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Limited genotype-phenotype correlation in FOXP3 gene within same family member

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Introduction: FOXP3 protein is crucial in enabling T-regulatory cells to maintain tolerance to self-antigens. Mutations in human Foxp3 gene are associated with immune diseases, such as multi-organ autoimmune disorder, immune dysregulation, polyendocrinopathy, enteropathy and X-linked syndrome (IPEX).

Case Presentation: A 15 months old male, presented initially at 2 weeks of age with failure to thrive hyperglycemia and severe DKA, and a consequent diagnosis of neonatal diabetes. Genetic testing identified p.(Pro75Leu)mutation in the foxp3. At 1.3yr along with his diabetes the patient was growing well with only mild asthmatic symptoms. Family history revealed that: the mother is asymptomatic, a maternal cousin has IDDM since the age of 6 months, associated with a history of lymphadenopathy, and due to (autoimmune? Hemolytic?)anemia required recurrent blood transfusion. Another cousin had a history of neonatal DM, diagnosed at 6 months of age, and died at 6yrs after severe DKA complicated

of 6 months. A grandmother in her 50s was diagnosed recently with DM and has rheumatoid arthritis. His aunt had a history of gestational diabetes. Genetic screening for affected family members indicated that all share the same p.(Pro75Leu) genetic mutation of foxp3.

Conclusion: The variability in organ involvement and in timing of clinical presentation within the same family in spite of caring an identical mutation is unique especially given the monoallelic expression of the FOXP3 gene in males. It does suggest modifying genes that are significantly involved in the pathogenesis of IPEX syndrome. FOXP3 sequences should be perform in males with a history of neonatal diabetes inspite of not having yet developed autoimmune associated conditions. Further studies will delineate genetic and other modifier of FOXP3 gene that contribute to the variable clinical severity within the same family.

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