchromosomal origin (87.5%, $p = 0.0042$, two-tailed binomial test). These findings indicate a preference for interchromosomal crossover ~~for~~ in the context of maternal type-1 deletions. If only the deletions of paternal origin are considered, then two of the three paternal deletions were mediated by intrachromosomal NAHR.

Discussion

Non-allelic homologous recombination (NAHR), also referred to as unequal crossover between LCRs during meiosis, is the mechanism responsible for recurrent disease-associated copy number variants (CNVs) including germline type-1 *NF1* deletions (reviewed by Watson et al. 2014). In contrast to CNVs with recurrent breakpoints, those *de novo* CNVs with non-recurrent breakpoints are caused by a variety of different mutational mechanisms including microhomology-mediated break-induced replication (MMBIR) and fork stalling associated with template switching (FoSTeS) (reviewed in Carvalho and Lupski, 2016). As an alternative to replication-associated mechanisms, non-recurrent CNVs can be caused by various DNA double strand repair mechanisms that are not dependent upon sequence homology at the breakpoints, e,g, non-homologous end joining (NHEJ) (reviewed in Weckselblatt and Rudd, 2015). Previous studies have indicated that *de novo* non-recurrent CNVs, in particular deletions, are preferentially of paternal origin (Thomas et al. 2006a; Itsara et al. 2010; Hehir-Kwa et al. 2011; Sibbons et al. 2012; Ma et al. 2017). This bias could be explicable in terms

of the higher number of cell divisions (and hence replications) in the male as compared with the female germline. Whilst the number of oogonia in females is fixed at birth and will not increase later in life, self-renewing spermatogenic stem cells undergo continuous proliferation and replication during a male's lifespan (reviewed by Drost and Lee, 1995; Wilson Sayres and Makova, 2011; Griswold, 2016). The higher number of cell divisions (and replications) in the male germ line is likely to be the cause of the paternal parent-of-origin bias for *de novo* mutations (Kong et al. 2012; Rahbari et al. 2016) and may also explain the paternal bias for large structural imbalances such as non-recurrent CNVs (Ma et al. 2017).

In contrast to *de novo* CNVs with non-recurrent breakpoints, recurrent CNVs such as type-1 *NF1* deletions exhibit a strong maternal parent-of-origin bias. In the study presented here, a considerable excess of maternally derived type-1 *NF1* deletions was observed (33 out of 37 deletions, 89.2% of cases; $p < 0.0001$, two-tailed binomial test). A strong maternal bias for type-1 *NF1* deletions has previously been reported by López-Correa et al. (2000) but their study was very limited in size since it included only six confirmed type-1 *NF1* deletions. If our results and those of López-Correa et al. (2000) are combined, 39 of 43 type-1 *NF1* deletions analysed have been of maternal origin (90.7%; $p < 0.0001$, two-tailed binomial test). A similarly pronounced maternal parent-of-origin bias has been reported for *de novo* disease-associated duplications and deletions of a 550 kb region on chromosome 16p11.2 (Duyzend et al. 2016) (Table 2). Such a high level of maternal bias in transmission has not however been reported for any other type of recurrent disease-associated CNV. Hence, the 16p11.2 CNVs and type-1 *NF1* deletions are so far without precedent in terms of their extremely high maternal parent-of-origin bias.

A rather more subtle but nevertheless still significant bias in favour of a maternal origin has been reported for the 22q11.2 microdeletions associated with DiGeorge and Velocardiofacial syndrome (Table 2) (Thomas et al. 2006b; Delio et al. 2013). However, the extent of this maternal bias was much lower than that observed for type-1 *NF1* deletions and the CNVs at 16p11.2. The significantly higher recombination rates in the 16p11.2 critical region in females as compared to males have been suggested as the explanation of the maternal bias for the 16p11.2 CNVs (Kong et al. 2010; Duyzend et al. 2016). We also observed differences between female and male recombination maps involving 7-17.5-fold higher recombination rates in females than in males across the type-1 *NF1* deletion region, a finding which could be responsible for the maternal parent-of-origin bias for type-1 *NF1* deletions (Supplementary Figure S4).

Higher recombination rates in females than in males have also been noted in the 22q11.2 microdeletion region associated with DiGeorge and Velocardiofacial syndrome (Delio et al. 2013). Taken together, these findings imply an association between gender-specific recombination rate differences across certain genomic regions and parent-of-origin bias for CNVs. However, the consideration of recombination rates across CNV regions may not be precise enough in this context; instead, it might be more informative to investigate local recombination rates at CNV breakpoints. However, the breakpoints of NAHR-mediated CNVs are located within LCRs. The assessment of recombination rates within these paralogs is difficult owing to their complex variation patterns characterized by the occurrence of multiple shared SNPs between the paralog~~ue~~s resulting from frequent non-allelic homologous gene conversion without crossover (Rozen et al. 2003; Pavlicek et al. 2005; De Raedt et al.

2006; Lindsay et al. 2006; Guo et al. 2016; Hillmer et al. 2017). Consequently, these paralogous genomic regions are not well represented in the currently available recombination maps. Future high-resolution analysis of recombination rates within LCRs at NAHR breakpoints will be necessary to confirm an association between parent-of-origin bias and gender-specific recombination rate differences.

In addition to recurrent CNVs exhibiting a maternal parent-of-origin bias, there are also some with a paternal bias, including the CNVs causing Sotos syndrome and Charcot-Marie-Tooth disease type 1A (Lopes et al. 1998, Miyake et al. 2003, Visser et al. 2005) (Table 2). By contrast, other NAHR-mediated CNVs such as those causing Williams-Beuren syndrome, Smith-Magenis syndrome and Potocki-Lupski syndrome, do not exhibit any gender bias of origin (Table 2). These differences indicate that a gender-of-origin bias for recurrent CNVs is not a feature that is inherent to NAHR as the causative mechanism but is instead dependent upon genomic region-specific features. Alternatively, the occurrence of a parent-of-origin bias for a CNV may be associated with negative selection against oocytes or spermatocytes harbouring the CNV in question. It therefore cannot be excluded that negative selection against spermatocytes harbouring type-1 *NF1* deletions contributes to the observed maternal parent-of-origin bias for these deletions.

Remarkably, type-1-*NF1* deletions are associated with the loss of two tumour suppressor genes, *NF1* and *SUZ12*. Among the other recurrent CNVs listed in Table 2, only the 3-Mb deletions at 22q11.2 causing Velocardiofacial or DiGeorge syndrome lead to the loss of a tumour suppressor gene, in this case, *LZTR1*. It is unclear as yet if the CNV-mediated loss of these tumour suppressor genes has any impact upon the maternal inheritance bias of the respective CNVs.

The vast majority of type-1 *NF1* deletions are of meiotic origin and are not associated with somatic mosaicism with normal cells not harbouring the deletion. Only 2-4% of patients with type-1 *NF1* exhibit somatic mosaicism with normal cells (Messiaen et al. 2011). In the study presented here, we investigated the chromosomal origin of 14 type-1 *NF1* deletions (11 of maternal and three of paternal origin; Table 1). If only the deletions of maternal origin are considered and our results are combined with those of López-Correa et al. (2000), then 14 of the 16 type-1 *NF1* deletions, for which the chromosomal origin could be determined, were of interchromosomal origin (87.5% of cases; $p = 0.0042$, two-tailed binomial test). This indicates a preference for maternal interchromosomal NAHR events causing type-1 *NF1* deletions. Since interchromosomal exchange derives from unequal crossover during meiosis I, the predominance of interchromosomal NAHR events causing type-1 *NF1* deletions confirms that these deletions are predominantly of meiotic origin. By contrast, no significant parent-of-origin bias has been observed for type-2 *NF1* deletions which are mostly of postzygotic origin and mediated by intrachromosomal NAHR (Roehl et al. 2010).

The predominance of maternally derived type-1 *NF1* deletions mediated by interchromosomal NAHR suggests that there are gender-specific differences in the meiotic processes that promote ectopic chromosome synapsis between the LCRs NF1-REPa and NF1-REPc, a prerequisite for NAHR or unequal crossover. Ectopic synapsis between these LCRs is likely to be promoted by specific chromatin conformations which are epigenetically regulated. Early germ cells have been shown to undergo a multitude of epigenetic changes that accompany their development and the onset of meiotic recombination (reviewed by Kota

and Feil, 2010; Sin et al. 2015; Sun et al. 2017; Maezawa et al. 2018). In relation to putative epigenetic differences between male and female germ cells, what is important is that the initiation of meiotic recombination occurs at completely different times during the human male and female lifespans. In human oocytes of the primordial follicle, meiotic recombination is initiated very early on during fetal development and is already complete before birth. Only after a pause of many years do some of these oocytes enter into the first meiotic division upon hormonal stimulation. By contrast, male germ cells are not involved in meiotic recombination during the fetal period but instead remain dormant until hormonally stimulated to further divide in the sexually mature adult (reviewed by El Yakoubi and Wassmann, 2017). Hence, early germ cells are likely to exhibit gender-specific differences in their epigenetically regulated chromatin conformation which could conceivably include the LCRs NF1-REPa and NF1-REPc. One consequence of these differences might be a higher rate of ectopic synapsis and unequal crossover between these LCRs in female germ cells than in their male counterparts resulting in the observed maternal parent-of-origin bias for type-1 *NF1* deletions. An intriguing sexual dimorphism has recently been observed pertaining to the width of the synaptonemal complex in the mouse (Agostinho et al. 2018). The synaptonemal complex is a proteinaceous tripartite, ladder-like structure that links homologous chromosomes and mediates recombination, in particular crossover formation, during meiotic prophase I (reviewed by Zickler and Kleckner, 2015). If gender-specific differences in the synaptonemal complex were also to exist in humans, they could influence the frequency of equal as well as unequal crossovers between certain LCRs. Further studies are now urgently required to address these issues in order to identify the underlying cause(s) of the strong parent-of-origin biases characterizing some CNVs including the type-1 *NF1* deletions studied here.

Conflict of interest

All authors declare that there is no conflict of interest.

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Legend to Figure

Figure 1: Chromosomal origin of type-1 *NF1* deletions as determined by the analysis of microsatellite markers located on chromosome 17 (nucleotide positions given according to hg19) performed in order to determine the parental origin of the deletions and whether they had been caused by interchromosomal NAHR (as in the case of the deletion in patient 450) or intrachromosomal NAHR (as in the case of the deletion in patient SB94).

The analysis of unaffected siblings indicated the phase of the markers and hence the haplotypes of the transmitting parents. The numbers in the coloured columns indicate the lengths of the PCR fragments representing the alleles in the individuals investigated. Markers within the red rectangles are located within the *NF1* microdeletion region. Alleles highlighted in yellow are informative with respect to the parental origin of the deletion. Grey marking denotes alleles that were not informative. del: allele is deleted.

Table 1

Parental origin of 37 *de novo* type-1 *NF1* deletions. The chromosomal origin of 14 deletions was determined by analysis of the siblings of the patients.

Number of deletions of maternal or paternal origin/ total number of deletions		Number of deletions of			
maternal origin	paternal origin	maternal origin mediated by		paternal origin mediated by	
		interchromosomal NAHR	intrachromosomal NAHR	interchromosomal NAHR	intrachromosomal NAHR
33/37 (89.2%)	4/37 (10.8%)	9/11 (81.8%)	2/11 (18.2%)	1/3 (33.3%)	2/3 (66.7%)

Table 2

Parental and chromosomal origin of recurrent pathogenic NAHR-mediated copy number variants (CNVs). CNVs occurring in genomic regions harbouring imprinted genes were not considered.

Disorder [MIM #]	**Disease-causing CNV/ chromosomal region**	**Number of CNVs of maternal or paternal origin/ total number of CNVs investigated (proportion, p-value for the two-tailed binomial test [reference]**	**Number of CNVs of intra- or inter-chromosomal origin/ total number of CNVs investigated**
Williams-Beuren syndrome [194050]	deletion of 1.5 Mb/ 7q11.23	333 maternal /639 (52.1%, p = 0.307), 306 paternal /639 (47.9%) [1]	61/84 (72.6%) interchromosomal 23/84 (27.3%) intrachromosomal [2]
22q11.2 deletion syndrome including Velocardiofacial syndrome [192430] and DiGeorge syndrome [188400]	deletion of 3 Mb/ 22q11.2	219 maternal /389 (56.2%, **p = 0.0148**), 170 paternal /389 (43.8%) [3]	31/34 (91.2%) interchromosomal 3/34 (8.8%) intrachromosomal [6]
		465 maternal /810 (57.4%, **p < 0.0001**), 345 paternal /810 (42.6%) [4]	
		185 maternal /318 (58.2%, **p = 0.0042**), 133 paternal /318 paternal (41.8%) [5]	
Chromosome 16p11.2 deletion syndrome [611913]	deletion of ~550 kb/ 16p11.2	59 maternal /66 (89.4%, **p < 0.0001**), 7 paternal / 66 (10.6%) [7]	26/50 (52%) interchromosomal 24/50 (48%) intrachromosomal [7]
Chromosome 16p11.2 duplication syndrome [614671]	duplication of ~550 kb/ 16p11.2	12 maternal /13 (92.3%, **p = 0.0034**), 1 paternal /13 (7.7%) [7]	7/12 (66.6%) intrachromosomal 4/12 (33.3%) interchromosomal [7]
17q21.31 microdeletion syndrome [610443]	deletion of 500-650 kb/ 17q21.31	12 paternal /20 (60%, p = 0.5034), 8 maternal /20 (40%) [8]	not determined
Smith-Magenis syndrome [182290]	deletion of 3.7 Mb/ 17p11.2	19 maternal /32 (59.3%, p = 0.3771), 13 paternal /32 (40.7%) [9,10]	not determined
Potocki-Lupski syndrome [610883]	duplication of 3.7 Mb/ 17p11.2	23 paternal /41 (56.1%, p = 0.5327), 18 maternal /41 (43.9%) [11]	38/59 (64.4%) interchromosomal 21/59 (35.6%) intrachromosomal [11]
Sotos syndrome [117550]	deletion of 1.9 Mb/ 5q35	18 paternal /20 (90%, **p = 0.0004**), 2 maternal /20 (10%) [12]	6/8 (75%) intrachromosomal 2/8 (25%) interchromosomal [12]
		16 paternal/ 18 (88.9%, **p = 0.0013**), 2 maternal /18 (11.1%) [13]	not determined
Charcot-Marie-Tooth disease type 1A CMT1A [118220]	duplication of 1.5 Mb/ 17p12	32 paternal /34 (94.1%, **p < 0.0001**), 2 maternal /34 (5.9%) [14]	32/34 (94.1%) interchromosomal 2/34 (5.9%) intrachromosomal [14]
Hereditary neuropathy with liability to pressure palsies (HNPP) [162500])	deletion of 1.5 Mb/ 17p12	3 maternal /4 1 paternal /4 [15]	2 intrachromosomal [15]

[**1**] According to Gilbert-Dussardier et al. (1995), Dutly and Schinzel (1996), Perez-Jurado et al. (1996), Urbán et al. (1996), Robinson et al. (1996), Baumer et al. (1998), Bayés et al. (2003), Thomas et al. (2006b), Hobart et al. (2010), Dutra et al. (2011). [**2**] According to Dutly and Schinzel (1996), Urbán et al. (1996), Baumer et al. (1998), Bayés et al. (2003), Thomas et al. (2006b).

[**3**] According to the original results reported by Delio et al. (2013). [**4**] According to the combined original results reported by Delio et al. (2013) and previously reported studies. [**5**] According to the original results of Thomas et al. (2006b) and previously reported studies summarized by these authors. [**6**] According to Baumer et al. (1998), Trost et al. (2000) and Saitta et al. (2004). [**7**] Duyzend et al. (2016). [**8**] Koolen et al. (2008). [**9**] Greenberg et al. (1991). [**10**] Juyal et al. (1996). [**11**] Sun et al. (2013). [**12**] Miyake et al. (2003). [**13**] Visser et al. (2005). [**14**] Lopes et al. (1998). [**15**] Lopes et al. (1997).