Deciphering genomic inversion events using optical mapping

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Background
Genomic inversions are a class of DNA structural variation (SV) that usually presents with two breakpoints that occur in cis and a subsequent 180-degree longitudinal turn of DNA. Copy-number neutral inversions are challenging to resolve using classical methods for SV detection as there may be no immediately obvious genomic alteration to infer orientation of the copy number neutral event. Inversions are often flanked by inverted repeats and have breakpoints embedded within repeat regions further complicating analysis.

Problems Characterizing Inversions

Copy number neutral inversions are challenging to resolve using classical methods for SV detection as there may be no immediately obvious genomic alteration to infer orientation of the copy number neutral event. Inversions are often flanked by inverted repeats and have breakpoints embedded within repeat regions further complicating analysis.

Methods

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Optical Mapping

Optical mapping (OM) is a new technology that can visualize single molecules along unbroken DNA strands >100 kb in length preserving the architecture of SVs harboring more than one breakpoint junction in cis.

Rationale

Given the mounting evidence for inversion rearrangements contributing to disease pathogenesis, we sought to employ optical mapping in combination with other genomic technologies to gain a more comprehensive picture of the genomic architecture at a given locus.

Results

Clinical Review:
- Delayed neuro-psychomotor development
- Craniofacial dysmorphisms
- Congenital heart disease

Optical mapping provides a complementary tool to characterize previously challenging structural variants.

Conclusions

The visualization of long lengths of unbroken DNA through optical mapping is critical in properly studying an SV with two breakpoints in cis.

As the role of structural variants in human disease becomes more clear, new methods like optical mapping may be required to study a structural aberration in its totality.

References

[Carvalho, C. M., Carvalho, J. R., & Krepsich, A. (2013). Molecular mapping of structural variants harboring repeat-mediating inversion breakpoints in the human genome. Hum Genet. 133(6), 751-760.]
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