On the Origin of the Origin of Down Syndrome (DS)

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Objective

Speculation on the molecular basis of chromatid synapsis and chromosome segregation is presented, There is evidence that the etiology of DS is associated with altered meiotic recombination, nondisjunction and advanced maternal age across populations. Knowledge of the molecular mechanisms of chromatid synapsis and chromosome segregation may provide insights into the biological origin of the origin of DS.

Methods

Sister chromatid cohesion is mediated by cohesin which is composed of the subunits, Smc1, Smc3, Scc1 and SA1 or SA2. Cohesin forms rings that can be opened to mediate entry and exit of DNA. Scc1 and Smc1 form entrance gates for sister chromatids, whereas Scc1 and Smc3 form exit gates. 1 (Gligoris et al., 2014; Huis in't Veld et al., 2014). Cohesin complexes that mediate sister chromatid cohesion must dissociate from DNA to allow chromosome segregation at the metaphase-to-anaphase transition.

Results

Mutations of the interface between Scc1 and Smc3 abolish cohesin’s ability to stably associate with chromatin and to mediate cohesion. The Scc1-Smc3 interaction is essential for a stable chromatin interaction. Cohesin with a destabilized exit gate does not support sister chromatid cohesion. Failure of sister chromatid cohesion may disrupt the normal pattern of disjunction by permitting sister chromatids to act as independent entities during meiosis (MI and MII). Similar effects may be anticipated in the cohesin complexes involving centromeres of homologous chromosomes.

Conclusion

It is proposed that de novo mutations in the cohesin complex, accumulating over time, prevent the correct and timely association of sister chromatids and homologous chromosomes, accounting for the altered meiotic recombination, nondisjunction and advanced maternal age across populations characteristic of DS. Analyses of the cohesin complex, particularly of the effect of mutations at various key complex sites, may provide further insight and delineation on the origin of the origin of DS.