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ABSTRACT BOOK

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Unique phenotype in a brazilian girl with syndromic robin sequence and a 5.6 mb deletion in xp11.4p11.3.

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Background: The Pierre Robin sequence is a rare condition characterized by micrognathia, glossoptosis, and upper airway obstruction. Almost half of the cases has associated multiples anomalies, being classified as syndromic Robin sequence or as Robin Plus sequence. The etiology of syndromic cases is heterogeneous and frequently unclear. Clinical follow up and molecular genetic tests are essential for a proper diagnosis.
Aims: To investigate the genetic etiology of the atypical phenotype of an patient with syndromic Robin sequence.
Methods: Clinical genetic evaluation and SNP array
Results: The patient is a 5–year-old Brazilian girl born to normal and nonconsaguineous parents. Clinical evaluation at age 7 months showed microtrigonocephaly, abnormal structural nervous system (Dandy-Walker variation), left microphthalmia, ocular hypertelorism, broad nasal bridge, abnormal skin crease in nasal tip, Robin sequence, abnormal ears, partial syndactity of 2nd and 3rd fingers, dysphagia, heart defect (atrial septal defect and bicuspid aortic valve) and developmental delay. The clinical follow-up at 5 years old showed worsening of the craniofacial phenotype with arched eyebrows, long palpebral fissures, arched upper lip, and low-set prominent and abnormal ears. She also had a short neck with pterygium coli. She showed a moderate developmental delay: she was able to walk with support, maintain eye contact, socially smile and understand simple orders. SNP-Array showed a heterozygous deletion in the X chromosome: arr[hg19] Xp11.4p11.3(40,648,211-46,310,832)x1. Parental samples were not tested.
Summary/Conclusion: The patient has a pattern of clinical anomalies that do not fit in a known syndrome. The deletion found by SNP-array include two X-linked dominant genes (KDM6A and CASK) that could, at least in part, contribute to the atypical phenotype. For instance, haploinsuficiency of *KDM6A* results in X-linked Kabuki syndrome. The patient shows clinical findings compatible with Kabuki syndrome, such as long palpebral fissure, abnormal ears, dysphagia and developmental delay. Additionally, MICPCH syndrome (Mental retardation and microcephaly with pontine and cerebellar hypoplasia) is caused by heterozygous mutation or deletion in the *CASK* gene. Although some features of MICPCH are compatible with the phenotype of our patient, such as microcephaly and hypertelorism, the brain and eye anomalies, sensorineural hearing loss and epilepsy do not match the symptoms of our patient. This variable phenotype could be due to the X-inactivation pattern. Furthermore, the overlap of our patient´s phenotype with other syndromes with midline defect such as Baraitser-Winter syndrome could point to a possible influence of other gene(s) variation(s) in the full phenotype. Atypical clinical presentations may be the expression of blended clinical phenotypes arising from independent pathogenic events at two loci. Whole exome sequencing could help elucidate this intricate syndromic Robin sequence phenotype.