Texas Children's Hospital

BCM
Baylor College of Medicine

A Child With Combined Immunodeficiency, Alopecia and Mucocutaneous Granulomas

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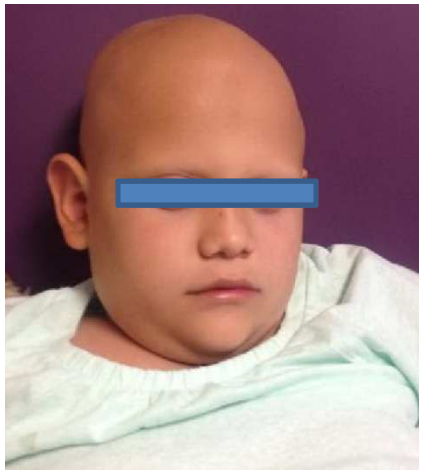
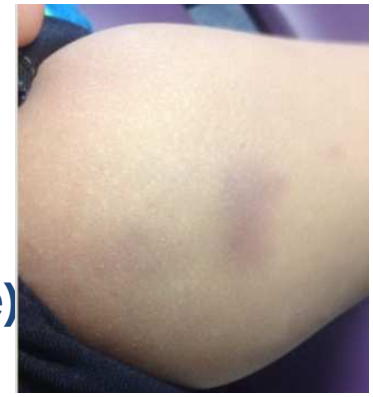
Clinical Presentation and Treatment

Initial presentation: 3 y/o Alopecia universalis, 10 nail dystrophy, recurrent infections: otitis media, diarrhea , >8 pneumonias
Low immunoglobulin levels, poor vaccine responses
-- **IVIG at 1gm/kg/month,** but continued viral infections



7 y/o: PJP pneumonia/intubation **(IV pentamidine)**
Diminished proliferative response (PWM)
Adequate T-cell numbers

7- 9 y/o: Ulcerating/scarring skin granulomas
Airway and bone granulomas
--nasal & tracheal masses **(4 surgical excisions)**
--Wrist mass with bony extension
Elevated CD20+, CD19/38+Br **(Rituximab; hydroxychloroquine)**



Lab Results

Immunoglobulins (mg/dL)	
IgG	543 [641 - 1353] ↓
IgA	<10 [66 – 295] ↓
IgM	<14 [40 – 180] ↓
IgE	<1 ↓

Vaccine titers (mg/dL)	
Diphtheria toxin IgG	<0.01 [>0.1] ↓
Tetanus toxoid IgG	<0.01 [>0.1] ↓
S. pneumoniae IgG	0/14 protective ↓

Lymphocyte proliferation	
Mitogens (PHA, ConA)	normal
Mitogens (PWM 10)	Low
Mitogens (PWM 100)	**normal**
Antigens(Candida, DT)	normal

NK cell function	normal
DHR Stimulation Index	192
Toll-Like Receptor Function	normal

Lymphocyte Phenotyping ALC = 4046cells/mm^3	
$CD3^+$	2225 (55% ↓)
$CD3^+CD4^+$	1643↓ (40.6%)
$CD3^+$ $CD8^+$	405 (10% ↓)
$CD19^+$	728 (18%)
CD20+	769 (19%) ↑
CD3-16^+ $CD56^+$	1052 (26%)↑
$CD4^+$ $CD45RA^+$	1214 (39%) ↑
$CD4^+$ $CD45RO^+$	343 (11%) ↓
$CD19^+$ 27^+	34 (2.26%)
CD19+CD27-IgM+IgD+	527 (89.7 %)↑
CD19+CD20+	586 (99.8%) ↑
CD19+CD38+Br IgM+Br	97 (16.6 %) ↑

Additional Diagnostic Labs	
Thyroglobulin Ab	92 ↑
Thyroid Peroxidase Ab	28 ↑
ANCA IgG	1:40 ↑

Differential Diagnosis

Clinical Summary:

- Hypogammaglobulinemia (4 isotypes), poor vaccine responses, B cell activation
- Poor but not absent T cell proliferation
- Normal NK cell function
- Autoimmune thyroiditis, granulomatous lesions (ulcerative skin & lymphoid), alopecia

Differential diagnosis:

- CVID
- AID deficiency
- Atypical ADA deficiency
- Atypical Jak 3 or IL7ra deficiencies
- Netherton syndrome
- Good Syndrome
- LRBA deficiency
- CTLA 4 deficiency
- Coronin 1A

Whole exome sequencing (WES) performed:

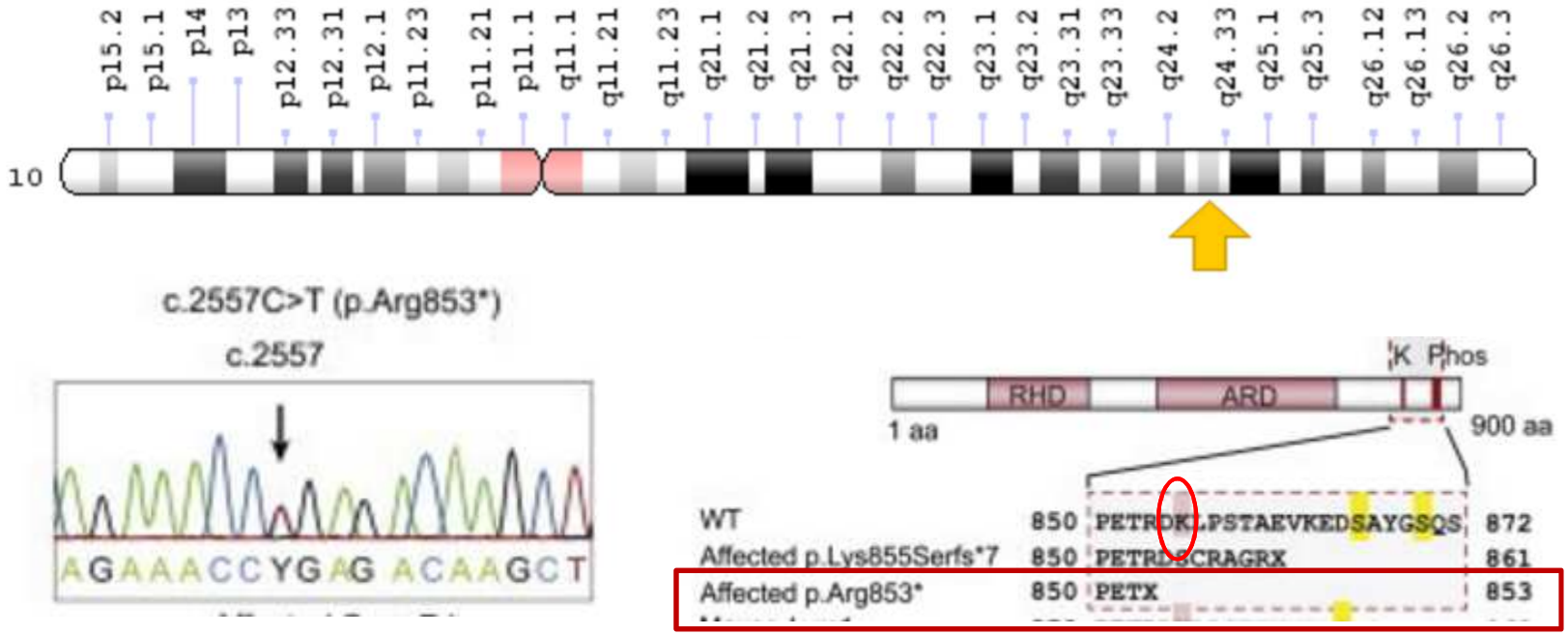
- AK2 het variant (VUS)
- **NFKB2 heterozygous variant**

Genetic Diagnosis by WES: NFKB2 Heterozygous Variant

Chromosomal Location

Cytogenetic Location: 10q24, which is the long (q) arm of chromosome 10 at position 24

Molecular Location: base pairs 102,394,110 to 102,402,529 on chromosome 10 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



NFKB2 Cohort Reports& Management

Cohort Description:

Immune: **Hypogammaglobulinemia and Recurrent infections**[1,2,3,4]

Endocrine: Adrenal insufficiency[1,2], **Thyroiditis**[2], Growth delay[2]

Autoimmune disease: **Alopecia**[2,3], **Nail Dystrophy** [2]

Our Patient: Ulcerative granulomatous lesions skin/bone/airway; PJP

1. Chen K, et al, **Germline mutations in NFKB2 implicate the noncanonical NF-κB pathway in the pathogenesis of common variable immunodeficiency.** Am J Hum Genet. 2013 Nov 7
2. Brue T, et al, **Mutations in *NFKB2* and potential genetic heterogeneity in patients with DAVID syndrome, having variable endocrine and immune deficiencies.** BMC Medical Genetics 2014 **15**
3. Lee CE, et al , **Autosomal-dominant B-cell deficiency with alopecia due to a mutation in *NFKB2* that results in nonprocessable p100.** Blood 2014 (124)
4. Liu Y, et al, **Novel NFKB2 mutation in early-onset CVID.** J Clin Immunol 2014 Aug;34(6)

Clinical Management:

Ig replacement

Thyroid replacement

Mineralocorticoid replacement

Growth hormone

Immunosuppressive therapy

Bone marrow transplant with T cell impairment?