Case report of Wolf-Hirschhorn Syndrome by Chromosomal Microarray Analysis: Importance of the Molecular Investigation for the Etiological Diagnosis of Short Stature.

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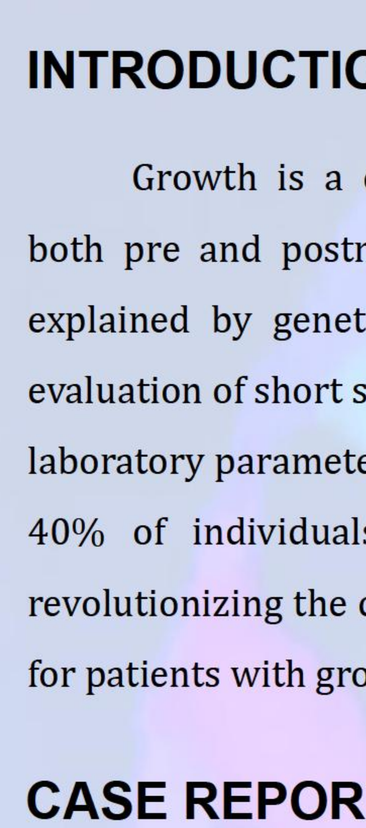
INTRODUCTION

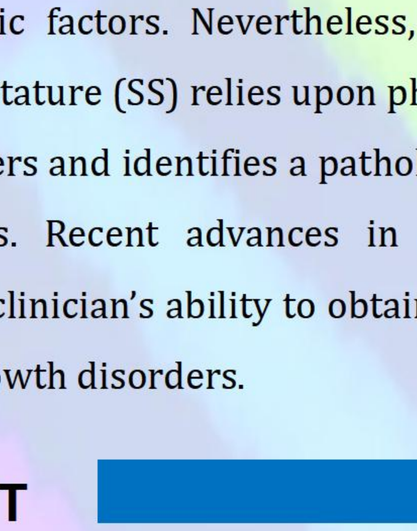
Growth is a complex process influenced by several factors both pre and postnatal, in which 80% of the height variation is explained by genetic factors. Nevertheless, the standard medical evaluation of short stature (SS) relies upon physical examination and laboratory parameters and identifies a pathological cause of SS in 1–40% of individuals. Recent advances in genetic diagnosis are revolutionizing the clinician's ability to obtain a molecular diagnosis for patients with growth disorders.

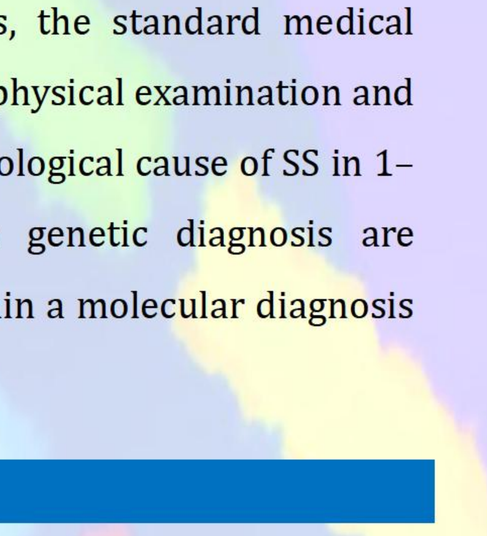
CASE REPORT

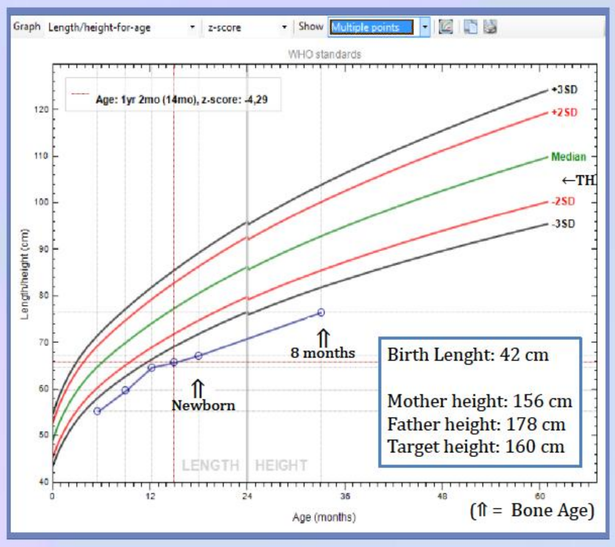
We report a female patient, 14 months old, presented with severe SS (- 4,29 Z-Score), IUGR, neonatal jaundice, syndromic *facies* (microcephaly, prominent glabella, high arched eyebrow, broad nasal bridge, ocular hypertelorism, short filtrum, mouth turned down, micrognathia, malformed ears), delayed psychomotor development, intra-atrial communication and seizures. She had normal thyroid function, IGF1, Ca, P, PTH, glycemia, cortisol, renal and hepatic functions, a female karyotype, without any suggestion of chromosome alteration.

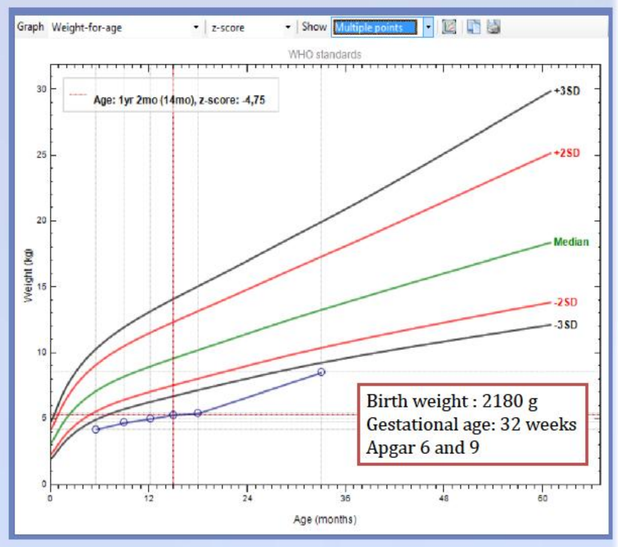
We performed the Chromosomal Microarray Analysis (CMA) on the proband and her parents (Affymetrix's GeneChip CytoScan™ HD SNP array). CMA detected four *de novo* genomic imbalances, corresponding to a 3.86 Mb microdeletion (mDEL) at 4p16.3, a 1.55 Mb mDEL at 4p16.3; a 320 kbp microduplication (mDUPL) at 5p13.2 and a 4.21 Mb mDUPL at 9p24.3. The mDELs at 4p included the genes *LETM1*, *WHSC1*, *WHSC2*, *MSX1* that have been described as related to the Wolf-Hirschhorn Syndrome. The mDUPL at 5p included the *NUP55* gene, and the mDUPL at 9p included *KANK1* and *VLDRL* genes.











***NUP155* = Nucleoporin 155kDa**
Nucleoporins are an essential component of nuclear pore complex, involved both in binding and translocating proteins during nucleocytoplasmic transport. Important for cardiac physiology and is associated with the pathogenesis of atrial fibrillation.

***KANK1*=KN Motif And Ankyrin Repeat Domains**
The encoded proteins are important for cytoskeleton formation by regulating actin polymerization. Mutations in this gene cause cerebral palsy and spastic tetraplegia.

***VLDRL* = Very Low Density Lipoprotein Receptor**
VLDL Receptor is important for triglyceride metabolism and reelin (glycoprotein that helps regulate processes of neuronal migration) signaling pathway. Diseases associated with VLDLR include cerebellar hypoplasia and mental retardation.

***LETM1*= Leucine Zipper-EF-Hand Containing Transmembrane**
The protein maintain the mitochondrial tubular shapes and is required for normal mitochondrial morphology and cellular viability.

***WHSC1* = Wolf-Hirschhorn Syndrome Candidate 1**
The protein is expressed ubiquitously in early development. It is involved in transcriptional misregulation in cancer and Lysine degradation.

***WHSC2* = Wolf-Hirschhorn Syndrome Candidate 2**
Encodes NELFA (Negative Elongation Factor Complex Member A). Expressed ubiquitously with higher levels in fetal than in adult tissues, regulates the RNA polymerase II transcription elongation.

***MSX1* = Msh Homeobox 1**
The encoded protein functions as a transcriptional repressor during embryogenesis, play a role in limb-pattern formation, craniofacial development, particularly odontogenesis, and tumor growth inhibition.

CONCLUSIONS

The CMA findings allowed identification of genomic cause for the clinical features of the proband. Molecular diagnosis is important because it can end the diagnostic workup for the patient, it may alert the clinician to other medical comorbidities for which the patient is at risk, and it is extremely valuable for the genetic counselling.

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