

Impaired Response to Interferon- γ in a Child with Recurrent Atypical Mycobacterial Infections

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Clinical Case

- 3 yo Hispanic boy, born in US, no BCG vaccine
- Product of consanguineous marriage
- four anti-TB meds for pneumonia at 4 months of age
- Positive gastric cultures for MAC at 8 mo while on anti-TB
 - Bronchoscopy with endobronchial caseating lesions
 - Clarithromycin, Rifabutin, Ethambutol, Ciprofloxacin for one year
- Fever, hepatosplenomegaly, lymphadenopathy, weight loss 4-5 months after discontinuing anti-MAC meds
 - Restarted on four anti-MAC meds on which he has continued

Laboratory Findings

- Normal ALC 3780, CD4+ 1172, CD8+ 1739
- Diminished T cell response to PHA and candida (prolif or cytokines?)
- HIV negative
- Normal immunoglobulin levels
- Bone marrow biopsy
 - Hypercellularity

Assessment for IFN- γ /IL-12 Pathway

- Cytokine production studies
 - Normal response to IL-12
 - Almost absent response to IFN- γ and IFN- γ & endotoxin
- Flow cytometry
 - Normal IFN- γ R1 expression
- STAT flow cytometry
 - Normal STAT phosphorylation to IFN α
- Gene sequencing
 - Normal IFNGR1 sequence

Preliminary Diagnosis: Mutation in IFN- γ R2

- Homozygous 2 basepair deletion in extracellular domain of IFNGR2
 - 1151delCC in exon 4
 - Frameshift mutation leading to stop
- Possible molecular consequences
 - Altered N-glycosylation site
 - Protein truncation**
 - Defective receptor recycling
- Inheritance pattern
 - Autosomal recessive
- Other IFNGR2 phenotypes
 - Dominant negative; no haploinsufficiency

Medical Management

- Long-term anti-MAC medications
- Long-term antimicrobials
 - May be indicated in this patient
- Candidate for IFN- γ therapy?

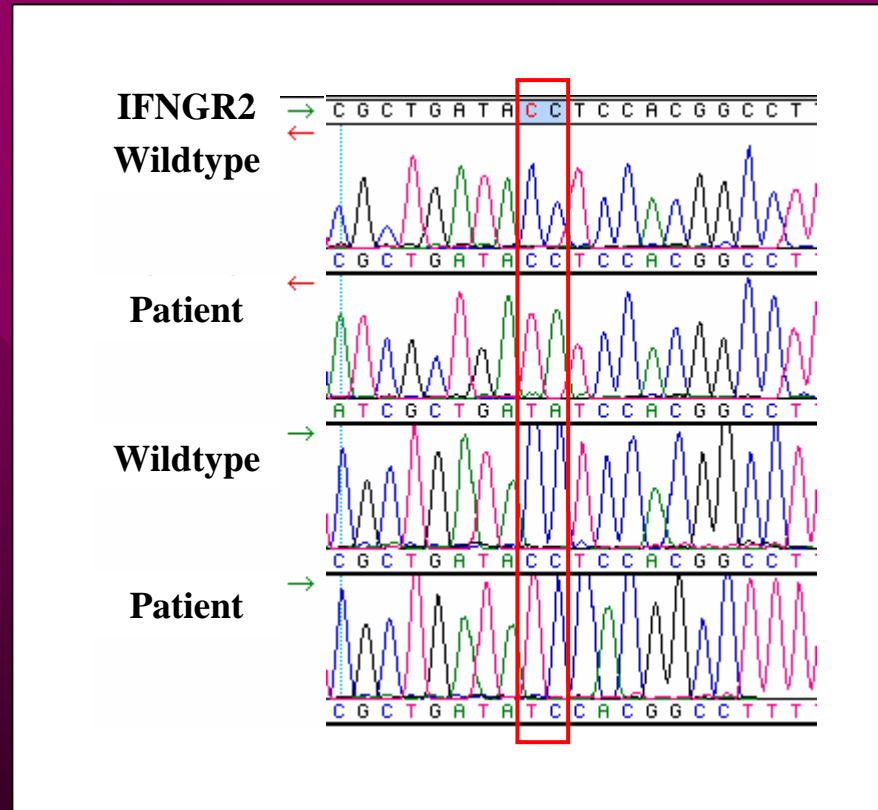
Issues to Consider

- Prognosis
 - Risk for morbidity and mortality
- Transplantation
 - Bone marrow or stem cell
- Genetic counseling
 - Probability that defect will be inherited by future siblings

Stem Cell Transplantation

- Roesler et al. :multi-institution survey of stem cell transplantation for autosomal recessive complete IFN γ R1 deficiency
 - High rate of graft failure, low rate of engraftment, unstable chimerism
 - Presence of mycobacterial disease may increase risk of failure
 - Survival advantage of IFN- γ R deficient cells
 - Best outcome with non-T cell-depleted transplant from HLA-identical sibling donor and fully myeloablative conditioning regimen

Mutation in IFNGR2



Interferon γ Receptor 2

