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Practical Tips for Paediatricians
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Lessons learned from a child with a chromosomal abnormality but no major congenital anomalies

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A 9-year-old female was referred to Genetics with the possible dual diagnoses of 3p deletion and 9p duplication syndromes based on a chromosomal microarray (CMA) report of an unbalanced chromosomal translocation resulting in 3p deletion and 9p duplication.

She was the first child born to non-consanguineous German parents with an unremarkable family history. Her mother had well-controlled type 1 diabetes throughout pregnancy. Our patient was delivered at 38 weeks via caesarean section with a birth weight of 3.28 kg. The perinatal course was otherwise unremarkable.

By 7 years of life, she had a history of poor growth due to feeding difficulties. The CMA was requested by her paediatrician as part of initial blood tests to investigate her poor growth. All other tests were normal. She underwent adenoidectomy after which her growth parameters improved.

Her CMA showed a 4 Mb terminal loss of 3p26.3–p26.1 which included the four OMIM morbid genes (*CHL1*, *CNTN6*, *CNTN4*, and *CRBN*) implicated in the characteristic features of 3p deletion. In addition, there was a 4.4 Mb 9p24.1–p24.3 duplication, previously reported in individuals with autism and cognitive delays.

When she presented to Genetics, her growth parameters were all above the fifth percentile. The patient had good overall health, no systemic anomalies, and no dysmorphic features. She had normal development and was performing well at school. Her mother was later confirmed to have the same CMA finding.

3p deletions and 9p duplications can each lead to recognizable syndromes characterized by developmental delay, autism, and distinct dysmorphic features (1,2). However, neither the patient nor her mother had any dysmorphisms or clinical signs suggestive of either syndrome. There have been reports of normal or minimal phenotypes found in patients with a 3p deletion or 9p duplication, but not both in the same patient; our case is certainly unusual, but given the normal phenotype, the findings are likely incidental.

By the time that our patient presented to Genetics, her growth parameters were within normal limits, which would not have qualified her for a CMA test. Follow-up parental studies confirmed that the copy number variants (CNVs) were maternal in origin. The patient's mother had well-controlled type 1 diabetes without anomalies or health concerns. We were able to research the literature for similar cases of normal phenotype associated with these changes (1,3,4). The family was reassured after viewing these reports. In such cases of discrepancy between cytogenetic findings and clinical presentation, a close collaboration between the paediatrician and genetic team is paramount to best counsel the patient's family.

While CMA is a powerful diagnostic tool, it should be ordered under appropriate clinical indications. In Ontario, Ministry of Health-funded CMA requires one of two indications: developmental delay and/or a minimum of two congenital anomalies. The list of those physical anomalies is broad and may range from major to minor birth defects. Paediatricians are now more aware of genetic testing and are proactive in requesting CMA for patients who meet the minimum criteria. Our patient initially presented with growth parameters below the third percentile

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for age, which met testing criteria. CMA was ordered as a routine 'screen' test as opposed to a diagnostic test. The family was unaware of the nature of the genetic test that was performed as part of routine blood work. Limitations of the test and potential outcomes (such as incidental findings [IFs], variants of uncertain clinical significance) were not discussed. The pathogenic change was concerning to both the referring paediatrician and the patient's family as it gave the patient a dual diagnosis, which she clearly did not have.

Our case illustrates many challenges of genetic testing, specifically test indications, informed consent, IFs, and result interpretation.

As a pangenomic test, CMA can identify CNVs that are IFs. IFs can cause significant parental anxiety and label patients with diagnoses they do not have. Pre-test counselling should be routinely performed prior to genetic testing; physicians need to educate patients on the risk of IFs and obtain informed consent. Current evidence shows that this is not routine practice (5,6). Interpretations of IFs can be equally challenging for physicians—many report uncertainties returning IF results to patients, which has ethical implications (5). This is further complicated by a lack of standardized training in genetics for paediatricians.

In summary, our case provides several important tips for paediatricians: choose CMA judiciously under proper indications, provide pre-test counselling including the risk of IFs and obtain informed consent, interpret reports with caution, utilize available genetic education resources, and refer to Genetics when further evaluation is needed.

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