

Oligogenic Heterozygous Mutations Manifesting as Combined Primary Immunodeficiency

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ABSTRACT

Combined immunodeficiencies involving T and B lymphocytes are most commonly thought to be results of monogenic homozygous mutations. Our case illustrates a pediatric patient with potential clinically significant oligogenic heterozygous mutations with phenotypical manifestations of combined humoral immunodeficiency.

With the improved accessibility to immunodeficiency genetic testing further evaluation to confirm novel immunodeficiencies potentially oligogenic heterozygous mutations which previously were thought to be clinically insignificant may actually be pathogenic.

INTRODUCTION

Combined immunodeficiencies are defined as a deficiency of the immune system immune system involving more than one immunologic cell lineage. Depending upon the genetic defect these combined immunodeficiencies can be fully, partially, or non-penetrant. For most combined immunodeficiencies, homozygous mutations are believed to be requisite to see clinically relevant findings on laboratory evaluation. During the last decade, genetic testing for patients with immunodeficiencies has become more common. With this testing many results are identified as variants of unknown significance and often considered to be irrelevant.

CASE

The patient is a 12-year-old Amish male who was a full term infant who was found to have a critical coarctation of the aorta requiring surgical repair in his first weeks of life.

During his first three years of life, he had severe recurrent lower respiratory tract infections. During this time he was admitted to the hospital for respiratory infections on four occasions due to viral and bacterial etiologies, three of which required intubation for respiratory failure.

Early in life he had an immunological evaluation that revealed a persistent CD3+ T cell lymphopenia as well as a non-responsiveness to polysaccharide and conjugate pneumococcal vaccination. Evaluation for IL-2 Receptor gamma chain deficiency, ADA, STAT-5, RAG1 and RAG2, RMRP mutations were not seen. Sweat Chloride testing was normal.

Over the subsequent years, he has developed progressive CD19+ B cell lymphopenia. Intravenous immunoglobulin replacement and trimethoprim/sulfamethoxazole prophylaxis were initiated which resolved all severe respiratory infections.

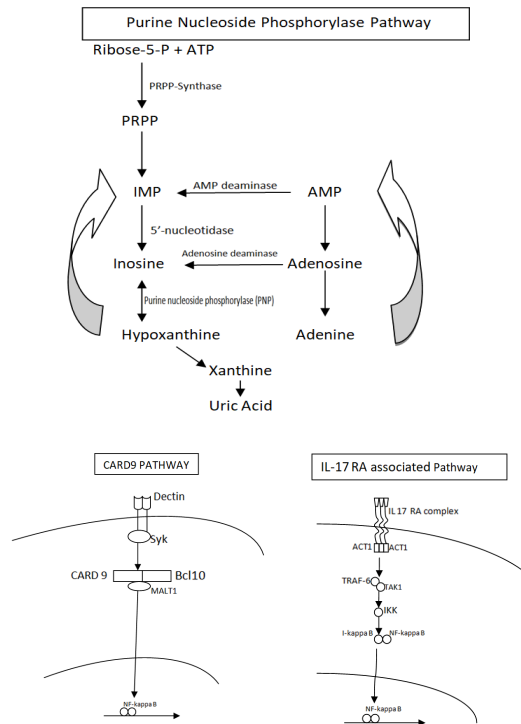
Recently genetic testing was performed revealing heterozygous variants of three genes involved in immunodeficiency including purine nucleoside phosphorylase (PNP), IL17RA, and CARD9.

His identified mutation via Invitae gene panel included:

Purine nucleoside phosphorylase (PNP) c.554G>A (p.Arg185His), heterozygous, Variant of Uncertain Significance

IL17RA c133C>A (p.Gln45Lys), heterozygous, Variant of Uncertain Significance

CARD9 c.1117G>A (p.Ala372Thr), heterozygous, Variant of Uncertain Significance



Discussion

Previously, many combined immunodeficiencies were thought to be monogenic in origin. This case represents the identification of suspected oligogenic heterozygous gene mutation variants which could potentially contribute as a source of his combined immunodeficiency. With the advancements and affordability genetic evaluation, previously underestimated gene variants and mutations may play a significant role in the understanding of the etiologies of immunodeficiencies as illustrated by this case.

We have found many individuals who have been classified with various forms of combined immunodeficiency or common variable immunodeficiency that genetic testing has revealed a number of variants of unknown significance. Clinically and by laboratory evaluation these patients have immunodeficiencies. These findings demonstrate that our current understanding of immunodeficiency inheritance will likely substantially advance in the coming years. Additionally, genetic mutations which previously thought to be insignificant may actually be pathogenic.

Conclusion

Our definitive previous understanding of combined immunodeficiency inheritance may not necessarily be correct. As genetic testing continues to become more affordable and readily available previously unrecognized significant mutations will become increasingly prevalent. It will be important to have further laboratory testing to confirm and understand the identified genetic defects.