Chromo Me Thriptic-chaos amongst the chromosomes!

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Those neat little packages of our nuclear genomes, parsed as 23 pairs one each from mom and dad, are creating much excitement and bemusement these days. Afterall, where would we be were it not for the mitosis or meiosis arresting actions of colchemid to splay and spread the chromosomes onto a two-dimensional substrate for deconstruction under the watchful eye of cytogeneticists then and now? Add a bit of coloration to reveal banding patterns and voila-the reconstructed map known as the karyotype displays our genomes front and center! 22 autosomes arranged in rank order according to size and the two sex chromosomes that follow comprise our most basic abstraction of who we are- genetically speaking. What happens to our chromosomes when cells are not dividing has been a long-standing question of how to keep track of the apportionment of 3 trillion base pairs when it comes time to sort these mischievous bearers of our genetic character during the M phase of meiotic or mitotic cell cycles.

With the completion of the human genome project, and the dawning of deep sequencing technology, the language of chromosomes has now reached well beyond the traditional anatomy of telomeres, centromeres and the like to the new age nomenclature of territories, domains, exomes, and introns. This new vernacular confers upon the concept of gene regulation in the two dimensional linear sense the character of vestigial. Instead, we have arrived at a place where we are finally able to probe the fidelities and infidelities of chromosomes in cells of the soma and germ line with remarkable resolution. The result-it is time to rethink the rules and

mechanisms that govern reshuffling of genes in the process of building an embryo with a unique genetic blueprint.

Long within the purview of homologous recombination, the repositioning and reconstitution of chromosome segments by translocation at breakpoints has been recognized as a source of genetic variability that is heritable and sometimes as the source of malignancies attributed to genetic instability. So too, the advent of preimplantation genetic screening (PGS), initially by fluorescence in situ hybridization (FISH), and later by the more reliable method of comparative genomic hybridization (CGH) has materially added to the toolbox of reproductive genetics enabling diagnosis of karyotypic signatures for the management of inherited diseases and embryo selection in the field of human ARTs. This issue of JARG covers both the history and future of applications of this kind in the review article featured this month from Gleicher. Also, readers will find in the paper from the Xuerong clinic a chance to measure the utility of such approaches for probing the underpinnings of recurrent pregnancy loss. But, the overarching question remains as to how these technologies serve the field of reproductive genetics at a time when some of the fundamental rules of chromosome order, rearrangement, and partitioning are undergoing revision at an alarming pace.

Enter the “new age” of **CHROMOTHRIPTIS** that was first described in a 2011 paper by Stephens and coworkers (Stephens, P.J. *et al.* Massive genomic rearrangement acquired in a single catastrophic event during cancer development. *Cell* **144**, 27–40 (2011).)

Chromothripsis refers to the remarkable observation of pulverization of whole chromosomes that then reorganize themselves into reconstituted iterations of their previous selves. Originally thought to be confined to cancer cells, and at the heart of the genetic instability that gives rise to certain tumors, Blumenthal and colleagues earlier this year provided compelling evidence to support the idea that chromothripsis does indeed occur in the germline (Nature Genetics 4 March 2012; doi:[10.1038/ng.2202](https://doi.org/10.1038/ng.2202)) often resulting

Capsule Human chromosomes are capable of rearranging themselves through a process known as chromothripsis, changing the way we view and monitor genetic variability in the somatic and germ cell lineages.

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in stable inversions that can be faithfully replicated and transmitted intact to viable offspring. What this will mean to the field of PGS is not yet clear and is unlikely to influence practical aspects of embryo selection. However, as Blumentahl and colleagues state, traditional karyotypic or chromosomal microarray approaches would be inadequate to reveal the origins of genetic rearrangements due to chromothripsis in either individuals of known carrier composition or in the case of events that may have taken place in the germ line during gametogenesis or following in vitro fertilization.

Discoveries of this kind mean that chromosome gymnastics like these will require discriminating investigations in the field of human ARTs and if demonstrated, contextualiz-

ing dynamic rearrangements during the life history of gametes and embryos will become a laudable future imperative beyond our traditional perspectives that embrace homologous recombination. Towards this end, I suggest the readers take to heart the imagery gracing our cover this month in the context of another important paper this year that identifies micronuclei in somatic cells as harboring those chromosomes that have engaged in the process of chromothripsis (Crasta et al., *Nature* doi:[10.1038/nature10802](https://doi.org/10.1038/nature10802)).

Time will tell as to our collective understanding of the chromosome further evolving or morphing into much more than that mainstay- the karyotype- as we face the fact that chaos amongst the chromosomes is here to stay!