A Novel Mutation Causing Mendelian Susceptibility to Mycobacterial Disease

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Introduction

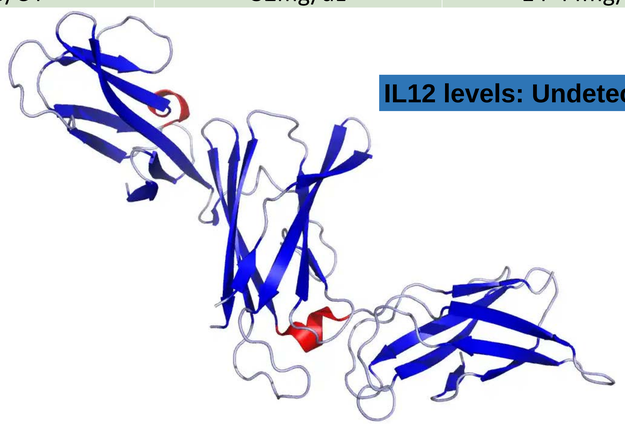
Mendelian Susceptibility to Mycobacterial Disease (MSMD) is a diverse group of diagnoses related to impairment in the immune response to intracellular pathogens, which can be mediated by defects at many points along the way in the mononuclear phagocyte/T helper cell type 1 axis. Symptoms typically present in childhood with infection caused by non-pathogenic mycobacteria such as the BCG vaccine. Immunodeficiency 29 is the subset of MSMD caused by mutations in IL-12. We describe a novel mutation causing Immunodeficiency 29 in an Active Duty patient.

Case Report

A 38y/o female was evaluated for frequent diarrheal illnesses and upper respiratory infections with prolonged treatment courses. Initial evaluation was concerning for common variable immune deficiency based on low immunoglobulin levels. Response to protein vaccines was normal, while response to polysaccharide vaccines was impaired. History concerning for recurrent infection with intracellular pathogens, including *Salmonella,* was not classic for CVID, so further evaluation with genetic testing was undertaken. This revealed a 5 base-pair duplication causing a frameshift mutation in the *IL12B* gene (p.TyrArgfs*59). Further testing revealed undetectable levels of IL12, consistent with Immunodeficiency 29.

*The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Air Force or the Department of Defense.

Lab Test	Result	Normal
IgA	212mg/dL	70-400mg/dL
IgG	**679mg/dL**	700-1600mg/dL
IgM	**29.4mg/dL**	40-230mg/dL
PCV Response	**43.50%**	>70%
Diphtheria Response	Positive	Positive
Tetanus Response	Positive	Positive
C3/C4	129mg/dL/ 32mg/dL	82-167mg/dL/ 14-44mg/dL



IL-12B Protein Crystal Structure[1]

IL12 levels: Undetectable

Discussion

Case reports have demonstrated Immunodeficiency 29 in patients of Middle Eastern and Central Asian descent with homozygous loss-of-function mutations in the *IL12B* gene[2,3]. These have typically resulted from consanguineous unions. Our patient shows some classic signs of MSMD including recurrent infections with intracellular bacteria such as *Salmonella*, though she has been generally healthy. Typically patients with one mutant *IL12B* allele would not be expected to have MSMD symptoms. However, this patient's clinical history with finding of a single mutation in the suspected culprit gene seem to suggest either a symptomatic carrier state or an autosomal dominant inheritance pattern of this previously undescribed variant.

Conclusion

Immunodeficiency 29 is a rare cause of immune deficiency, previously only described as an autosomal recessive disease seen in children of consanguineous couples in the Middle East and Central Asia. Our patient demonstrates a novel mutation in a Caucasian female with no history of consanguinity. We hope this finding can add to the understanding of MSMD.

References

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