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REVIEW

Homozygosity for constitutional chromosomal rearrangements: a systematic review with reference to origin, ascertainment and phenotype

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Chromosomal translocations and inversions are present in ~0.6–1% of individuals. Although the majority are inherited, and the familial transmission across generations is well reported, reports of homozygosity are relatively rare, with most data in the form of individual case reports. A systematic review of all published cases was performed with particular attention to origin, ascertainment and phenotype of the reported homozygosity. A total of 10 cases of Robertsonian translocation (RBT), 6 reciprocal translocation and 19 cases of inversion homozygosity were identified. In RBT homozygosity, the majority of individuals are phenotypically normal, arise from inbreeding within a family that carries a familial translocation, and are ascertained following identification of an existing familial rearrangement rather than any feature specific to the homozygosity. In addition, they are fertile and as expected, their offspring are heterozygous for the translocation. For reciprocal translocations, homozygosity arises in individuals born to related parents from a family who harbor a unique familial translocation. Ascertainment is following investigation of phenotypic abnormalities resulting from consanguinity *per se* and/or the unmasking of a specific gene mutation. For chromosomal inversions, homozygosity may originate from either related or non-consanguinous parentage. Although many cases are ascertained because of an associated phenotypic abnormality, a high proportion of cases are of normal phenotype and a direct causal relationship is uncertain. There are fewer reports of both Robertsonian and inversion homozygosity than may be expected from the relative frequencies of each class within the population.
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INTRODUCTION

Structural chromosomal rearrangements detected under light microscopy fall under three broad categories: Robertsonian translocations (RBTs), reciprocal translocations and chromosomal inversions.[1] Data suggest that such rearrangements are present in ~0.6–1% of individuals, with reported differences dependant on the population studied (for example unselected newborns or selected prenatal or population studies) and the level of banding techniques used.[2–6] Additional considerations include the proportion of balanced versus unbalanced abnormalities and origin of the rearrangement; that is whether inherited or *de novo*. The relative prevalence and the underlying mutations rate vary for each category of rearrangement and for specific types within each category.

RBTs include non-homologous translocations and homologous forms, with non-homologous RBTs being far more common.[1] Non-homologous RBTs are the most common recurrent whole-scale structural chromosomal rearrangement in humans being found in approximately 1 in 1000 live births.[2,5] These arise from whole arm exchanges between the short arms of the acrocentric chromosomes (13–15, 21 and 22) to form a single-metacentric chromosome. Although all 10 possible acrocentric rearrangements have been reported to occur, the distribution within the population is highly non-random with t(13q14q) accounting for over 70% and t(14q21q) for 8%.[7] Reciprocal translocations involve exchanges between non-homologous chromosomes of any form, and while as a group are more common than non-homologous RBTs, with the exception of the well-recognized t(11;22)(q23;q11) translocation, the majority are assumed to be unique.[8] Chromosomal inversions arise from an intrachromosomal break and subsequent intrachromosomal rearrangement, and may be divided into pericentric and paracentric forms based on the position of the breakpoints relative to the centromere.[9–12] The majority of all inversions (66%) are of pericentric type.[12] As with reciprocal translocations, inversions may involve any chromosome and most are considered unique.[9] However, some notable exceptions are reported, and may be considered as normal chromosomal variants. These include the well-documented pericentric inversion inv(9)(p11q13) estimated to occur in 1–3% of individuals,[13,14] and pericentric inversions of chromosome 2; inv(2)(p12q14)—and its variant inv(2)(p11q13).[15] Approximately 90% of all non-homologous RBTs and reciprocal translocations are balanced, with the estimated

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prevalence of balanced chromosomal inversions even higher.[3,8,16–18] Studies suggest that the majority of constitutional rearrangements are inherited; ~60% of non-homologous RBTs; between 65 and 75% of reciprocal translocations and over 90% of inversions.[2,8,16–18]

Although the familial transmission of such rearrangements across generations is well reported, reports of homozygosity are relatively rare, although include examples of all three forms.[19–21] Most data are in the form of individual case reports with description of ascertainment and any associated phenotypic abnormalities, for which great variation exists for individual homozygosities. Of some importance is that homozygosity may be identified during prenatal screening, which may raise clinical and parental concerns regarding the implications of a particular homozygosity.[20,22,23] At present, the data available to counsel parents (and patients) regarding the outcome of any identified homozygosity consists solely of individual case reports or small case series. Although useful, these may have some associated bias because of the presentation of case-specific features. As such, a systematic survey of constitutional homozygosity may be of some assistance. Furthermore, there has been no direct comparison between different classes of rearrangement regarding mode of inheritance, ascertainment or phenotype, which may help identify any rearrangement-specific features. The purpose of this study was to identify all reports of homozygosity where ascertainment and mode of inheritance are reported, with a view to determine any such trends.

MATERIALS AND METHODS

A structured bibliographic search on Medline and EMBASE databases was performed to include the period 1970–2009. Keywords included RBT, reciprocal translocation, inversion, pericentric, paracentric, homozygosity and consanguinity, used in a variety of search strings. References identified were reviewed by he author and supplemented with relevant citations from both the reference lists of the consulted papers and from articles citing such reports.

RESULTS

Robertsonian translocations

A total of nine cases of confirmed RBT homozygosity were identified, involving t(13;14)[19,24–26] and t(14;21).[22,27,28] A further case of t(14;22) homozygosity[29] was also considered with some caveats (Table 1; cases 1–10). Those fully documented show various modes of inheritance and methods of ascertainment although some trends emerge. In the majority of cases, both parents were heterozygous for the specific translocation and each contributed to the subsequent homozygous offspring. In most instances (cases 1–5, 8), there was a consanguinous parental relationship with a familial translocation. These include three siblings (cases 1–3) each heterozygous for t(13;14).[19] Exceptions to this included the sole case of unbalanced homozygosity (case 9), that of translocation Down's syndrome, where the parents were unrelated but each heterozygous for t(14;21),[28] and case 7 where only the father was heterozygous, with the second rearrangement arising *de novo*.[22]

For all cases of balanced homozygosity fully reported, ascertainment was following cytogenetic investigation prompted by the presence of an existing RBT within a family member, rather than any specific clinical concern. In all such cases, the proband was phenotypically normal.[19,22,24,25,27,29] These include a t(13;14) homozygote identified following an extensive pedigree analysis on a large kindred from an isolated community in Finland (case 4), where data inferred a familial t(13;14) translocation transmitted through nine generations.[24] RBT homozygotes are fertile, as seen in cases 1 and 6, producing one and six children, respectively, with unrelated and karyotypically normal partners. Each child, as may be expected was heterozygous for the RBT.[19,24] A third case of successful fertility may include the additional

Table 1 Homozygosity for Robertsonian translocations

Case	*Karyotype*	*Ascertainment*	*Parental relationship/karyotype*	*Phenotype*	*Additional comments*
1[19]	44,XX,der (13;14) der (13;14)	Husband (normal karyotype) with subfertility	First cousins; each heterozygous for t(13;14)	Normal; one previous spontaneous miscarriage	Mother of phenotypically normal heterozygote
2[19]	44,XY,der (13;14) der (13;14)	Sister with known t(13;14) homozygosity	First cousins; each heterozygous for t(13;14)	Normal	
3[19]	44,XY,der (13;14) der (13;14)	Sister with known t(13;14) homozygosity	First cousins; each heterozygous for t(13;14)	Normal	
4[24]	44,XX,der (13;14) der (13;14)	Pedigree analysis of extensive kindred with known familial t(13;14)	Third cousins once removed; each heterozygous for t(13;14)	Normal	Mother of six phenotypically normal heterozygotes
5[25]	44,XX,der (13;14) der (13;14)	Brother heterozygous for t(13;14) with UPD(14)	First cousins; each heterozygous for t(13;14)	Normal	
6[26]	44,XY,der (13;14) der (13;14)	Prenatal screening	Not known	Not known	
7[22]	44,XX,der (14;21) der (14;21)	Prenatal screening; sister with known unbalanced t(14;21)	Not related; father heterozygous for t(14;21)	Normal	Assumed *de novo* t(14;21) translocation in maternal germ cell; elective termination
8[27]	44,XY,der (14;21), der (14;21)	Prenatal screening; parents and sister confirmed as heterozygous for t(14;21)[30]	First cousins; each heterozygous for t(14;21)	Normal	
9[28]	45,XY,der (14;21), der (14;21)+21mat	Clinical phenotype of Down's syndrome	Not related; each heterozygous for t(14;21)	Down's syndrome	Biparental inheritance of t(14;21) with maternal free chromosome 21
10[29]	44,XY,der (14;22), der (14;22)	Pedigree analysis[a]	Third cousins; each heterozygous for t(14;22)[a]	Normal	Eight offspring; all heterozygous for t(14;22)

Abbreviation: UPD, uniparental disomy.
[a]Unconfirmed and inferred from pedigree analysis of extensive kindred with known familial t(14;22).

report of homozygosity (case 10) inferred from pedigree studies.[29] This reported a large kindred with a t(14;22) translocation documented over three generations, with an inferred transmission through the previous five, where a male in generation IV was the son of related parents each with inferred carrier status. This individual fathered five sons and three daughters, each with documented heterozygosity for t(14;22). The authors speculated that this was as a consequence of homozygosity.[29] However, as an excess of heterozygotes from a carrier is recognized, homozygosity in this case remains uncertain.

Chiefly, with the exception of a single-unbalanced translocation (case 9), homozygosity was determined for reasons other than an identifiable pathology. Three cases (6–8) were ascertained during prenatal screening.[22,26,27] Case 7 represents the first published report of RBT homozygosity, with fetal t(14;21) homozygosity ascertained after diagnosis of paternal t(14;21) heterozygosity through family cytogenetic analyses because of an earlier child born with significant motor and mental abnormalities and abnormal karyotype. This marriage was non-consanguinous and the mother was of normal karyotype. In this case, parental anxiety over the implications of homozygosity in the fetus led to an elective termination, although the fetus was phenotypically normal on necropsy.[22] This outcome is in contrast to case 8. In this, the related parents were each known carriers of a familial t(14;21) inherited from their fathers, with an existing child heterozygous for this translocation.[30] During a subsequent pregnancy, chorionic villus sampling showed a male fetus homozygous for t(14;21). In this case, the physicians, in part guided by the outcomes observed in earlier reports of homozygosity,[19,22,24] counseled continuation of the pregnancy and a healthy, phenotypically normal child was delivered.[27]

Two cases were ascertained following sibling karyotypic or phenotypic abnormalities.[22,25] In case 5, a phenotypically normal female t(13;14) homozygote was discovered following analysis of a younger brother in which t(13;14) heterozygosity was the cause of uniparental disomy 14.[25] The other was of the electively terminated phenotypically normal fetus described above (case 7).[22] In only one case was RBT homozygosity ascertained because of a phenotypical abnormality in the proband, that of case 9, who, as outlined above, also carried an unbalanced translocation.[28]

Reciprocal translocations

Six reports of homozygosity for a reciprocal translocation were identified, involving five different translocations; t(Y;22); t(3;16); t(17;20); t(7;12) and t(10;11) (Table 2; cases 11–16).[20,31–34] In each instance, a consanguinous parental relationship existed, with each parent being heterozygous for the translocation. Furthermore, with the exception two siblings (cases 13–14), no cases involved the same translocation. In all cases, ascertainment was following cytogenetic investigations prompted by an abnormality in prenatal studies or in the postnatal proband. The effect of reciprocal translocation homozygosity on phenotype varied, with most abnormalities a direct outcome specific to the rearrangement.

Two cases were diagnosed prenatally. This included the earliest report of reciprocal translocation homozygosity (case 11), that of a t(Y;22), identified following amniocentesis for severe intrauterine growth retardation. In this case, the rearrangement involved the acrocentric chromosome 22, which also carried a portion of the long arm of the Y chromosome, a rare but recognized phenomenon feature in the heterozygous state, which in this case was inherited from both heterozygous father and mother.[20] Although delivered preterm, the infant showed subsequent normal development, and no specific association between the translocation and the prenatal abnormalities can be made. Another, case 12, involved a fetus homozygous for a balanced t(17;20) translocation, where diagnosis followed the detection of cardiac and facial abnormalities on ultrasound.[31] Elective termination was performed with multiple abnormalities detected at autopsy, which may have resulted from either the presence of an unidentified recessive gene or gene disruption on either of the involved chromosomes.

Three cases (13–15) were ascertained postnatally during work up for congenital single gene disorders, where homozygous inactivation of specific genes directly led to an abnormal phenotype.[32,33] In cases 13 and 14, homozygosity for t(7;12) was discovered after evaluation and diagnosis of a rare neurodevelopmental disorder, lissencephaly with cerebellar hypoplasia.[32] The parents were phenotypically normal heterozygote first cousins, with a history of previous episodes of miscarriage. Subsequent molecular analyses showed homozygous inactivation of the *RELN* gene, which is located near the translocation breakpoint at 7q22 in both affected children. Additional investigations of the mother showed reduced presence of RELN product consistent with reduced gene dosage because of heterozygosity for t(7;12).[32] In case 15, an infant presented with congenital sensorineural hearing loss, whose consanguinous parents reported a history of both successful pregnancy and previous spontaneous abortions.[33] Banding analysis of the family showed homozygosity for a t(10;11) in the affected child

Table 2 Homozygosity for reciprocal translocations

Case	*Karyotype*	*Ascertainment*	*Parental relationship/karyotype*	*Phenotype*	*Additional comments*
11[20]	46,XX,t(Y;22),t(Y;22)	Prenatal screening; severe IUGR	Third cousins once removed; each heterozygous for t(Y;22)	Normal	Healthy postnatal development
12[31]	46,XX,t(17;20),t(17;20)	Prenatal screening; cardiac/facial abnormalities detected on US	First cousins; each heterozygous for t(17;20)	Multiple developmental abnormalities	Elective termination; an older brother was of normal karyotype
13[32]	46,XX,t(7;12),t(7;12)	Severe neurodevelopmental disorder (LCH)	First cousins; each heterozygous for t(7;12)	LCH; homozygous inactivation of the *RELN* gene	
14[32]	46,XX,t(7;12),t(7;12)	Severe neurodevelopmental disorder (LCH)	First cousins; each heterozygous for t(17;12)	LCH; homozygous inactivation of the *RELN* gene	
15[33]	46,XY,t(10;11),t(10;11)	SNHL	First cousins once removed; each heterozygous for t(10;11)	Non-syndromic SNHL; homozygous inactivation of the *PDZD7* gene	Four siblings each heterozygous for t(10;11)
16[34]	46,XX,t(3;16),t(3;16)	Infantile seizures	Second cousins once removed; each heterozygous for t(3;16)	Mild dysmorphic features	

Abbreviations: IUGR, intrauterine growth retardation; LCH, lissencephaly with cerebellar hypoplasia; SNHL, congenital sensorineural hearing loss.

with both parents and four siblings each heterozygous. Molecular studies showed that the translocation led to disruption of the *PDZD7* gene located near the translocation breakpoint on chromosome 10. Both parents showed some hearing impairment with the authors, suggesting that haplo-insufficiency because of t(10;11) heterozygosity may have some impact on hearing function.[33] In Case 16, cytogenetic evaluation showed homozygosity for t(3;16) in an infant who presented with severe seizures and mild-dysmorphic features, which may represent a consequence of consanguinity rather than the translocation itself.[34]

Chromosomal inversions

Nineteen reports of homozygosity for a chromosomal inversion were identified (Table 3). As might be expected, the majority were of homozygosity for pericentric inv(9).[21,23,35–43] However, reports of homozygosity for pericentric inv(2),[44] inv(4),[45] inv(3)[46] and also for a paracentric inv(12)[47] also exist. Analysis of mode of inheritance showed various patterns of origin and ascertainment. Of the cases of pericentric (inv)9 homozygosity (cases 17–30), 50% showed inheritance from related parents, each of whom were inversion heterozygotes.[21,35–38] In most cases, where no parental relationship

Table 3 Homozygosity for chromosomal inversions

Case	*Inversion homozygosity*	*Ascertainment*	*Parental relationship; karyotype*	*Phenotype*	*Additional comments*
17[21]	Pericentric inv(9)	Half-sister known heterozygote	Second cousins; each heterozygous for inv(9)	Normal	Three siblings each heterozygous for inv(9)
18[23]	Pericentric inv(9)	Prenatal screening; advanced maternal age	Not related; each heterozygous for pericentric inv(9)	Normal	
19[23]	Pericentric inv(9)	Prenatal screening; severe IUGR	Not related; each heterozygous for pericentric inv(9)	Died in utero	UPD for chromosome 9 excluded
20[35]	Pericentric inv(9)	Mother known heterozygote; siblings with developmental abnormalities	Fourth cousins; each heterozygous for inv(9)	Mental retardation with psychomotor disability; hyperglycinemia	One surviving sibling heterozygous for inv(9)
21[36]	Pericentric inv(9)	Ambiguous genitalia	Consanguinous; specific relationship inferred from extensive family pedigree; father homozygous/mother heterozygous for inv(9)		One brother with similar phenotype heterozygous for inv(9); one phenotypically normal sister heterozygous for inv(9)
22[36]	Pericentric inv(9)	Father of above	Inferred consanguinity; each heterozygous for pericentric inv(9)	Normal	Five offspring; one homozygous and four heterozygous for inv(9)
23[37]	Pericentric inv(9)	Genital abnormality	First cousins once removed; each heterozygous for inv(9)		
24[38]	Pericentric inv(9)	Extensive neuromuscular, ocular and intracranial developmental abnormalities	First cousins; each heterozygous for inv(9)	Walker–Warburg syndrome	
25[39]	Pericentric inv(9)	Cytogenetic study following stillbirth	Non-consanguinous; each heterozygous for inv(9)	Normal	
26[40]	Pericentric inv(9)	Prenatal screening; advanced maternal age	Second cousins three times removed; each heterozygous for inv(9)	Normal	
27[40]	Pericentric inv(9)	Prenatal screening; advanced maternal age	Non-consanguinous; each heterozygous for inv(9)	Normal	
28[41]	Pericentric inv(9)	Ocular abnormalities and developmental delay	Non-consanguinous; each heterozygous for inv(9)	Ocular abnormalities and developmental delay	
29[42]	Pericentric inv(9)	Multiple developmental abnormalities	Non-consanguinous; each heterozygous for inv(9)	Cornelia de Lange syndrome	
30[43]	Pericentric inv(9); low level of trisomy 9 mosaicism	Mental retardation with dysmorphic features	Non-consanguinous; mother heterozygous for inv(9); father with normal karyotype	Mental retardation with dysmorphic features	All copies of chromosome 9 are of maternal origin; UPD 9mat
31[44]	Pericentric inv(2)	Prenatal screening; advanced maternal age	Consanguinous; specific relationship unreported; each heterozygous for inv(2)	Normal	
32[44]	Pericentric inv(2)	Following diagnosis of homozygosity of sibling	Consanguinous; specific relationship unreported; each heterozygous for inv(2)	Normal	
33[45]	Pericentric inv(4)	Neurodevelopmental delay	Non-consanguinous; mother heterozygous for inv(2); father not karyotyped	Neurodevelopmental delay; hearing loss	
34[46]	Pericentric inv(3)	Mental retardation		Mental retardation	Sibling with mental retardation heterozygous for inv(9)
35[47]	Paracentric inv(12)	Severe neurodevelopmental delay	First cousins; each heterozygous for inv(12)	Neurodevelopmental delay	Phenotypically normal sibling heterozygous for inv(12)

Abbreviations: IUGR, intrauterine growth retardation; UPD, uniparental disomy.

existed, both parents were inversion heterozygotes.[23,39–42] In case 30, where the mother was heterozygous for inv(9), and the father of normal karyotype, the homozygosity and accompanying low level of trisomy 9 mosaicism was determined to be due to uniparental disomy with all copies of this chromosome being of maternal origin.[43] Ascertainment for inv(9) homozygosity was made after prenatal diagnosis in four cases (18, 19, 26 and 27), most commonly after routine amniocentesis for advanced maternal age. In these instances, the homozygotes were phenotypically normal.[23,40] In case 19, severe intrauterine growth retardation developed, which prompted cytogenetic studies, and this fetus died in utero.[23]

Six cases were ascertained following evaluation of a variety of developmental abnormalities, which included genital abnormalities (cases 21 and 23), mental retardation (case 30) and more severe neurodevelopmental defects (cases 24, 28 and 29). Three inv(9) homozygotes were discovered after diagnosis of heterozygosity or homozygosity in a family member (cases 17, 20 and 22). Of these, cases 17 and 22 were phenotypically normal,[21,36] with case 20 showing mental retardation with psychomotor disability, possibly associated with a co-existent hyperglycinaemia.[35] In case 22, the only instance where the fertility of a known inv(9) homozygote is documented, this individual (with his consanguinous heterozygous partner) has fathered five children (one homozygote and four heterozygotes).[36]

Of the less common inversions, two cases of inv(2) homozygosity were identified, in two siblings born to related heterozygous parents.[44] Ascertainment was following amniocentesis for advanced maternal age, with demonstration of fetal homozygosity in case 31, prompting cytogenetic analysis and confirmation of homozygosity in the elder sibling (case 32). Both homozygotes were of normal phenotype.[44] The individual cases of inv(4), inv(3) and paracentric inv(12) homozygosity were each ascertained following investigation of neurodevelopmental abnormalities in the proband.[45–47] In case 33, with inv(4) homozygosity, the parents were unrelated and only the mothers heterozygous state was confirmed.[45] In case 35, that of paracentric inv(12) homozygosity, the heterozygous parents were related.[47]

DISCUSSION

It should be recognized that reports of homozygosity for constitutional chromosomal rearrangements are rare, as evident in the relatively low number of cases identified. Although this precludes any formal statistical analysis, some general observations may be made. RBT homozygosity was seen chiefly for the most common translocations t(13;14) and t(14;21), which probably represents the greater frequency of heterozygotes for these RBTs in the population.[7] The majority of individuals with RBY homozygosity are phenotypically normal, arise from inbreeding within a family that carries a familial RBT, and are ascertained following identification of an existing familial rearrangement rather than any feature specific to the homozygosity. In addition, they are fertile and as expected, their offspring are heterozygous for the RBT. This is important to acknowledge, given the likelihood of future cases being identified, and the contrasts in clinical decision making described above.[22,27]

Reciprocal translocation homozygosity arises in individuals born to related parents from a family who harbor a unique familial translocation. Ascertainment is following investigation of phenotypic abnormalities, resulting from consanguinity *per se* and/or the unmasking of a specific gene mutation. This may be expected as reciprocal translocations, although common, remain unique in the population, with most inherited by descent and so remain within families.[10] For the one exception to this generality, that of the t(11;22) translocation that is recurrent among different ancestries,[48] and so could arise through a non-consanguinous relationship, no cases of homozygosity were identified.

Inversion homozygosity may arise from either consanguinous or unrelated parentage, and ascertainment is often following investigation of a co-existing phenotypic abnormality. However, such features may be coincidental, and the causal relationship between a chromosomal inversion (in either the heterozygous or homozygous state) has been the subject of earlier discussion.[23,36,40] In this, mention has been made of the relative frequency in the population, proportion of cases of normal phenotype, the variety of phenotypic abnormalities seen when present, and the potential role of consanguinity as a cause of these rather than any direct effect of homozygosity *per se*. The findings of this study would seem to be in agreement with previous authors that no direct association exists. For the most frequent inversion, inv(9), homozygosity arose both within an inbred pedigree and from unrelated parents in equal numbers. This in part may reflect the relatively high frequency of this rearrangement in the population.[16,17] In most cases, the parents were inversion heterozygotes, and this is in keeping with the view that *de novo* mutation of inv(9) is rare.[49]

It is worth commenting on the relative rarity of reports identified. Although few cases of reciprocal translocation homozygosity may be expected, the limited number of reports for RBT and inversion homozygosity requires some consideration. Whether this represents a genuine rarity for such homozygosity or is due to underreporting is uncertain. For example, if one assumes a frequency for t(13;14) of 7 in 10 000 in the normal population,[11] then the probability of homozygosity in random mating between unrelated individuals is $\sim 1.2\times10^{-7}$ ($0.0007\times0.0007\times0.25$). This is in effect approximately 1 in 8 200 000 conceptions, and if one accepts that RBT homozygotes are phenotypically normal, then one may expect a similar frequency of homozygous liveborns. Indeed, this figure may be slightly greater as a result of meiotic drive favoring the production of balanced gametes carrying the translocation in the maternal line.[50] In a similar manner, there is perhaps an even greater paucity of reports for chromosomal inversion homozygosity, particularly for pericentric inv(9), the most common constitutional rearrangement in man and considered a normal variant. This has been commented on previously by Cotter *et al.*,[23] who calculated that the frequency of such homozygosity should be from 1 in 3000 to 1 in 82 000 depending on ethnic background. Such low numbers of reports for homozygosity may have various explanations. The balanced RBT homozygotes identified show no phenotypic abnormalities and 50% of inv(9) were also of normal phenotype. As such, it is likely that many of all such homozygotes remain unidentified. However, it should be considered that cases of homozygosity may be recognized but not reported. This may be influenced by patterns in the medical literature whereby publication of case reports, in general, is becoming less common, and/or more difficult (whether real or perceived). Perhaps this may limit the number of reports submitted for publication, especially if the subjects are of normal phenotype. It is of interest to note that for RBTs, only two full reports of homozygosity have been published since 1989, and each of these was ascertained because of an unbalanced karyotype and abnormal phenotype either in the proband[28] or (heterozygous) sibling.[25] One of the t(13;14) homozygotes included in this study was ascertained during a larger prenatal study to identify fetal carriers of an RBT at risk of uniparental disomy, with this case mentioned only briefly within the data.[26] As such, any possible underreporting of translocation or inversion homozygosity cases may reflect, in part, the lack of a suitable forum for which such information may be deposited and made available.

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