Unraveling the Diverse Landscape of Genomic Abnormalities From Conception to Childhood

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Background: Genomic rearrangements are an important cause of genetic disease and a source of genetic and phenotypic variation. A comprehensive overview of the nature and frequency of cytogenomic abnormalities with adverse effects on human growth and development, from conception through pregnancy and into childhood, has never been attempted.

Methods: We undertook a comprehensive, multi-year analysis of the outcomes from preimplantation genetic screening (PGS) of embryos (N=3349) and chromosomal microarray analysis (CMA) of pregnancy loss (N=8118), prenatal (N=3245), neonatal (N=1351) and pediatric (N=7047) samples. All samples were analyzed by CMA except for a subset of PGS samples that were evaluated by next-generation sequencing.

Results: An interesting spectrum of unbalanced genomic abnormalities was identified in each of the sample types. For embryo samples, 47% (1583/3349) demonstrated clinically significant chromosomal abnormalities (CSCAs), the majority of which (77%) were single or multiple whole chromosome aneuploidies (WCAs) and interestingly, monosomies were 1.2 times more frequent than trisomies. For pregnancy loss, 54% (3975/7396) demonstrated WCAs or unbalanced structural abnormalities. The most common findings included single trisomies (63%), triploidy (12%) and monosomy X (11%). For prenatal samples, 13% (418/3245) demonstrated CSCAs. Trisomies were most common (41%) followed by segmental deletions and/or duplications (45%). Of 1351 neonatal samples (0- ≤29 days) evaluated, 18% had CSCAs with WCAs being the most common (6%) followed by segmental abnormalities (12%). For pediatric samples, CSCAs were present in 12% cases (854 of 7047), the majority of which were microdeletions (60%) or microduplications (23%).

Conclusions: The severity of the chromosomal abnormalities, primarily aneuploidies, detected in embryos or early pregnancy loss reflect the incompatibility with successful implantation or progression to viable pregnancy. In contrast, the frequency of significant genomic alterations detected prenatally and neonatally correlates with the incidence of significant physical and developmental abnormalities, but not necessarily incompatible with life. The pediatric samples showed a preponderance of less drastic microdeletions/duplications, which resulted in both syndromic and non-syndromic phenotypic abnormalities. These data reveal an interesting evolution of genomic alterations of decreasing severity as human growth progresses from conception though childhood.