


Interchromosomal Effect in Carriers of Structural Abnormalities

Tomas Escudero, BSc

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INTERCHROMOSOMAL EFFECT DEFINITION

Reprogenetics 

Interchromosomal effect (ICE) is the disruption of meiotic behavior of chromosomes not involved in a structural rearrangement favoring the non-disjunction of such chromosomes

INCIDENCE OF TRANSLOCATIONS AND INVERSIONS

TRANSLOCATIONS:

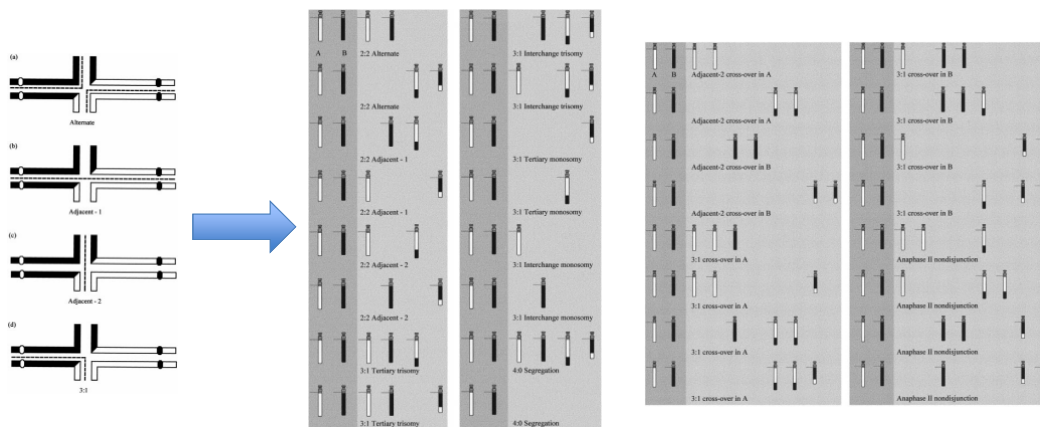
RECIPROCAL TRANSLOCATIONS 0.16%

INVERSIONS:

PERICENTRIC INVERSIONS 0.012-0.07%

PARACENTRIC INVERSIONS 0.01-0.05%

THE PROBLEM WITH RECIPROCAL TRANSLOCATIONS

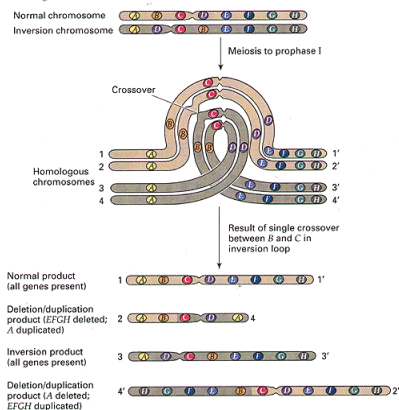


Scriven et al, 1998 Prenat Diag

THE PROBLEM WITH INVERSIONS

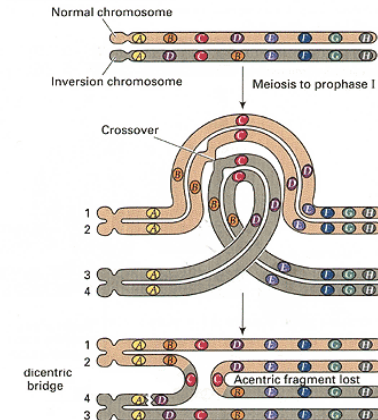
PERICENTRIC INVERSION

Meiotic products resulting from a single crossover within a heterozygous, pericentric inversion loop. Crossing-over occurs at the four-strand stage, involving two non-sister homologous chromatids.



PARACENTRIC INVERSION

Products of meiotic crossover



STUDIES ON ICE

FISH STUDIES IN SPERM:

- Altered segregation pattern and numerical chromosome abnormalities interrelate in spermatozoa from Robertsonian translocation carriers. Godo et al, 2015

Godo et al, 2015

- Interchromosomal effect analyses by sperm FISH: incidence and distribution among reorganization carriers. Anton et al, 2011

FISH STUDIES IN EMBRYOS:

- Negligible interchromosomal effect in embryos of Robertsonian translocation carriers. Munne et al, 2005

- Possible interchromosomal effect in embryos generated by gametes from translocation carriers. Ginaroli et al, 2002

CCS TECHNIQUES IN EMBRYOS:

- Embryos of Robertsonian translocation carriers exhibit a mitotic interchromosomal effect that enhances genetic instability during early development. Alfarawati et al, 2012

STUDIES ON ICE

FISH STUDIES IN SPERM:

- Godo et al, 2015 → ICE linked to some segregation products for Robertsonian translocation carriers
- Anton et al, 2011 → Study several types of abnormalities, more ICE in translocations, less ICE in inversions

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FISH STUDIES IN EMBRYOS:

- Munne et al, 2005 → No ICE for Robertsonian translocations in blastomere biopsies
- Ginaroli et al, 2002 → Possible ICE for reciprocal translocations

Clinical results on translocations

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Outcome of preimplantation genetic diagnosis of translocations

Santiago Munné, Ph.D.,^a Mireia Sandalinas, M.Sc.,^a Tomas Escudero, M.Sc.,^a Jingly Fung, Ph.D.,^{b,c} Luca Gianaroli, M.D.,^a Jacques Cohen, Ph.D.,^a and the Saint Barnabas Medical Center PGD Network^a

Conclusion(s): PGD of translocations achieves a statistically significant reduction in spontaneous abortion, both for polar-body and blastomere biopsy cases. Pregnancy outcome depended on the number of normal embryos available for transfer, with patients having <50% abnormal embryos achieving the most pregnancies. Because robertsonian translocations caused fewer abnormal embryos than reciprocal translocations, they also resulted in higher rates of implantation. (Fertil Steril® 2000;73:1209-18. ©2000 by American Society for Reproductive Medicine.)

Human Reproduction Vol.17, No.12 pp. 3201-3207, 2002

Possible interchromosomal effect in embryos generated by gametes from translocation carriers

L.Gianaroli^{1,3}, M.C.Magli¹, A.P.Ferraretti¹, S.Munné², B.Balicchia¹, T.Escudero² and A.Crippa¹

CONCLUSIONS: An interchromosomal effect seems to play a role in the case of Robertsonian translocations, where the relevant contribution of aneuploidy exposes the couple to an additional risk of abnormal pregnancy.

Submitted on November 13, 2001; resubmitted on July 25, 2002; accepted on August 15, 2002



Comments from Reviewer 1

I have pasted my report below. I have difficulty filling in the standard form, basically because, if the data are true, then this is very original and important work. However, it contradicts so much previous data that I remain, frankly, sceptical, and wonder whether the results could have a substantial element of technical artefact.....

STUDIES ON ICE

FISH STUDIES IN SPERM:

- Godo et al, 2015 → ICE linked to some segregation products for Robertsonian translocation carriers
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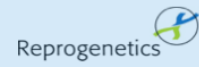
FISH STUDIES IN EMBRYOS:

- Munne et al, 2005 → No ICE for Robertsonian translocations in blastomere biopsies
- Gianaroli et al, 2002 → Possible ICE for reciprocal translocations

CCS TECHNIQUES:

- Alfawati et al, 2012 → ICE in Robertsonian translocations at mitotic level

LATEST STUDIES ON ICE BY REPROGENETICS-USA

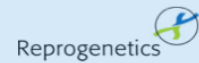


Is Interchromosomal Effect (ICE) Related to the Sex of the Translocation Carrier? Escudero et al, 2015

Types of Abnormal Embryos in Inversion Cases. Suhotliv et al, 2015

The weight of the Interchromosomal Effect in Reciprocal Translocation Carriers. Escudero et al, 2016 (submitted)

Is Interchromosomal Effect (ICE) Related to the Sex of the Translocation Carrier?



| | Female carrier | Percentage | Male Carrier | Percentage | p value |
|----------------------------|----------------|------------|--------------|------------|------------------|
| Normal or Balanced | 46 | 17.90% | 54 | 17.88% | ns |
| Unbalanced | 155 | 60.31% | 166 | 54.97% | ns |
| Other Abnormalities | 34 | 13.23% | 62 | 20.53% | p<0.05 |
| No Result | 22 | 8.56% | 20 | 6.62% | ns |
| Total | 257 | | 302 | | |

Average maternal age for female carrier group is 33.62

Average maternal age for male carrier group is 33.69

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Is Interchromosomal Effect (ICE) Related to the Sex of the Translocation Carrier?

- Male translocation carriers have a significantly higher chance of having abnormalities unrelated to the chromosomes involved in the translocation compared female translocation carriers
- Because female translocation carriers produce a higher proportion of unbalanced embryos (though no significantly higher), the proportion of abnormal embryos in both groups is the same

Types of Abnormal Embryos in Inversion Cases

| | Inversion | % | Translocation | % | p value |
|-------------------------|------------|-------|---------------|-------|-------------------|
| Normal or Balanced | 32 | 25.2% | 100 | 17.9% | ns |
| Unbalanced | 38 | 29.9% | 321 | 57.4% | p<0.001 |
| Other Abnormalities | 52 | 40.9% | 96 | 17.2% | p<0.001 |
| No Result | 5 | 3.9% | 42 | 7.5% | ns |
| Total of embryos | 127 | | 559 | | |

Average maternal age for inversion carrier group is 36

Average maternal age for translocation carrier group is 32

Types of Abnormal Embryos in Inversion Cases

| | Inversion | % | Translocation | % | p value |
|----------------------------|-----------|-------|---------------|-------|---------|
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Average maternal age for inversion carrier group is 36

Average maternal age for translocation carrier group is 32

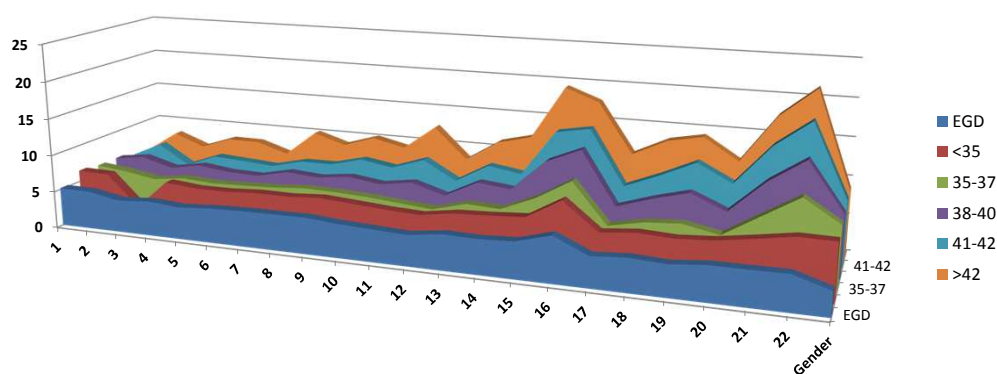
Types of Abnormal Embryos in Inversion Cases

| INVERSION CASES BY AGE | | | | | |
|----------------------------|---------------|-------|-----------------|-------|---------|
| | Under 35 y.o. | % | 35 y.o. or over | % | p value |
| Normal or Balanced | 17 | 27.0% | 15 | 23.4% | ns |
| Unbalanced | 18 | 28.6% | 20 | 31.3% | ns |
| Other Abnormalities | 24 | 38.1% | 28 | 43.8% | ns |
| No Result | 4 | 6.3% | 1 | 1.6% | ns |
| Total | 63 | | 64 | | |

Types of Abnormal Embryos in Inversion Cases

- The difference in the proportions and types of abnormalities between the inversion group and the translocation group points to a heightened ICE effect in inversion cases
- Maternal age is not the only factor in contributing to the increase of aneuploidy as both age subgroups in the inversion group did not show any significant differences
- The high proportion of aneuploid embryos, and the low proportion of pure unbalanced embryos (8.7%), indicate Comprehensive Chromosome Analysis is the better strategy for these kind of cases as opposed to FISH techniques which focus only in the affected chromosomes

Aneuploidy vs Age: A study Chromosome by Chromosome



Escudero et al, 2016

The weight of the Interchromosomal Effect in Reciprocal Translocation Carriers

PGS group (normo-chromosome patients):

- 12,790 cycles
- 68,861 embryos
- 1,583,803 pair of chromosomes studied
- Average maternal age: 35.4 y.o.

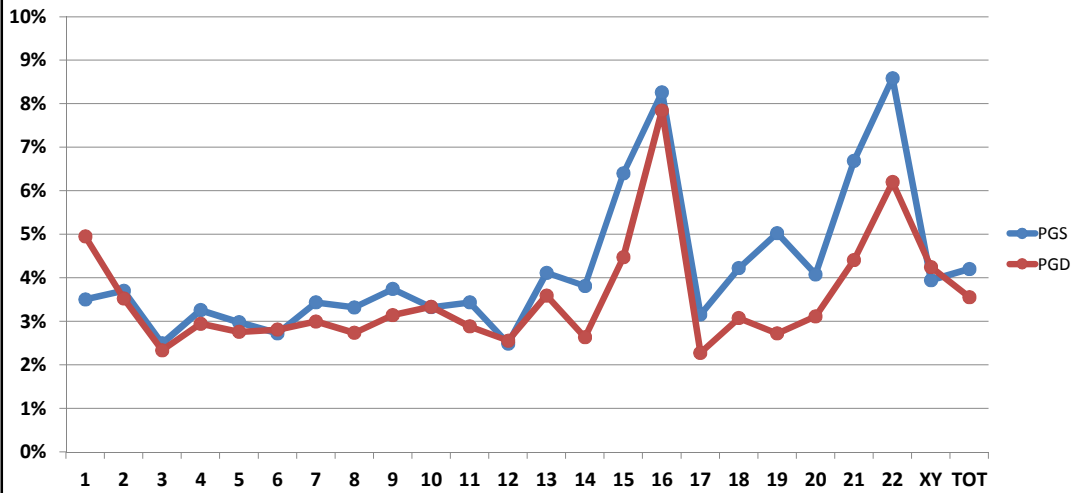
PGD group (reciprocal translocation carriers):

- 199 cycles
- 1,184 embryos
- 24,339 pair of chromosomes studied
- Average maternal age: 33.4 y.o.

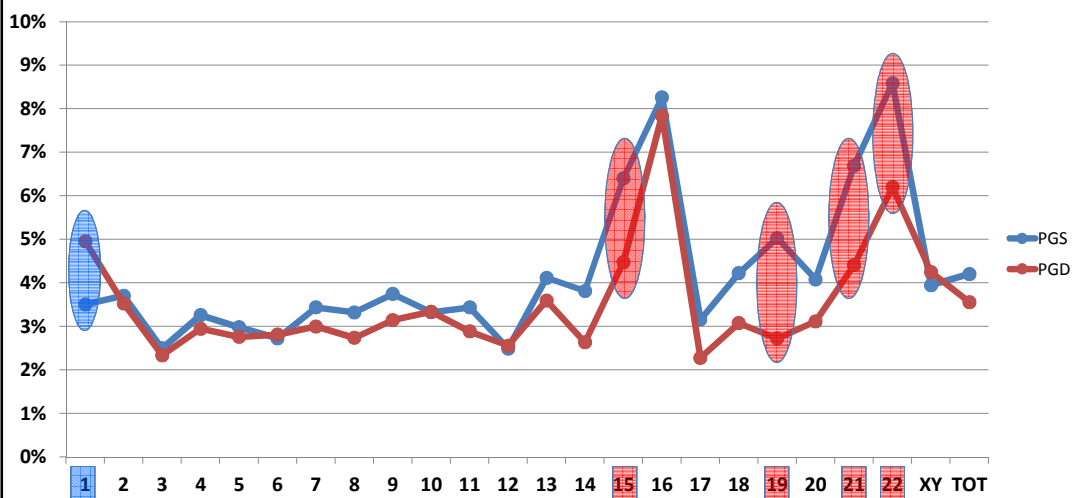
The weight of the Interchromosomal Effect in Reciprocal Translocation Carriers

| chro | PGS | PGD | P values | chro | PGS | PGD | P values |
|----------|--------------|--------------|--------------|------------|--------------|--------------|--------------|
| 1 | 3.51% | 4.96% | 0.025 | 13 | 4.12% | 3.60% | NS |
| 2 | 3.70% | 3.53% | NS | 14 | 3.82% | 2.64% | NS |
| 3 | 2.50% | 2.34% | NS | 15 | 6.40% | 4.48% | 0.01 |
| 4 | 3.26% | 2.95% | NS | 16 | 8.26% | 7.85% | NS |
| 5 | 2.98% | 2.76% | NS | 17 | 3.16% | 2.28% | NS |
| 6 | 2.73% | 2.81% | NS | 18 | 4.23% | 3.08% | NS |
| 7 | 3.44% | 3.00% | NS | 19 | 5.03% | 2.72% | 0.001 |
| 8 | 3.32% | 2.74% | NS | 20 | 4.08% | 3.12% | NS |
| 9 | 3.75% | 3.15% | NS | 21 | 6.69% | 4.41% | 0.005 |
| 10 | 3.33% | 3.34% | NS | 22 | 8.59% | 6.20% | 0.01 |
| 11 | 3.44% | 2.89% | NS | XY | 3.95% | 4.25% | NS |
| 12 | 2.49% | 2.56% | NS | TOT | 4.21% | 3.56% | 0.001 |

The weight of the Interchromosomal Effect in Reciprocal Translocation Carriers



The weight of the Interchromosomal Effect in Reciprocal Translocation Carriers



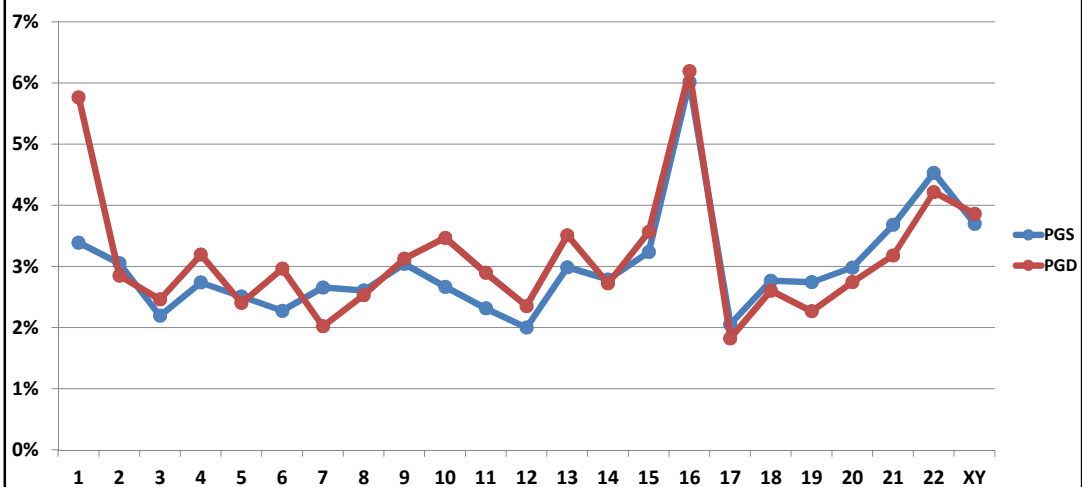
The weight of the Interchromosomal Effect in Reciprocal Translocation Carriers

Patients below 35 y.o.

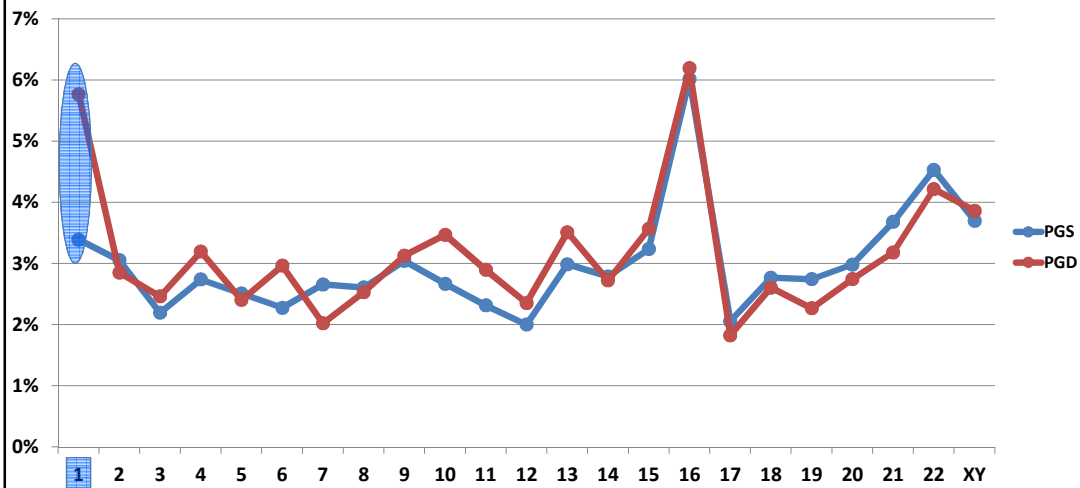
| chro | PGS | PGD | P value |
|------|-------|-------|---------|
| 1 | 3.39% | 5.77% | 0.005 |
| 2 | 3.05% | 2.85% | NS |
| 3 | 2.19% | 2.46% | NS |
| 4 | 2.74% | 3.19% | NS |
| 5 | 2.51% | 2.40% | NS |
| 6 | 2.28% | 2.97% | NS |
| 7 | 2.66% | 2.02% | NS |
| 8 | 2.61% | 2.53% | NS |
| 9 | 3.04% | 3.13% | NS |
| 10 | 2.67% | 3.47% | NS |
| 11 | 2.32% | 2.90% | NS |
| 12 | 2.00% | 2.35% | NS |

| chro | ANE | RECT | P value |
|------|-------|-------|---------|
| 13 | 2.99% | 3.51% | NS |
| 14 | 2.79% | 2.72% | NS |
| 15 | 3.24% | 3.57% | NS |
| 16 | 6.01% | 6.19% | NS |
| 17 | 2.06% | 1.83% | NS |
| 18 | 2.77% | 2.61% | NS |
| 19 | 2.75% | 2.27% | NS |
| 20 | 2.98% | 2.74% | NS |
| 21 | 3.68% | 3.18% | NS |
| 22 | 4.53% | 4.22% | NS |
| XY | 3.70% | 3.86% | NS |
| TOT | 3.00% | 3.16% | NS |

The weight of the Interchromosomal Effect in Reciprocal Translocation Carriers



The weight of the Interchromosomal Effect in Reciprocal Translocation Carriers

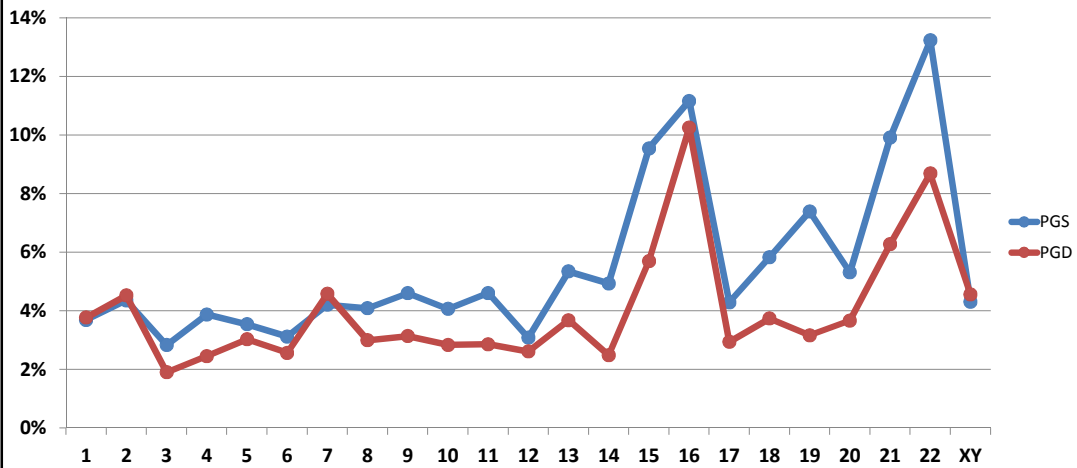


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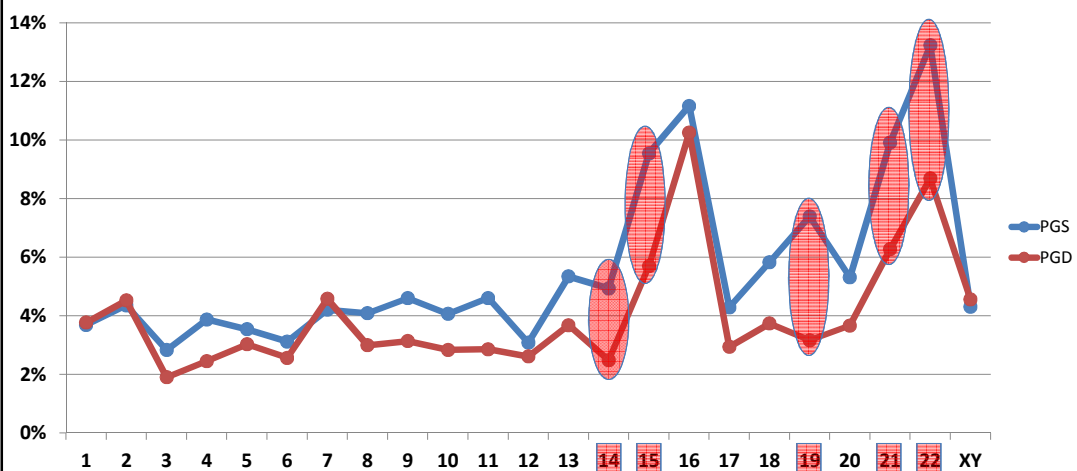
Patients 35 y.o. or over

| chro | PGS | PGD | P value | chro | ANE | RECT | P value |
|------|-------|-------|---------|------|--------|--------|---------|
| 1 | 3.69% | 3.77% | NS | 13 | 5.35% | 3.68% | NS |
| 2 | 4.36% | 4.52% | NS | 14 | 4.93% | 2.48% | 0.05 |
| 3 | 2.83% | 1.90% | NS | 15 | 9.54% | 5.70% | 0.025 |
| 4 | 3.88% | 2.46% | NS | 16 | 11.16% | 10.25% | NS |
| 5 | 3.54% | 3.03% | NS | 17 | 4.29% | 2.94% | NS |
| 6 | 3.12% | 2.56% | NS | 18 | 5.83% | 3.74% | NS |
| 7 | 4.21% | 4.58% | NS | 19 | 7.39% | 3.17% | 0.005 |
| 8 | 4.09% | 3.00% | NS | 20 | 5.31% | 3.67% | NS |
| 9 | 4.60% | 3.14% | NS | 21 | 9.92% | 6.28% | 0.025 |
| 10 | 4.07% | 2.84% | NS | 22 | 13.23% | 8.69% | 0.01 |
| 11 | 4.61% | 2.86% | NS | XY | 4.31% | 4.57% | NS |
| 12 | 3.08% | 2.61% | NS | TOT | 5.54% | 4.04% | 0.001 |

The weight of the Interchromosomal Effect in Reciprocal Translocation Carriers



The weight of the Interchromosomal Effect in Reciprocal Translocation Carriers



The weight of the Interchromosomal Effect in Reciprocal Translocation Carriers

CONCLUSIONS:

- The comparison of the younger subgroups did not reveal any statistic differences in the overall rates and only chromosome 1 showed a marked increase of aneuploidy
- The comparison of the older subgroups showed an overall decrease in the aneuploidy rate in the subgroup of PGD patients (translocation carriers), and in the analysis chromosome by chromosome, chromosomes 14, 15, 19, 21, and 22 showed statistically significant reduction of the aneuploidy rate in this subgroup
- This suggests that translocation carriers do not have an altered meiotic patten that will subsequently lead to an increase of aneuploidy in most chromosomes. Just chromosome 1 appears to be affected for such phenomena and just in patients less than 35 yo.

The weight of the Interchromosomal Effect in Reciprocal Translocation Carriers

CONCLUSIONS:

- In counseling reciprocal translocation carrier patients in regards to aneuploidy, it is fair to state that younger patients do not have a significant increase of aneuploidy due to the presence of this type of translocation. The aneuploidy rate per chromosome for these patients is 3.1%, while for patients with normal chromosome is 3.0%
- Older patients actually have a reduction of aneuploidy when compared with patient with normal chromosomes, from a 5.5% per chromosome to a 4.0% per chromosome

Overall Conclusions on Interchromosomal Effect

- Reciprocal translocation does not show interchromosomal effect, but...

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- ICE might be reversed in female carriers
- ICE might be reduced or even reversed with age
- Chromosome 1 seems to be greatly affected by ICE in young carriers

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- ICE might be more present in other types of structural abnormalities like inversions

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- ICE might be sex dependant and with enhanced presence in male carriers
- ICE might be reversed in female carriers
- ICE might be reduced or even reversed with age
- Chromosome 1 seems to be greatly affected by ICE in young carriers
- ICE might be more present in other types of structural abnormalities like inversions
- We are just starting to understand ICE

Reprogenetics

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