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Intronic mutations affecting splicing of INTS12 cause VACTERL-like phenotype in a Palestinian family

By

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Abstract:

Background: VACTERAL association involves anal atresia, cardiac defects, renal anomalies, and limb abnormalities. The aim of our study was to identify the genetic causes of this disorder in a Palestinian family affected with similar phenotype which could also be a new syndrome.

Methods: Blood samples were collected from five members of a family with VACTERAL association and then DNA was extracted and subjected to Polymerase Chain Reaction (PCR) for suspected genes. Karyotyping analysis was performed. Whole exome sequencing was performed to investigate the causative mutation.

Results: Whole exome sequencing revealed a novel splice site mutation in integrator complex subunit 12 (INTS12) gene located on chromosome 4. This SNP (106,629,790 C>G) alteration leads to an inclusion for 66 bp from the intron into the coding sequence resulting in a larger polypeptide chain. 100 control cases were found negative for this INTS12 change.

Conclusion: Our results revealed an autosomal recessive association which affects many body systems in the embryo in the early prenatal life. This association results in presence of a cluster of congenital malformations. A splice site mutation in INTS12 that may affect the TGF-B1 pathway which is important in collagen expression and thus affect body tissue formation

Keywords: SALL1, SALL4, TOWNS BROCKS, VACTERAL association, INTS12, TGF-B.

DECLARATION

I declare that the Master Thesis entitled

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Signature: Walaa Hassan Mashahreh.

Dedication

I dedicate this thesis to my parents who were always there for me, to my beloved and supportive husband Kareem, and to all who supported me.

Acknowledgment

I wish to express my sincere thanks to my supervisor Prof. Mazin Qumsiyeh, to Prof. Moein Kanaan and the Hereditary Research Laboratory members Amal Abu Rayan and Lara Kamal for their help and support.

List of Abbreviations

ACTR	Activin Receptors
ALK	Activin Receptor-Like Kinase
AMH	Anti-Muellerian Hormone
ASD	Atrial Septal Defect
BMPs	Bone Morphogenetic Proteins
CBD	Congenital Birth Defect
FA	Fanconi Anemia
GDFs	Growth and Differentiation Factors
INTS12	Integrator Complex Subunit 12
LSVC	Left Superior Vena Cava
SALL1	Spalt Like Transcription Factor 1
SALL4	Spalt Like Transcription Factor 4
TBS	Townes-Brocks Syndrome
TGF-B1	Transforming Growth Factor Beta 1
VACTERAL	Vertebral anomalies, Anal atresia, Cardiac defects, Tracheoesophageal fistula, Esophageal atresia, Renal & Radial anomalies, Limb defects.
VCD	Ventricular Septal Defect

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