ORIGINAL ARTICLE

Redefining the risks of prenatally ascertained supernumerary marker chromosomes: a collaborative study

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A supplementary appendix is available at <http://www.jmedgenet.com/supplemental>

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Background: A marker chromosome is defined as a structurally abnormal chromosome that cannot be identified by routine cytogenetics. The risk for phenotypic abnormalities associated with a marker chromosome depends on several factors, including inheritance, mode of ascertainment, chromosomal origin, and the morphology, content, and structure of the marker.

Methods: to understand the karyotype-phenotype relationship of prenatally ascertained supernumerary de novo marker chromosomes, we combined data from prenatal cases obtained from 12 laboratories with those from studies in the literature. We were able to obtain cytogenetic and phenotypic data from 108 prenatally ascertained supernumerary de novo marker chromosomes to refine the phenotypic risk associated with these markers. Because of the growing number of cases and because more techniques are available to delineate marker morphology, we have been able to group risk estimates into subcategories, such as by marker type and whether there are ultrasound abnormalities.

Results: If a de novo supernumerary marker chromosome is found prenatally, our data suggest there is a 26% risk for phenotypic abnormality when there is no other information defining the marker (such as chromosomal origin or information about the existing phenotype). However, if high resolution ultrasound studies are normal, this risk reduces to 18%.

Conclusions: Our findings strongly support the value of additional genetic studies for more precisely defining the risk in individual cases involving marker chromosomes.

A marker chromosome is defined as a structurally abnormal chromosome that cannot be identified by routine cytogenetics. Examples of marker chromosomes include unidentified rings, derivatives, dicentrics, and minute chromosomes. Supernumerary marker chromosomes are found at a rate of 0.14–0.72 per 1000 newborns and more commonly in prenatal testing at a rate of 0.65–1.5 per 1000.¹ The risk for phenotypic abnormalities associated with a marker chromosome depends on several factors, including inheritance, mode of ascertainment, chromosomal origin, and the morphology, content, and structure of the marker.

Some markers are inherited directly from a phenotypically normal parent. In such cases, there are often no phenotypic consequences for individuals who inherit the marker. However, there are exceptions to this, such as when there are imprinting effects from uniparental disomy (UPD), or low level, tissue specific mosaicism for the marker chromosome in a parent without phenotypic manifestations.^{1–4}

Most marker chromosomes ascertained postnatally are associated with a phenotypic abnormality. Marker chromosomes ascertained prenatally are problematic because only a proportion of cases will have associated phenotypic abnormalities.

There are numerous case reports and collections of cases of particular types of marker chromosomes and associated phenotypes. However, for purposes of risk estimation, the most useful studies are those that collect data from consecutive chromosomal analyses with no bias towards clinical presentation. The first major study to offer general risk figures for marker chromosomes analysed data from over 377 000 amniocenteses.⁵ Based on 133 prenatal cases

involving marker chromosomes, that study suggested an overall 13% risk for phenotypic abnormalities in prenatally ascertained, de novo cases of supernumerary marker chromosomes. However, the study was completed before the advent of fluorescence in situ hybridisation (FISH) technology, which limited the ability to fully characterise the markers.

The largest study since Warburton⁵ to characterise the risk for phenotypic abnormalities was completed by Crolla.⁶ Utilising FISH analysis and combined data from reported cases of autosomal supernumerary marker chromosomes (168 cases in total and 68 prenatal cases), markers were stratified and studied. This study excluded common markers that were often associated with phenotypic abnormalities, such as those derived from chromosome 15, the markers derived from chromosome 22 associated with cat-eye syndrome, and isochromosomes 9, 12, and 18. In addition to providing information about markers derived from specific chromosomes, Crolla confirmed that most marker chromosomes originate from acrocentric chromosomes (chromosomes 13, 14, 15, 21, and 22). Even excluding chromosome 15 derived markers, the remaining acrocentric chromosomes still accounted for 60% of the markers. In addition, markers derived from the acrocentric chromosomes were much less likely to be associated with a phenotypic abnormality (7.1% v 28.6%).

Abbreviations: CVS, chorionic villi sampling; FISH, fluorescence in situ hybridisation; IUFD, intrauterine fetal demise; SAB, spontaneous abortion; TAB, therapeutic abortion; UPD, uniparental disomy

Over the past decade, molecular techniques have aided in the characterisation of marker chromosomes. However, little is yet known about the exact significance of many supernumerary marker chromosomes. This is extremely problematic, especially in cases of markers ascertained prenatally. With the sequencing of the human genome, a vast array of single copy and repetitive probes has become available to evaluate the structure of the markers and relate the structure to the phenotypic significance of these chromosomes.

In a collaborative effort, we collected over 700 cases involving marker chromosomes, ascertained either prenatally or postnatally. Molecular techniques (using PCR with microsatellite markers) and molecular cytogenetic techniques (FISH with yeast artificial chromosomes, bacterial artificial chromosomes, and cosmids) were used to characterise the markers. We sought to confirm or update the currently accepted phenotypic risks when a marker is ascertained prenatally. These additional studies should also allow us to group types of markers by morphology and chromosomal origin.

METHODS

Twelve laboratories provided information on cases involving marker chromosomes ascertained since 1990. This information was combined with data from published studies. We included only large published collections of cases involving prenatal marker chromosomes, rather than individual case studies, to minimise bias of ascertainment. We asked the contributing collaborators to include information from any marker chromosome, including those derived from the sex chromosomes and those such as iso(12p) and iso(18), even though these are not truly marker chromosomes because they can often be reliably identified by G-banding. However, most of these markers were excluded when making phenotype-genotype correlations, as described below. We asked for information regarding ascertainment, inheritance, and phenotypic abnormalities, and FISH studies were performed to characterise the marker chromosomes. We also asked whether the case had been published previously, in an attempt to eliminate duplication.

Exclusion criteria and assumptions

Like authors of similar studies, we fully appreciated the risk of bias of ascertainment when collecting retrospective data on chromosome abnormalities. Therefore, we have attempted to describe in detail how the cases were ascertained and why certain cases were excluded.

Numerous cases involving marker chromosomes were originally referred to the contributing laboratories to delineate the chromosomal abnormality found at another laboratory. It is thought that such cases could cause a bias of ascertainment, as it is likely that more cases involving phenotypic abnormalities or unusual chromosome abnormalities would be referred for additional studies. We only included such cases if we were able to determine the original reason for referral and were certain that the case was not duplicated in the literature.

We excluded cases that involved a supernumerary marker chromosome in addition to another chromosomal or molecular abnormality, such as 48,XX, +21, +mar, or Fragile X syndrome. Markers that were determined to be derivative chromosomes as the result of an unbalanced gamete of a parent who has a balanced translocation were also excluded because these would usually be associated with an abnormal phenotype.

The study by Warburton³ excluded any case that had an abnormality detected by prenatal ultrasound as it was felt that this would create a bias. We chose not to exclude cases with ultrasound abnormalities but rather calculated two

separate risk estimates, with or without these cases. In general, if the ultrasound abnormality was the perceived basis for the prenatal chromosome analysis, the case was grouped as having possible bias. If ultrasound findings were detected during or after an amniocentesis or chorionic villi sampling (CVS), the case was considered to have an unbiased abnormal phenotype. If we were unable to obtain a definite reason for referral, but the case had an abnormal phenotype, we assumed that the reason for referral was likely to be an abnormal ultrasound and was therefore biased. If no reason for referral was noted for cases with a normal phenotype, we assumed the reason for referral must be one that would be unbiased, such as advanced maternal age or an abnormal triple or quadruple marker screen.

Several prenatal cases were referred because of a previous child with an abnormality (either chromosomal or physical). Unless the previous abnormality was also associated with a marker chromosome, these cases were not excluded as there should be no association between the previous abnormality and the current marker chromosome.

Cases in which the marker chromosome was found during an analysis of fetal tissue after a spontaneous abortion (SAB) or intrauterine fetal demise (IUFD) were not included in either risk estimate, because the cases were not comparable to those detected via prenatal diagnosis. If an SAB, IUFD, or therapeutic abortion (TAB) occurred after the amniocentesis or CVS, the case was included only if there was a documented ultrasound or autopsy providing some phenotypic information.

If an ultrasound (most of which were high resolution ultrasounds carried out in the second trimester) was normal and we obtained no additional information after birth, we counted the case as having a normal phenotype. We acknowledge that an ultrasound will not detect all physical abnormalities and cannot detect any developmental abnormalities, so this risk should be taken as a minimal risk figure. It is difficult to know whether "soft" ultrasound findings such as isolated choroid plexus cysts, pyelectasis, echogenic bowel, shortened limb long bones, etc, should be considered abnormal. For the purposes of our study, we did not include such ultrasound findings as abnormal if they were isolated abnormalities. In addition, if one of these soft ultrasound findings was the primary basis for the prenatal study, we chose not to count that referral as biased. The majority of clinical assessments were carried out at birth and thus did not include developmental assessments. Only in rare circumstances were any developmental assessments carried out when the subjects were older.

Cases without any phenotypic information were excluded from risk estimates even if they involved marker chromosomes not expected to have clinical consequences. Although it was tempting to count these cases as normal, if we had no documented phenotypic information on the case, we did not assume it had a normal phenotype and the case was excluded from all phenotypic risk estimations. On the other hand, there were several types of non-mosaic marker chromosomes that are felt to result in phenotypic abnormalities without exception. These marker chromosomes include isochromosomes of 9p, 9q 12p, 18p, and 18q, markers derived from chromosome 22 associated with cat-eye syndrome, and markers derived from chromosome 15 that were found to contain at least one of the following FISH probes within the critical region for Prader-Willi/Angelman syndromes: SNRPN, D15S10, D15S11, or GABRB3. Cases involving these types of chromosome abnormalities were excluded from this study because they are either cytogenetically identifiable or easily identified using FISH studies that would confirm their relatively well-documented association with abnormalities.

A total of 38 cases reported by Crolla⁶ were also used in our study. Some of the prenatal cases that could not be included did not offer an original reason for referral. In addition, there were several cases (15) from the Crolla study that were ascertained through a consecutive liveborn study. Because they were not ascertained prenatally, these cases were excluded from all prenatal calculations.

Chromosomal morphology

Previous studies have grouped marker chromosomes by morphology, but had limited those groupings to such labels as dot markers, acrocentrics, and non-acrocentrics.^{5,6} The expanded use of FISH technology has allowed us to group markers into more descriptive labels, which provided additional information when ascertaining a certain type of marker chromosome prenatally. The different morphology groups are listed below in table 1.

Several assumptions were necessary to complete this grouping. In cases involving markers derived from the acrocentric chromosomes, if there was no information about whether the marker was dicentric or monocentric, we assumed it was monocentric. In cases where there was no information about the morphology, the marker chromosome was labelled as a "marker" (morphology group 6). A marker was grouped as a "ring" only if a "doughnut" or circular appearance was seen or if that was how the marker was described in the literature. "Dot" markers and "minutes" were grouped as "markers" (group 6). As stated above, familial derivative marker chromosomes (group 11) and markers that were associated with an additional chromosomal or molecular abnormality (group 12) were excluded from this study.

RESULTS

In total, 733 cases were obtained from 12 laboratories and the recent literature. After the initial exclusion as described above, 264 prenatal cases remained. Of these, there was no phenotypic information on 79 and parental chromosomes were not studied in 56, leaving 138 prenatal cases of de novo supernumerary marker chromosomes for this study. Of these, 30 had no useful phenotypic information and could not be used. Therefore, most of the information from this study was gained from 108 prenatal cases involving supernumerary de novo marker chromosomes. Of these cases, 38 were obtained from the review by Crolla,⁶ 15 were from reports published since the Crolla review,⁷⁻¹⁷ and 55 were new cases from the

collaborating laboratories (see supplementary information on abnormal phenotypes at www.jmedgenet.com/supplemental).

Of the remaining 108 prenatal cases, 80 had no documented phenotypic abnormalities (13 were TABs with normal autopsies and one was a TAB with a normal ultrasound). The other 28 cases (nine were TABs and one was an IUFD after an amniocentesis) had abnormalities detected during ultrasound, at birth, or by autopsy. This results in a 26% (28/108) minimum risk of abnormality at the time of amniocentesis for prenatally ascertained supernumerary de novo marker chromosomes.

If cases ascertained because of ultrasound abnormalities are excluded, the number of abnormal cases is reduced from 28 to 17. Therefore, the minimum risk for phenotypic abnormality at the time of amniocentesis, if there are no detectable ultrasound findings, is 18% (17/97).

We excluded all cases that were part of morphology groups 11 (result of an unbalanced gamete from a parental rearrangement) and 12 (marker is associated with another chromosome abnormality). This was done because it is assumed that almost all of these markers would be associated with an abnormal phenotype, which was confirmed when reviewing our data from the excluded prenatal and postnatal cases involving these morphology types (data not shown). Also excluded were all non-mosaic cases involving markers that were isochromosomes of 9, 12, and 18 and the markers derived from chromosome 15 with at least one FISH signal from the Prader-Willi/Angleman syndrome critical region (SNRPN, GABRB3, D15S10, or D15S11 probes) because these have previously been shown in many studies to be associated with abnormalities.

A total of 61% (66/108) of cases involved mosaicism with a normal cell line. The phenotypically abnormal cases involved mosaicism in 64% (18/28) of cases, while the cases with no known phenotypic abnormalities were mosaic in 60% (48/80) of cases, showing that there was no statistical difference in frequency of mosaicism between these two groups.

Table 2 shows the risks for abnormality based on different morphology for all prenatally ascertained marker chromosomes.

DISCUSSION

This study has provided additional information for cases of prenatally ascertained marker chromosomes. In general, the risk estimates provided in this study appear to support the risk figures provided by previous authors.^{5,6} For example, the study by Warburton⁵ suggested the risk of phenotypic abnormality was 10.9% and 14.7% for supernumerary de novo satellited (acrocentric) and non-satellited (non-acrocentric) marker chromosomes, respectively, while Crolla⁶ suggested a 7% and 28% risk for the same type of markers. Our data show that there is an 18% (7/40) risk for supernumerary satellited (morphology groups 1-4) markers and a 31% (21/68) risk for non-satellited markers (groups 5-9). However, it is important to note that these studies had different inclusion criteria. Some of these differences are described in table 3.

Better technology has allowed a more detailed assessment based on chromosome morphology and ultrasound findings. Our data suggest that there is at least a 26% (28/108) risk for phenotypic abnormality for any non-sex chromosome de novo supernumerary marker chromosome. This figure is higher than that reported by Warburton⁵ (10.9%–14.7%), but this can be explained partially by the fact that Warburton's study excluded any case that showed an ultrasound abnormality. We chose to provide an alternative risk figure when such cases were excluded. After removing any case that was at least partially referred for prenatal study because of an ultrasound abnormality, the minimum risk for phenotypic

Table 1 Marker morphology subgroups

1. Bisatellited and dicentric (includes isodicentric and pseudodicentric)
2. Bisatellited and tricentric
3. Bisatellited and monocentric
4. Monosatellited and monocentric
5. Ring
6. Marker, unrecognised structure
7. Acentrics
8. Isochromosomes that are monocentric but not from an acrocentric chromosome
9. Isodicentric but not acrocentric
10. When two markers are found in the same sample. If both markers are derived from the same chromosome, they are included in the appropriate category above because the additional markers are likely the result of a mitotic error.
11. Familial derivative (result of an unbalanced gamete from a parental rearrangement)
12. When a marker is associated with another chromosome abnormality (that is, 48,XY, +21, +mar)

Table 2 Risk for phenotypic abnormality

Supernumerary marker type	Normal outcome	Abnormal outcome	Risk for abnormality	Risk for abnormality after normal ultrasound
1. Bisatellited and dicentric	15	4	21%	6%
2. Bisatellited and tricentric	0	0	–	–
3. Bisatellited and monocentric	15	3	17%	17%
4. Monosatellited and monocentric	3	0	0%	0%
5. Ring	13	10	44%	32%
6. Markers, unrecognised structure	31	7	18%	14%
7. Acentric	3	2	40%	0%
8. Isochromosomes (not acrocentric)	0	1	100%	100%
9. Isodicentric	0	0	–	–
10. Multiple markers in one sample	0	1	100%	100%
Totals	80	28	26%	18%

abnormality when a marker was found prenatally was reduced from 26% to 18% (17/97). Therefore, if no information is known about a marker chromosome and there was a normal ultrasound, the minimum risk for phenotypic abnormality was 18%. Our risk estimates were also higher than those proposed by Crolla⁶ (7–28%), probably because, unlike Crolla, we excluded all familial cases and only excluded certain markers derived from chromosome 15 (those that had the critical region for Prader-Willi/Angelman syndromes).

As can be seen from table 2, some morphology groups of marker chromosomes had a higher risk for abnormality. Ring chromosomes have been associated with abnormal phenotypes, most likely due to the large amount of genetic material that must be present in order for the marker to show this ring appearance. Other cases that had higher risks for abnormality include markers that were bisatellited dicentrics, acentrics, and isodicentrics. This was not surprising as these cases had only euchromatin (in the case of most acentrics) or had euchromatin in addition to one or two centromeres. On the other hand, cases with marker chromosomes that could not be further delineated by morphology (morphology group 6) typically had a lower risk for abnormality (18%). Therefore, if a marker can be proven to be monocentric and non-satellited, and does not have a ring appearance, the risk for phenotypic abnormality would be significantly reduced. It is, therefore, imperative for laboratories to attempt to delineate a marker chromosome by FISH or other molecular techniques, as described elsewhere.¹⁸ One minor surprise was the 17% (3/18) risk for cases involving bisatellited, monocentric markers (morphology group 3). These are the common 13/21 or 14/22 type marker chromosomes that are usually not associated

with phenotypic abnormalities. It is possible that a small proportion of the cases involving 14/22 markers had an abnormal phenotype because of UPD 14.

Many cases had incomplete information, resulting in exclusion from the study. In total, 79 of the 264 (30%) prenatal cases with supernumerary marker chromosomes had no phenotypic information available. In addition, for 21% (56/264) of the cases there was no documentation that parental chromosomes were studied. This may be because another laboratory performed the chromosome studies on the parents. Alternatively, the parents may have decided not to have these studies performed because of financial reasons or because they made a pregnancy decision without this information. If one of the parents was found to have the marker chromosome (in a non-mosaic state), this study revealed that there is a 4% (2/49) risk for phenotypic effects for the pregnancy (data not shown). This risk is similar to the background risk for phenotypic abnormalities for all pregnancies (3–5%). Therefore, to provide more accurate risk assessments in future studies, it is imperative for laboratories and health care professionals to make additional attempts to obtain information about the inheritance pattern of marker chromosomes.

Although every attempt was made to limit the possible biases introduced into this study, it is still possible that certain types of included cases, or certain assumptions, could influence the risk estimates of these prenatal markers. For example, when collecting data from the literature (15 new cases since the review by Crolla⁶), an attempt was made to focus on larger collections of marker chromosomes rather than individual case reports. It is possible that smaller studies or single case reports would provide exceptions to certain assumptions that were made in this study. In addition, studies involving only specific types of markers (that is, inverted duplications of chromosome 15) were not included, which could have provided additional information for those types of markers.

In conclusion, we show that the risk of phenotypic abnormalities associated with the prenatal detection of a supernumerary de novo marker chromosome is 26%. The calculated risk depends on a number of factors, including ultrasound findings, whether the marker is familial, and whether it is associated with an established syndrome. Our findings strongly support the value of additional genetic studies for more precisely defining the risk in individual cases involving marker chromosomes.

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Table 3 Criteria for inclusion in studies

Criteria	Warburton	Crolla	This study
Derived from chromosome 15	Included	Excluded	Included
Derived from chromosome 22	Included	Included	Excluded
Derived from X or Y chromosomes	Excluded	Excluded	Excluded
Iso 9p, 12p, 18p	Excluded	Excluded	Excluded
Unknown inheritance	Excluded	Included	Excluded
Cases with known ultrasound abnormalities	Excluded	Included	Included, but also grouped separately
Consecutive liveborn studies	Excluded	Included	Excluded

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