Dear Editor,

Chromosome heteromorphisms are described as variations in size and morphology at specific regions that can be detected through classical banding methods. They are mitotically stable variants usually present in a heterozygous state (only one of the homologous chromosomes is heteromorphic). In humans, the most commonly detected heteromorphisms involve the heterochromatic regions of chromosomes 1, 9, 16, and Y (designated as 1qh, 9qh, 16qht, and Yqh respectively), and the short-arms, satellites, or stalks of the acrocentric chromosomes 13, 14, 15, 21, and 22 (e.g., for chromosome 13 designated as 13p, 13ps, and 13pstk, respectively). Pericentric inversions involving the heterochromatic region of chromosomes 1, 9, and Y are also frequently observed.

Heteromorphisms are not associated with any phenotypic alteration. Nevertheless, several pieces of data suggest an association between the presence of heteromorphic variants and infertility. Moreover, the presence of a heteromorphism in one member of an infertile couple appears to have a detrimental effect on the outcome of assisted reproduction treatments and has been related to an increased frequency of miscarriage.

The underlying mechanisms behind the relationship between male infertility and the presence of such chromosomal variants are not fully understood. One of the current hypotheses has been related to a possible deleterious effect of the heteromorphisms on meiotic chromosome pairing and segregation. In this sense, some studies suggest the existence of a genetic reproductive risk associated with heteromorphisms in the study population, as well as the most prone chromosomes to produce sperm with numerical imbalances in infertile patients.

Sperm chromosome analysis was done using an Olympus BX60 epifluorescence microscope (Olympus Iberia, L’Hospitalet de Llobregat, Spain) equipped with filter sets for fluorescein isothiocyanate (FITC), Texas Red, Aqua, and 4’,6-diamidino-2-phenylindole dihydrochloride (DAPI)/Texas Red/FITC using standard assessment criteria.

In this study, we provide additional information about the impact of chromosomal variants on the production of sperm chromosomal aneuploidies in carriers of different chromosome heteromorphisms.

Among the 16 heteromorphism carriers analyzed, 11 (68.8%) presented significantly increased rates of numerical abnormalities for at least one of the analyzed chromosomes. This result suggests the existence of a genetic reproductive risk associated with this population, supporting previously published data. We would like to highlight the high heterogeneity regarding the chromosomes with significant aneuploidy increases among the carriers of the same chromosome heteromorphism. This is clearly observable in inv(9) carriers, which include cases without any significant increase (i.e., 940z) and carriers presenting significant increases affecting up to three chromosomes (i.e., 929z).
It is also noticeable that in 4 (36.4%) of the 11 individuals with increased frequencies of numerically abnormal sperm, one of the chromosomes involved in the aneuploidies was the heteromorphic chromosome itself (cases 923z, 911z, 931z, and 929z; Table 1). Similar to our results, a previous sperm-FISH study performed on a carrier of a heteromorphic chromosome 9 inversion detected increased frequencies of sperm with numerical abnormalities for several chromosomes also including the rearranged chromosome itself.10 All these data reinforce the hypothesis that in some cases, the establishment of heterosynapsis during prophase I might entail subsequent nondisjunction events at anaphase I that would affect both the segregation of the rearranged chromosomes and the segregation of other bivalents. This bidirectional phenomenon has been previously described in carriers of chromosomal translocations,14,15 and this article extends its occurrence to heteromorphism carriers.

In the remaining 7 (63.6%) individuals with altered sperm FISH results in which the heteromorphic chromosome was unaffected by these increases, chromosomes 18 and 22 were the most frequent sperm anomalies detected (Table 1). This finding argues in favor of the participation of other factors besides heterosynapsis in the production of such numerical anomalies. That is, in a scenario of meiotic disturbances produced by the heteromorphism with other unsynapsed regions, X and Y chromosomes (which contain large nonhomologous segments) would be among the most suitable candidates involved.20 Thus, a preferential increase in the incidence of sex chromosome aneuploidies should be expected. Nevertheless, only one individual (919z) showed increased incidences of sex chromosome aneuploidies.

Other factors besides heterosynapsis may also influence the frequency of chromosome imbalances in sperm. For example, abnormal seminal parameters have been generally associated with the presence of increased frequencies of sperm abnormalities.16 Accordingly, one could say that the increased sperm aneuploidies observed in some cases would be the consequence of an abnormal semenogram, rather than a heterosynapsis phenomenon derived from the presence of a heteromorphic form. However, in our study, only two of the 11 individuals (i.e., 935z, 929z) that displayed increased frequencies of abnormal sperm had an altered semenogram (Table 1). This low incidence of seminal anomalies among the carriers analyzed also agrees with other previous studies which indicated that the presence of heteromorphisms is not something directly related to the presence of altered seminal parameters.7

Another factor that has been suggested to have a possible influence in the production of aneuploid/diploid sperm is paternal age. Up to present, controversial data have been obtained in this area with some studies reporting a correlation of age with certain types of numerical abnormalities while others do not observe such effect.17 In our study, individuals without altered FISH results ranged 32–39 years old, while individuals with increased frequencies of aneuploid/diploid sperm ranged 27–48 years old. The presence of such a broader age range in individuals with higher ratios of abnormal sperm does not support an effect of this factor on the production of sperm chromosomal abnormalities by heteromorphisms carriers.

Regardless of the origin of the observed sperm alterations, published data suggest a detrimental effect of heteromorphisms on assisted reproductive treatments4,18–21. Ultimately, this means that in reproductive counseling, significant differences in sperm chromosome anomaly rates should be taken into consideration. Accordingly, we suggest that a risk assessment through sperm FISH should be offered to these individuals, at least for cautionary purposes. Future studies examining larger populations of heteromorphism carriers would be of high interest to divide the individuals into “at-risk” and “without-risk” categories and clarify the effects of these variants over assisted reproductive treatments.

**AUTHOR CONTRIBUTIONS**

EA, MS, and JB conceived, designed, and coordinated the study. EGG and MS were involved in sample collection. MRM and AG carried out the sperm FISH analysis. EA, EGG, MRM, AG, MS, and JB were
involved in data analysis and interpretation; EA and JB wrote the manuscript with support from EGG and MS. All authors provided critical feedback, read, and approved the final manuscript.

COMPETING INTERESTS
All authors declared no competing interests.

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