Original Article

Pericentric Inversion of Human Chromosome 9 Epidemiology Study in Czech Males and Females

(pericentric inversion / human chromosome 9 / heterochromatin variants / infertility)

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Abstract. Pericentric inversion of human chromosome 9 [inv(9)] is a relatively common cytogenetic finding. It is largely considered a clinically insignificant variant of the normal human karyotype. However, numerous studies have suggested its possible association with certain pathologies, e.g., infertility, habitual abortions or schizophrenia. We analysed the incidence of inv(9) and the spectrum of clinical indications for karyotyping among inv(9) carriers in three medical genetics departments in Prague. In their cytogenetic databases, among 26,597 total records we identified 421 (1.6 %) cases of inv(9) without any concurrent cytogenetic pathology. This study represents the world's largest epidemiological study on inv(9) to date. The incidence of inv(9) calculated in this way from diagnostic laboratory data does not differ from the incidence of inv(9) in three specific population-based samples of healthy individuals (N = 4,166) karyotyped for preventive (amniocentesis for advanced maternal age, gamete donation) or legal reasons (children awaiting adoption). The most frequent clinical indication in inv(9) carriers was "idiopathic reproductive failure" – 37.1 %. The spectra and percentages of indications in individuals with inv(9) were further statistically evaluated for one of the departments (N = 170) by comparing individuals with inv(9) to a control group of 661 individuals with normal karyotypes without this inversion. The proportion of clinical referrals for "idiopathic reproductive failure" among inv(9) cases remains higher than in controls, but the difference is not statistically significant for both genders combined. Analysis in separated genders showed that the incidence of "idiopathic reproductive failure" could differ among inv(9) female and male carriers.

Introduction

Pericentric inversion of chromosome 9 – regularly referred to as inv(9) – is one of the most common variations of the human karyotype; the estimated frequency varies from 1 to 4 %, depending on the population studied (Boué et al., 1975; Metaxotou et al., 1978; Serra et al., 1990; Demirhan et al., 2008). This inversion involves the heterochromatic region of chromosome 9 (Fig. 1) and exists in multiple forms, with inv(9) (p12q13) being the most common (Starke et al., 2002). Since the first description in 1972 (Wahrman et al., 1972), the clinical significance of inv(9) has been widely discussed. The latest version of the ISCN nomenclature (Schaffer et al., 2012) refers to inv(9)(p12q13) as a chromosomal polymorphism (or generally heteromorphism) with no clinical significance. By contrast, several authors have suggested possible associations of inv(9) with certain clinical diagnoses, e.g., schizophrenia (Lee et al., 1998; Kunugi et al., 1999), increased risk of offspring with Down syndrome (Serra et al., 1990; Uehara et al., 1992), and particularly infertility and habitual abortions (e.g., Uehara et al., 1992; Collodel et al., 2006;

Fig. 1. Microphotograph of human chromosome 9 with the most common type of pericentric inversion: inv(9)(p12q13) on the left; G-banding.

Ceylan et al., 2008). However, many of these studies concern only limited, small numbers of inv(9) carriers and use no statistical analyses. More recent studies have shown a significantly higher incidence of heterochromatin variants (including those on chromosome 9) among patients with a poor reproduction anamnesis, but no explanation for this phenomenon has been widely accepted so far (Madon et al., 2005; Minocherhomji et al., 2009; Dana and Stoian, 2012; Šípek Jr. et al., 2014).

The structure and variability of the heterochromatic region of chromosome 9 have been previously studied: a specific role of repetitive DNA sequences (α-satellites and III-DNA satellites) in the structure was shown by Samonte et al. (1996), and specific homology of the 9p12 and 9q13 sequences was reported by Starke et al. (2002). The evolutionary aspects of this heterochromatic region are also interesting because the inversion of chromosome 9 heterochromatin is one of the structural differences observable between human karyotypes and chimpanzee karyotypes (Kehrer-Sawatzki et al., 2005). Importantly, standard cytogenetic examination (using the G-banding visualization method) is unable to distinguish between specific subvariants of inv(9) that can be described using molecular cytogenetic methods such as FISH (Starke et al., 2002). A total of 21 different heterochromatin 9 subvariants were identified by Kosyakova et al. (2013) using specific combinations of BAC, centromeric, and microdissection FISH probes.

Only a few reports of inv(9) have involved a larger population (Yamada, 1992; Demirhan et al., 2008; Sheth et al. 2013). Furthermore, no such population-based surveys have been performed in Slavic or Czech populations.

In our previous study (Šípek Jr. et al., 2014), we demonstrated that the heterochromatin variants of chromosome 9 (compared with those on chromosomes 1, 16, and Y) are more frequently found in the Czech population and occur more frequently in patients with idiopathic reproductive failure than in controls with no such reproductive history. The most significant difference between the study and control groups was found for the 9qh+ (heterochromatin block enlargement) variant.

Here, we present, as a principal aim, estimates of the inv(9) frequency in the Czech population in the world's largest epidemiological study of inv(9) incidence to date. As a second task, we also tried to evaluate and discuss the possible association of inv(9) and a variety of clinical referrals in investigated individuals.

Material and Methods

Our data were collected from the work-up databases in cytogenetic laboratories of three medical genetics departments in the city of Prague (at the General University Hospital, Thomayer Hospital and Pronatal® Sanatorium). Cytogenetic examinations were performed according to standard laboratory protocols. The cells used for cultivation were peripheral blood leukocytes or amniocytes, and a standard G-banding method was used for the chromosome analysis. All slides were analysed by two independent readers, and the results were reported according to the current version of the international cytogenetic nomenclature (Schaffer et al., 2012). Informed consent was obtained from all patients (or their legal representatives) before the examination.

For the epidemiological survey, 26,597 results from standard postnatal cytogenetic examinations were obtained (the reference period comprised years 1981 to 2011). From these data, we created a subset of all individuals with inv(9) with no pathological chromosomal rearrangements. For each individual record, the karyotype formula, gender and clinical indication for the cytogenetic examination were noted. We determined the overall incidence of inv(9) in the whole cohort and in each laboratory; the incidences of inv(9) were also analysed separately for females and males.

For a more precise estimate of the population incidence of inv(9), three specific groups were analysed: a) a group of gamete donors (N = 2288; cytogenetic laboratory at Pronatal® Sanatorium; time period 2002–2011), b) a group of children (N = 814) awaiting adoption (from the database of cytogenetic laboratory at Thomayer Hospital, 1997–2011), and c) a cohort created from foetuses (N = 1064) who were karyotyped solely because of the advanced maternal age of their mothers (from the database of the cytogenetic laboratory at the General University Hospital (GUH), 2003–2011).

To further analyse the putative association between inv(9) and indications, we compared two specific cohorts from the cytogenetic database at the GUH: the "GUH inv(9)" and the "GUH control" cohort. The GUH inv(9) cohort comprised 170 inv(9) carriers. The GUH
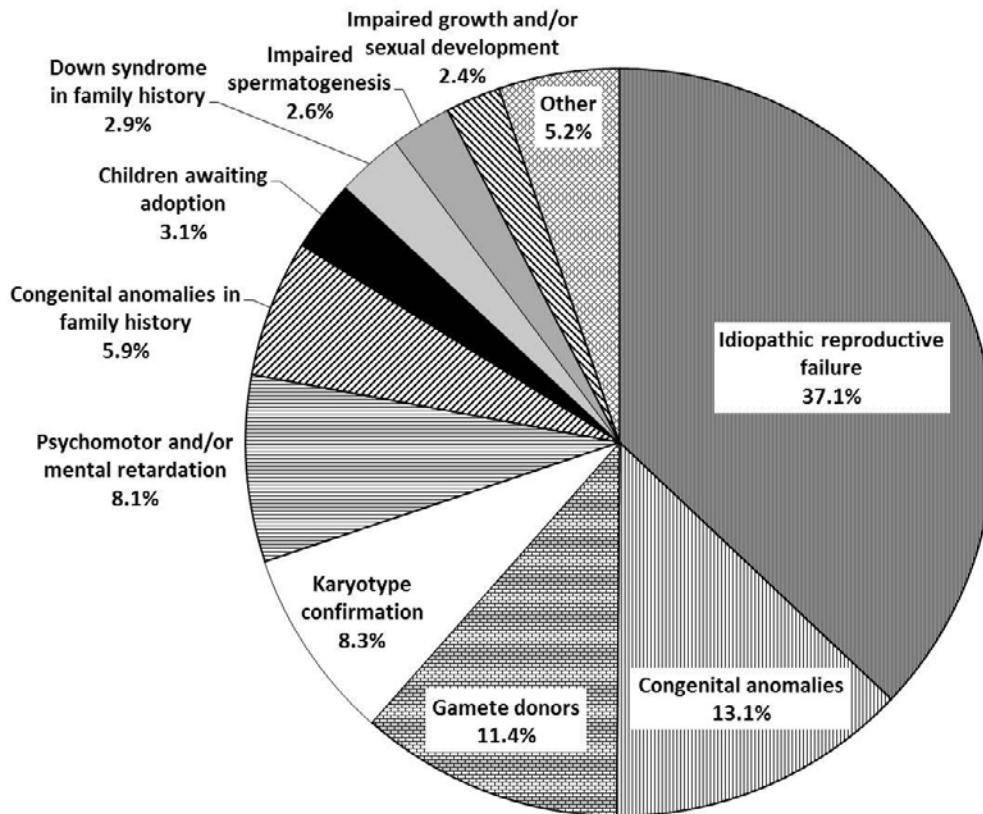
Fig. 2. Frequency of selected referral indications in the whole cohort of patients (three genetic departments, Prague) with inv(9) (N = 421)

control cohort was created from the same cytogenetic database using a systematic sampling method (Brewer, 1963). The systematic sampling was applied among all individuals who were indicated for cytogenetic examination but diagnosed with a normal karyotype (46,XX or 46,XY) with no chromosomal pathologies or variants. Using this method, a group of 661 individuals was identified as the control cohort. Afterwards, using the clinical indication data, we distributed all cases in both GUH cohorts into 11 clinical diagnosis (sub)groups.

The name of each diagnosis group (listed in Fig. 2 and Fig. 3) represents the type of major clinical indication criteria. Three of the group names need to be explained in detail. The "idiopathic reproductive failure" indication group covers only cases of poor reproduction history (including sterility and/or repeated abortions) with unknown cause, i.e., cases in which all explainable reproductive pathologies were excluded; those with explainable reproductive pathologies are represented by other groups such as "impaired spermatogenesis" or "congenital anomalies in family history," etc. The "karyotype confirmation" indication group includes individuals karyotyped because of balanced chromosomal abnormality and/or uncommon heteromorphism in a relative. The group "other diagnoses" is composed of a variety of neonatal, haematological, oncological or other diagnoses with individual numbers too small to create separate groups.

Finally, we were able to compare the frequency of each indication diagnosis group both in the GUH inv(9)

cohort and GUH control cohort. The incidences of inv(9) in both cohorts were further analysed separately for both sexes. The statistical analysis was performed using the R software (R Development Core Team, 2011). Fisher's exact test was used to compute the P values and 95% confidence intervals (CIs) for the odds ratios (ORs). A P value < 0.05 was considered statistically significant.

Results

Among 26,597 karyotyped individuals, we identified 421 total cases of inv(9); the total laboratory incidence of inv(9) was 1.6 % (Table 1). There were no statistically significant differences in the incidences for each of the three laboratories, and the standard deviation (SD) computed from individual laboratory values was 0.1 %. The gender-specific incidences varied considerably among all three departments (Table 1): in one laboratory, the incidence in females was even slightly lower than in males. The overall laboratory incidence of inv(9) was higher in females than in males, but the difference was not statistically significant (P = 0.18).

The population incidence of inv(9) was estimated using three special groups. Among 2,288 gamete donors, we identified 42 cases (1.8 %) of inv(9). Among children awaiting adoption, the total incidence of inv(9) was 1.7 % (14/814), and in the last group of foetuses karyotyped via amniocentesis, the proportion of inv(9) was 1.1 % (12/1064). The overall incidence in special groups
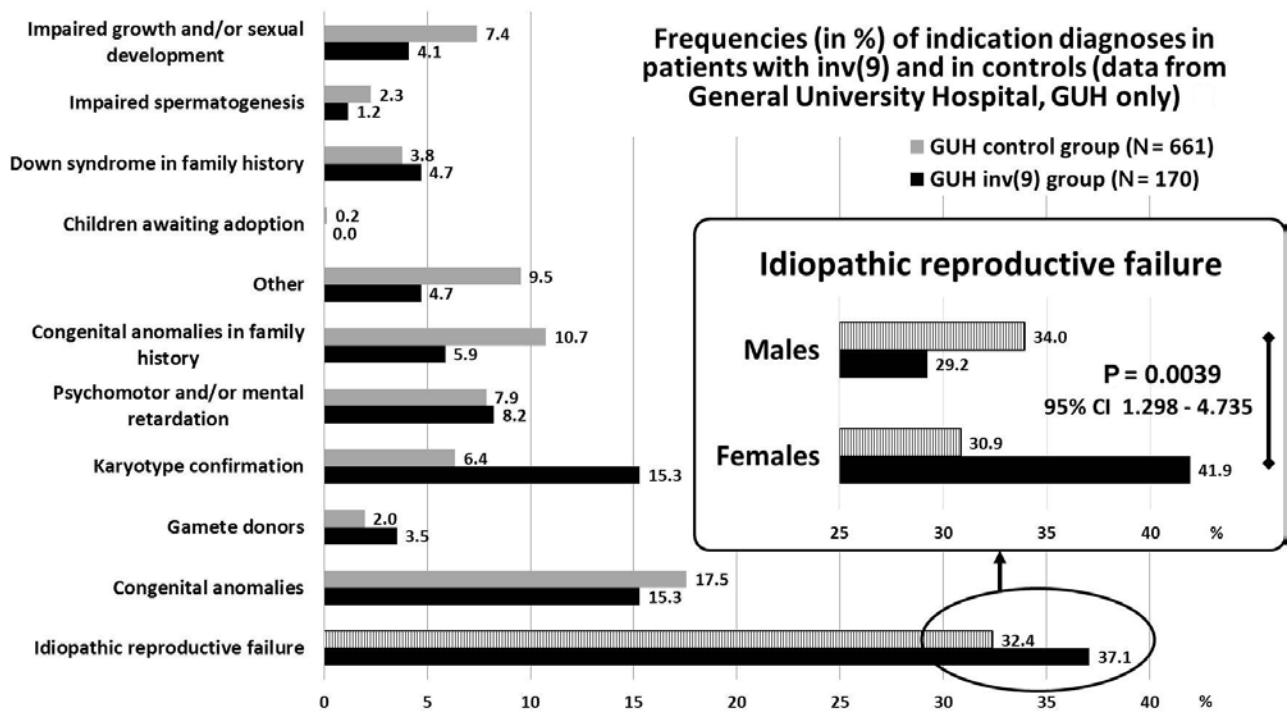
Fig. 3. Comparison of frequencies (in %) of referral indications in the group of patients with inv(9) and in the control group (data from General University Hospital only).

Table 1. Numbers and laboratory incidence of cases with inv(9) – data from three cytogenetic laboratories, Prague, Czech Republic

Laboratory	Data available for period	Total			Females			Males			Female/male difference
		inv(9) cases	All records	Laboratory Incidence (%)	inv(9) cases	All records	Laboratory Incidence (%)	inv(9) cases	All records	Laboratory Incidence (%)	P value (95% CI for OR)
General University Hospital	1986–2011	170	10 933	**1.55 %**	105	5943	1.77 %	65	4990	1.30 %	0.052 (0.988–1.891)
Thomayer University Hospital	1981–2011	131	8 611	**1.52 %**	66	4553	1.45 %	65	4058	1.60 %	0.597 (0.630–1.297)
Pronatal® Sanatorium	2002–2011	120	7 053	**1.70 %**	81	4562	1.78 %	39	2491	1.57 %	0.564 (0.768–1.716)
Total		421	26597	**1.58 %**	252	15058	**1.67 %**	169	11539	**1.46 %**	0.181 (0.937–1.400)

Table 2. Numbers and estimate of population incidence of cases with inv(9) – data from three specific population samples, Prague, Czech Republic

	Total			Females			Males			Female/male difference
	inv(9) cases	All cases	Population incidence (%)	inv(9) cases	All cases	Population incidence (%)	inv(9) cases	All cases	Population incidence (%)	P value (95% CI for OR)
Gamete donors	42	2288	**1.84 %**	41	2092	1.96	1	196	0.51 %	0.257 (0.654–158.39)
Children awaiting adoption	14	814	**1.72 %**	7	380	1.84	7	434	1.61 %	1.0 (0.339–3.862)
Foetuses of mothers with advanced maternal age	12	1064	**1.13 %**	8	551	1.45	4	513	0.78 %	0.389 (0.498–8.555)
Total	68	4166	**1.63 %**	56	3023	**1.85**	12	1143	**1.05 %**	0.075 (0.938–3.660)

was 1.6 % (Table 2) with an SD = 0.3 % (computed from individual values). When the genders were evaluated separately, the incidence of inv(9) was higher in females (women, girls, and foetuses) than in males in all three groups (Table 2). Again, this difference was not statistically significant (P = 0.075).

The distribution of all inv(9) individuals (N = 421) into 11 groups based on clinical referral diagnoses is shown in Fig. 2. The most frequent clinical diagnoses in inv(9) carriers were "idiopathic reproductive failure" with 156 cases (37.1 %), "congenital anomalies" with 55 probands (13.1 %) and "gamete donors" with 48 individuals (11.4 %).

To test the possible association of inv(9) heteromorphism with particular referral diagnoses, we compared the incidences of all 11 diagnoses in the GUH inv(9) and GUH control cohorts. Idiopathic reproductive failure was the most common diagnosis in both the GUH inv(9) and GUH control cohorts (37.1 % compared with 32.4 %, respectively) (Fig. 3). However, the difference observed between the two cohorts was not statistically significant (P= 0.27, and 95% CI = 0.85–1.77).

The same calculations were performed separately for each gender in the GUH inv(9) study group and the GUH control group. For the "idiopathic reproductive failure" clinical indication, the proportion among inv(9) female carriers was higher than the proportion in male inv(9) carriers with the same referral diagnosis; these results were statistically significant (P = 0.0039; 95% CI = 1.298–4.735) (Fig. 3).

Discussion

We present here the results of the world's largest epidemiological study on inv(9) to date (421 cases from 26,597 cytogenetic records); the second largest inv(9) cohort, reported by Turkish authors (Demirhan et al., 2008), involved only 157 inv(9) cases (among 15,528 records). The total laboratory incidence of inv(9) in our study was 1.6 ± 0.1 % (with individual laboratory values of 1.6 %, 1.5 %, and 1.7 %). This type of epidemiological analysis of certain cytogenetic variants (e.g., in heterochromatic regions) using cohorts of patients (or healthy individuals) with various clinical indications could be problematic because the laboratory incidence may not reflect the incidence in the general population. The design chosen by Sheth et al. (2013) represents another difficulty. They studied a cohort of 4,859 Indian individuals having history of aetiologically unclassified recurrent miscarriages. They found 25 (0.51 %) cases of chromosome 9 heterochromatin variants, but no comparative group of individuals was reported.

Nevertheless, karyotyping studies of the general healthy population (preferably with good reproduction anamneses) are not available in the recent literature. Therefore, we used three specific (and separate) groups of individuals to estimate the population frequency. These individuals, who were not karyotyped because of a pathological phenotype but preselected randomly, can

therefore serve as a convenient population sample of "apparently" healthy controls for this type of estimate. The overall population incidence in all three groups (1.6 ± 0.3 %) was not different from the laboratory incidence mentioned above.

Both these results agree with the findings published in the literature in which the inv(9) incidence ranges from approximately 1 % (Serra et al., 1990) to 4 % (Metaxotou et al., 1978). This relatively broad range in inv(9) incidences and the differences between individual reports (Metaxotou et al., 1978; Serra et al., 1990; Demirhan et al., 2008) could reflect the different structures (various referral diagnoses), total sizes, and respective ethnicities of the analysed cohorts.

In all three of the specific population samples we studied (Table 2), the incidences of inv(9) were markedly higher in females. In our diagnostic laboratory cohorts (Table 1), we also found that overall inv(9) cases were more frequent among females. The sex difference (between the incidences) in the laboratory cohorts was smaller than in the population cohorts; however, neither was statistically significant (P = 0.18 for laboratory vs. P = 0.075 for population samples). Nevertheless, the overall numbers of cytogenetic data in our study (15,058 females and 11,539 males) are sufficiently large to conclude that this gender difference in inv(9) incidences, seen most likely for the first time by Yamada (1992) in the Japanese population, is true in the Czech population as well. There is no reliable explanation for this phenomenon in the literature. We may only hypothesise that the suggested mechanisms of meiotic cell division interference (as discussed below) affect male and female gametogenesis differently. Seeing the overall numbers of female and male cases in the study (females sampled at higher rate) we still need to add that this imbalance does really reflect the composition of the cohorts, namely the numerical superiority of female gamete donors.

Various authors have reported possible associations between inv(9) and several clinical diagnoses, and many have mentioned reproductive failure (sterility and/or repeated abortions) among the most common associated diagnoses (Uehara et al., 1992; Mozdarani et al., 2007; Demirhan et al., 2008). For completing our second task we have thoroughly studied the referral diagnoses in all individuals with inv(9) and in our control cohort. We have also found idiopathic reproductive failure (and congenital anomalies) as the most frequent indication diagnoses for karyotyping, but not only in our inv(9) cohort – they were the most common in controls as well. None of the studies on inv(9) mentioned above used a control cohort (or another system of controls) to further analyse the clinical significance of inv(9). Therefore, our results cannot be compared with other studies at present.

The possible role of human karyotypic heterochromatin variants (including those of chromosome 9, and inv(9) itself) in the aetiology of idiopathic reproductive failure has been studied by various authors, and several studies showed statistically significant results (Madon et

al., 2005; Minocherhomji et al., 2009; Dana a Stoian, 2012). We have observed this possible association as well (Šípek Jr. et al., 2014). However, the group of heterochromatin variants studied, which affect human chromosomes 1, 9, 16 and Y, is so broad and heterogeneous (as documented e.g. by Kosyakova et al., 2013) that no simple explanation for these observations may be given; it may be more informative to focus on only one relatively frequent rearrangement, such as inv(9). The sex difference in the incidence of inv(9) (i.e. higher frequency of female carriers) is larger in patients with idiopathic reproductive failure.

This observation agrees with our previous work in which we found a statistically significantly higher incidence of heterochromatin variants (including the group of variants on chromosome 9) only in females, but not in males, with idiopathic reproductive failure (Šípek Jr. et al., 2014). The role of inv(9) in human infertility remains unclear. Since most cytogeneticists believe inv(9) to be a simple heteromorphism (Brothman et al., 2006), the clinical importance of any individual inv(9) in a specific clinical pathology may be challenging to determine. Some authors have proposed that the inversion itself could interfere with the pairing of homologous chromosomes during meiosis; this mechanism of recombination aneusomy is well described in some types of pericentric inversions (Anton et al., 2005). Nevertheless, we have not found any report of recombination aneusomy resulting from parental inv(9)(p12q13) or inv(9)(p12q21). Likewise, in our study, we did not find any individual with recombinant chromosome 9 among the offspring of inv(9) carriers that would support this theory. The second suggested mechanism is the so-called interchromosomal effect.

Some authors believe that inv(9) can influence the pairing of other chromosomes because the unpaired segments of homologous chromatids can interfere with other bivalents as well (Anton et al., 2005). The interchromosomal effect in an inv(9) male carrier leading to an increased number of aneuploid sperms has been described only once in the literature (Amiel et al., 2001). The possible sex-dependent difference in both these potential meiotic mechanisms remains to be clarified.

Obviously, most cases of inv(9) are harmless, yet any particular inv(9) could be harmful. Several authors have confirmed that the molecular-cytogenetic characteristics of specific cases of inv(9) are also diverse and different (Samonte et al., 1996; Starke et al., 2002; Kosyakova et al., 2013). Apparently, basic G-banded karyotyping will not be a sufficient detection method for this type of association study in the future, and more precise, molecular cytogenetic methods will be needed.

Conclusions

We have confirmed that in the Czech population at present, inv(9) is a relatively common occurrence with a higher, although not statistically significant, prevalence in females. According to our findings, there is no principal difference between inv(9) incidence estimates based on healthy population samples and laboratory incidence(s) of inv(9) in individuals indicated for analysis (because of various reasons) by clinical geneticists. In our retrospective study, the most common clinical indication to karyotyping in individuals with inv(9) was idiopathic reproductive failure, and/but compared with controls without inv(9), this observation was not a statistically significant association. Nevertheless, comparing inv(9) carriers and controls for each gender separately, we have seen an interesting trend: in our cohort, albeit the largest, still one of limited extent, the proportion of "idiopathic reproductive failure" as a clinical indication is higher in female than that in male inv(9) carriers. Most pericentric chromosome 9 variants, including inv(9), are clinically benign, but some specific (sub)variants could interfere with fertility. Standard cytogenetic examination (even using high-resolution (HR) techniques) is not sufficient to differentiate subvariants of chromosome 9. More studies using (modern) molecular cytogenetic approaches will be needed to evaluate potential clinical consequences of chromosome 9 variants.

Acknowledgement

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