

Department of Pathology

"Karyotype-Phenotype Correlations for Mosaic Down Syndrome"

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Little is known about the pathogenesis of the phenotype of mosaic Down syndrome (MDS). Thus, the primary goal of this study was to identify factors contributing to phenotypic variation by studying 107 individuals having MDS. To investigate a potential "threshold" effect due to trisomic imbalance, lymphocyte and buccal mucosa nuclei were scored using FISH. Overall, buccal cells had significantly higher frequencies of trisomy than lymphocytes ($p < 0.0001$). Also, diagnostic analyses showed higher trisomic percentages than assessments at later ages, suggesting a possible selection against trisomic lymphocytes over time ($p < 0.0001$).

Using latent class analysis, two phenotypic "classes" were identified. Patients from class 1 had significantly fewer traits and a lower percentage of trisomic cells compared to those from class 2. Tissue-specific influences were also detected, with buccal mucosa trisomy levels being significantly correlated with IQ ($p = 0.0094$) (both ectodermal derivatives), while congenital heart defects were significantly correlated with lymphocytes ($p = 0.0286$) (both mesodermal). Phenotypic influences due to the nondisjunction/recombination event(s) resulting in mosaicism were also seen, with significantly more traits being observed in probands having 2 copies of an identical allele(s).

(MII/mitotic errors)($p=0.03$). However, the majority (35/37) of mosaic cases arose from two nondisjunctional errors (meiotic and mitotic).

The potential impact of trisomy 21 on telomere length was evaluated in the isogenic trisomic and euploid cells of mosaic probands using a semi-quantitative FISH assay. Significantly longer telomeres were seen in the trisomic cells from the youngest probands (5 months to 11 y.o.), with significantly shorter telomeres being seen in the trisomic cells from the oldest (11 y.o) proband.

In conclusion, variation in phenotype (allowing for the distinction of two classes) was influenced by the percentage of trisomic cells (with tissue-specific effects being observed), as well as the chromosomal malsegregation/recombination error(s) that gave rise to the mosaicism. Furthermore, the impact of a trisomic imbalance for chromosome 21 was observed on a cellular (telomere lengths) as well as an organismal level. The results of this study should provide geneticists and other health care professionals with more complete information regarding optimal diagnostic approaches, anticipated clinical outcomes, and recurrence risks for families having a child with MDS.