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Abstract Topic: - Molecular and cytogenetic diagnostics

Abstract Title: - When the eye fails to see what the mind knows: Is there a role for further testing in patients with Down phenotype and normal karyotype?

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Aims: - 1. To estimate the frequency of partial trisomy 21 in patients with Down phenotype and a normal karyotype.

2. To estimate the frequency of complete trisomy 21 mosaicism in patients with Down phenotype and a normal karyotype.

Methods: - All patients clinically suspected to have Down syndrome who were karyotyped in our center between 2016 and 2022 and found to exhibit normal karyotypes were included in the study. Clinical and laboratory data were retrieved from medical records. FISH testing was performed on stored cell pellets where available, or otherwise on de-stained previously banded slides. A commercial FDA approved probe targeting sequences mapping to 21q22.13q22.2 (chr21:39,372,983-39,784,773 on GRCh37) located in the DSCR was used. FISH signals were read on 100 interphase cells by two independent readers. A laboratory derived cut-off for trisomic signal patterns was used to determine positivity.

Results: - During the study period, a total of 375 patients with clinically suspected Down syndrome were karyotyped, of which only 35 (9.3%) patients showed a normal karyotype. All of the 35 patients were subjected to FISH. One patient among the 35 (2.9%; 95% confidence interval range -2.7% to 8.4%) showed 3 signals representing trisomy of the target sequence in 100% interphase cells. Furthermore, this finding was confirmed by chromosomal microarray (CMA) which showed a segmental trisomy involving 95 OMIM genes within the DSCR (arr[GRCh37] 21q22.12q22.3(37394747-48093361)x3). None of the patients showed evidence of low level mosaicism for trisomy 21. The patient with the duplication was a 3-year-old female who presented with mild developmental delay, bilateral club foot and facial dysmorphism suggestive of Down syndrome.

Conclusions: - One among 35 patients in our study showed duplication of the DSCR which was not evident on karyotype. Further studies would help to determine a more accurate estimate of the proportion which, based on the upper limit of the 95% confidence interval in our study, could reach upto one in 12 patients who are negative on karyotype. Based on our findings, we conclude that when karyotype is negative in a patient with a suspected Down syndrome, further testing by FISH or other molecular tests is indicated to exclude a cryptic duplication within the DSCR.

Keywords: - During the study period, a total of 375 patients with clinically suspected Down syndrome were karyotyped, of which only 35 (9.3%) patients showed a normal karyotype. All of the 35 patients were subjected to FISH. One patient among the 35 (2.9%; 95% confidence interval range -2.7% to 8.4%) showed 3 signals representing trisomy of the target sequence in 100% interphase cells. Furthermore, this finding was confirmed by chromosomal microarray (CMA) which showed a segmental trisomy involving 95 OMIM genes within the DSCR (arr[GRCh37] 21q22.12q22.3(37394747-48093361)x3). None of the patients showed evidence of low level mosaicism for trisomy 21. The patient with the duplication was a 3-year-old female who presented with mild developmental delay, bilateral club foot and facial dysmorphism suggestive of Down syndrome.