Lifestyle and aneuploidy: Is there a correlation?

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Chromosome aneuploidy

- Hallmark of human reproduction
- Leading cause:
  - Pregnancy loss
    - ~60-80% of conceptions
    - ~4% clinically recognized pregnancy
  - Mental impairment
  - Developmental disabilities
Parental origin of aneuploidy

<table>
<thead>
<tr>
<th></th>
<th>Paternal (%)</th>
<th>Maternal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 13</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>45,X</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>47,XXX</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>47,XXY</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>47,XYY</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
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Sex-specific meiotic timelines
Risk factors for aneuploidy

- Advancing age
- Karyotype aberrations
- Lifestyle (diet/exercise)
  - Alcohol/drug use/smoking/caffeine
- Environmental/occupational exposures:
  - Air pollution, BPA, phthalates, benzene, pyrethroids
  - Infections
- Therapeutic exposures:
  - Chemotherapy/radiation

Advanced maternal age

![Graph showing incidence of aneuploidy by maternal age]
Lifestyle/environmental influence on oocyte aneuploidy

- Humans: link has been difficult to establish
  - Importance of maternal age
  - Separation in time: sensitive window (fetal) & nondisjunction
  - Heterogeneity in nondisjunction

- Mice: bisphenol A (BPA) exposure increased aneuploidy
  - Study could not be replicated
  - Complex interaction between diet on BPA aneugenic potential
    - Phytoestrogens in feed varied between batches
    - If exposed during fetal life, higher rates of aneuploidy

Risk factors for sperm aneuploidy

- Advancing paternal age?
- Infertility/karyotype aberrations
- Lifestyle (diet/exercise)
  - Alcohol/drug use/smoking/caffeine
- Environmental/occupational exposures:
  - Air pollution, BPA, phthalates, benzene, pyrethroids
  - Infections
- Therapeutic exposures:
  - Chemotherapy/radiation
Sperm aneuploidy

- All men have a proportion of aneuploid sperm (2-4%)
- > 50 published studies
- More frequent for chromosomes 21, 22, X & Y

Are sperm aneuploidy levels variable?

- 10 normal men - (340,534 sperm)
  - Sperm aneuploidy levels over 2 year period
    - 6 month intervals
    - Baseline remarkably constant
    - Stable variants consistently produce higher frequencies
    - Sporadic events significant increase or decrease in aneuploidy frequencies at a single time point
    - “life event” can exert an effect on sperm aneuploidy
Karyotype aberrations & sperm aneuploidy

- Frequency of unbalanced gametes reported varies:
  - Robertsonian translocations: 3-36%
  - Reciprocal translocations: 29-81%
  - Inversions: 1-54%
- PGD ESHRE consortium data collection X
  - 3,652 embryos: 74% unbalanced; 26% normal/balanced
- 47,XXY & 47,XYY males: 0-25%


Male infertility & aneuploidy

- Infertile men ~3x increase
- Aneuploidy increases with severity of the infertility phenotype
Lifestyle, environmental & therapeutic exposure studies

- Generally small sample sizes
- Comparisons between studies are problematic:
  - Age
  - Heterogeneity (subjects & study design)
  - Duration & length of exposure
  - Self-reported vs. measured exposures
  - Compounding effects that are near impossible to separate:
    - Lifestyle & occupation
    - Susceptibility
    - Metabolism
    - Interactions
    - Transient vs. fixed

Lifestyle exposures

- Smoking
  - Disomy: 3 (2x) 13 (3x); XX (1.5x); YY (2x); XY (2x)

- Alcohol: Disomy XY (1.38x); XX (linear increase)
  (Robbins et al 2005; Robbins et al 1997)

- Folate, zinc & antioxidants: Folate disomy XX (-0.75x)
  (Young et al 2008)

- Large study (n=212) associations with:
  - Coffee: Disomy 18; Tight underwear: Disomy 18 & nullisomy 13;
    Obesity: Disomy 21; Cell phone usage >11 yr: Disomy X & Y
  (Jurewicz et al 2014)
Environmental & occupational exposures

- Agents:
  - Pyrethroids (e.g., CDCCA, TDCCA, 3BPA)
  - Phthalate (e.g., DEHP, DEP, DBP)
  - Benzene
  - Air pollution
  - Polycyclic aromatic hydrocarbons (e.g., 1-OHP)
  - Organochlorines (e.g., PCBs, p,p’-DDE)

- Most studies report significant increases (<3x)

Chemotherapy exposure

- Testicular cancer & Hodgkin lymphoma patients
- Pretreatment aneuploidy levels significantly higher
  - Presence of cancer alone increased sperm aneuploidy
- Chemotherapy increased sperm aneuploidy levels
- Levels return to fertile range 18-24 months later
- Greater susceptibility of meiotic vs. premeiotic cells
Emerging picture (for males)

- Almost all studies have identified significant increases in aneuploidy correlated with all investigated exposures
- Moderate increases
  - 1 - 3x higher
  - Not a globally increased & not always the same error
- Exposures are often transient
  - Sperm aneuploidy levels therefore will likely fluctuate

Can epigenetic alterations induce aneuploidy?

- Exposures shown to affect DNA methylation, genomic stability, posttranslational histone modifications
  - Could contribute to the generation of aneuploidy
- “Silent” sperm cell carries unique epigenetic markings
  - Delivers “poised” set of developmental genes to the embryo
- Chromatin organization perturbations?
  - Could affect chromosome pairing & delivery of “poised” genes
Conclusions

- Association NOT causation
  - Mechanism of action?

- Are increased sperm aneuploidy levels clinically significant?
  - Transient vs. fixed?

- Significant differences between males & females
  - Temporal differences in meiosis
  - Timing of exposure

- Genetic differences (mRNA, spindle function, cohesins) susceptibility?

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