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Large-scale cytogenomic analysis of samples from conception to childhood: a comprehensive assessment of the landscape of unbalanced genomic abnormalities

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Background: No large studies have cataloged chromosomal imbalances and their phenotypic consequences over the course of human development, from conception through early childhood.

Methods: We undertook a multi-year analysis of ~32,000 samples submitted for cytogenomic evaluation at different stages of human development, including embryo biopsies (N=6883), miscarriage (N=12324), prenatal (N=4176), neonatal (N=1564), and pediatric (N=7047) samples. Embryo biopsy samples were analyzed by arrayCGH or NGS and all other samples were analyzed by chromosomal microarray analysis (CMA).

Results: Clinically significant chromosome abnormalities (CSCAs) were identified in 45% (3105/6683) of embryo biopsies. The majority (70%) were autosomal whole chromosome aneuploidies (WCAs): 32% monosomies, 29% trisomies and 8% with monosomy and trisomy. Another 17% samples had complex abnormalities. In miscarriage samples, 54% (6665/12324) demonstrated CSCAs, the most common being autosomal trisomies (63%), triploidy (12%) and monosomy X (11%). Autosomal monosomies were rare (<1%). CSCAs were present in 13% (542/4176) of prenatal samples, with trisomies (41%) and segmental deletions/duplications (44%) being the most common. In neonatal samples 18% (273/1564) had CSCAs; WCAs (34%) and segmental abnormalities (65%) were the most frequent. For pediatric samples, CSCAs were present in 12% cases (854/7047); most frequent were deletions (60%) or duplications (23%).

Conclusions: This study provides a comprehensive view of the evolution of unbalanced genomic abnormalities with adverse effects on development from conception up to early childhood. Across all groups studied, the most severe chromosome abnormalities were detected in embryos and early pregnancy loss, resulting in failed implantation and/or non-viable pregnancy. The high frequency of autosomal monosomies in embryonic samples, rarely seen at later developmental stages, reflects the extreme vulnerability of cellular mechanisms that help maintain normal and stable genomic content. In contrast, the genomic alterations detected prenatally and neonatally are not necessarily incompatible with life, and the pediatric samples demonstrated a preponderance of less drastic deletions/duplications with significant diversity in terms of type and chromosomal involvement. These data reveal an interesting pattern of genomic alterations of decreasing severity as human growth progresses from conception through childhood.