# Twins with .....?..... Suspected to Early Onset Inflammatory Bowel Disease

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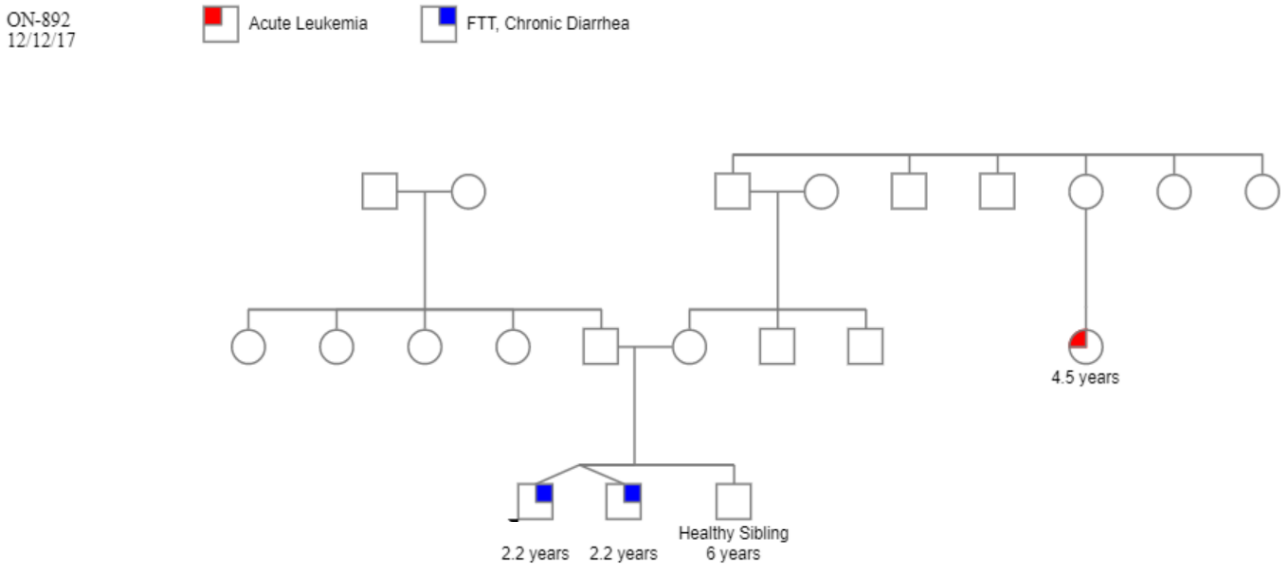
# Statement of the Problem

- This report describes clinical and laboratory features of twin brothers who were referred to the PID clinic with early-onset inflammatory bowel symptoms.



# History

- Two-year-old Iranian twin brothers were referred to “Children’s Medical Center” with a history of chronic non-bloody diarrhea.
- They were born to non-consanguineous parents.
- Their 7-year-old brother and both parents were apparently healthy.

# Hospital Course

- Their first hospital admission was at the age of 2 months following pneumonia.
- Both had experienced recurrent respiratory symptoms and two episodes of otitis media.
- Pancolitis revealed for one of the brothers with more severe gastrointestinal symptoms (B1).
- PCR confirmed CMV + EBV colitis > B1 underwent intravenous Gancyclovir.
- They had failure to thrive and several admissions due to severe watery diarrhea.
- Complementary investigations demonstrated *G6PD* deficiency in the twins, that was in accordance with episodes of jaundice and hemolytic anemia.

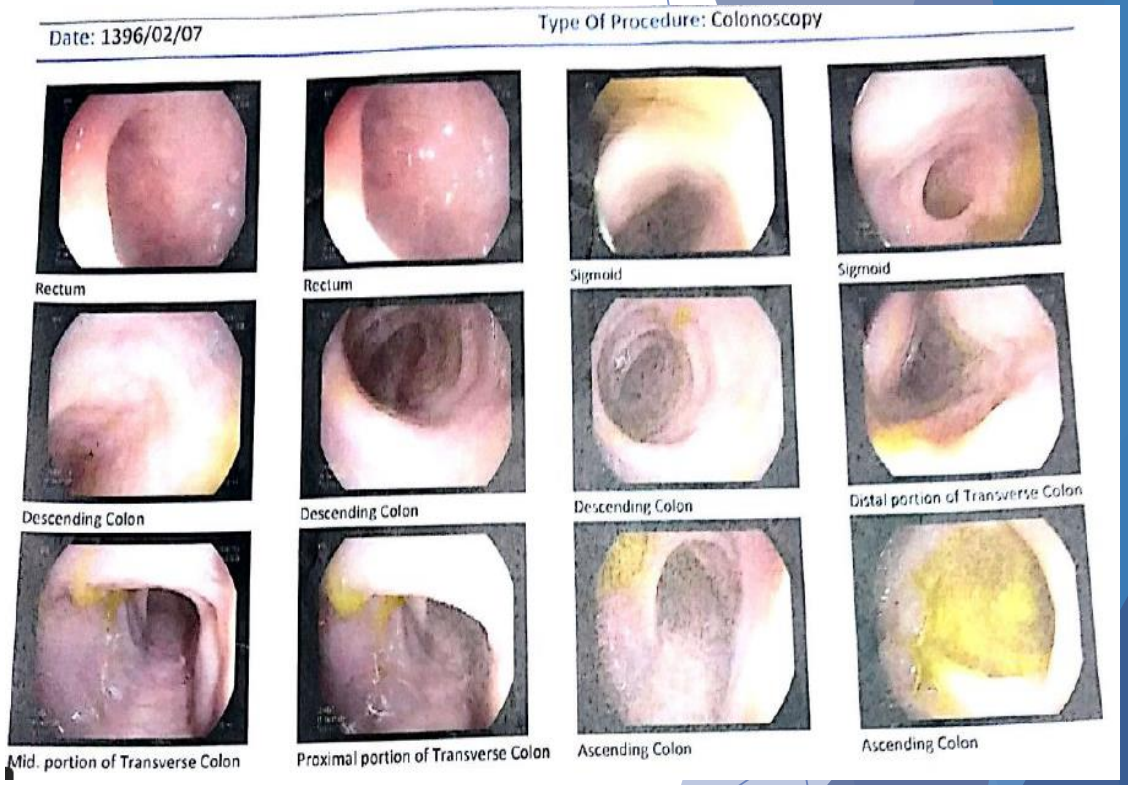
# Investigations

| | B1 | B2 |
|---|---|---|
| Birth Weight | 2400 | 2750 |
| Current Weight | 7500 | 9000 |

| | B1 | B2 |
|---|---|---|
| WBC | 16.4 | 14.9 |
| Lymph. | %40 | %60 |
| NEU. | %48 | %28 |
| Mono. | %5 | %8 |
| RBC | 4.4 | 4.11 |
| Hb | 9.8 | 11.4 |
| Plt | 912000 | 852000 |

# Investigations

- Pancolitis revealed for one of the brothers with more severe gastrointestinal symptoms (B1).
- PCR confirmed **CMV + EBV colitis** > B1 underwent intravenous Gancyclovir.
- **Barium swallow**, **Barium Meal**, and **Small Bowel Follow Through**: NL for B1
- Endoscopy: NL for B1 and B2



# Investigations

| | B1 | B2 |
|---|---|---|
| **CD3** (%39-73) | 44 | 72 (upper NL) |
| **CD4** (%22-62) | 5 (very low) | 4 (very low) |
| **CD20** (%25-50) | 14 | 16 |
| **CD8** (%11-32) | 36 | 64 |
| **CD16** (%8-17) | 1.36 | 4 |
| **CD19** (%13-29) | 14 | 15 |
| CD4/CD8 (%1-3) | 0.13 | 0.06 |

| | B1 | B2 |
|---|---|---|
| **IgG** (6.58-18.37 g/l) | 7.6 | 9.2 |
| **IgA** (0.8 – 3.5 g/l) | 0.52 | 1.1 |
| **IgM** (0.4 – 2.5 g/l) | 0.49 | 0.9 |
| **IgE** (<144 g/l) | 33 | 29 |

| | B1 | B2 |
|---|---|---|
| **CMV IgM (<0.85)** | 0.3 | neg. |
| **CMV IgG (<6)** | 208 | Neg. |
| **EBV VCA IgM (<0.5)** | 1.89 | Neg. |
| **EBV VCA IgG (<0.75)** | 3.65 | Neg. |
| **HIV AB** | Neg. | Neg. |

# Next generation Sequencing-based gene panel

HOM

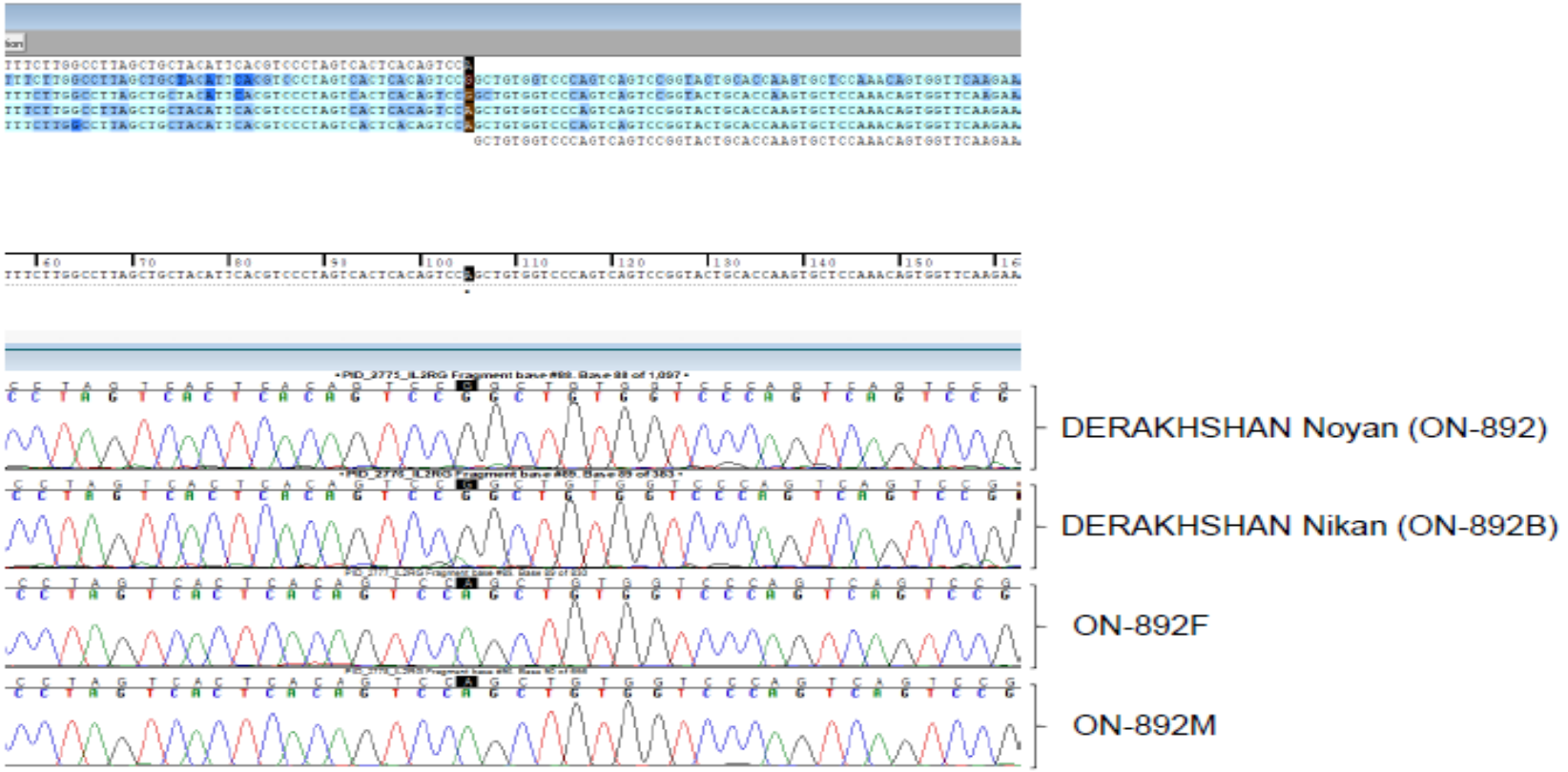
| GENE | CHR | POS | SNP ID | R | A | IMPACT | AA | ID | MAF | READS | SIFTcat | PolyPhenCat | CADD score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| G6PD | X | 153761205 | rs5030869 | C | T | MISSENSE | A381T | ENST00000369620 | 0.0001918 (23 hemi, 35 het) | 436 | deleterious | possibly_damaging | 23,6 |

HET

| GENE | CHR | POS | SNP ID | R | A | IMPACT | AA | ID | MAF | READS | SIFTcat | PolyPhenCat | CADD score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SLC11A1 | 2 | 219257737 | . | C | T | MISSENSE | R400C | ENST00000233202 | 0.00001269 (3 het) | 794 | deleterious | probably_damaging | 24,4 |
| AK2 | 1 | 33486974 | rs192209857 | G | A | MISSENSE | T140I | ENST00000354858 | 0.000007959 (2 het) | 1323 | deleterious | probably_damaging | 27,1 |
| COL7A1 | 3 | 48616679 | . | C | T | MISSENSE | R1780Q | ENST00000328333 | 0.00003895 (11 het) | 234 | deleterious | probably_damaging | 28,3 |
| ROR1 | 1 | 64240096 | . | G | A | MISSENSE | R3Q | ENST00000371079 | NA | 14 | NA | benign | 23,1 |
| TRNT1 | 3 | 3186381 | . | T | CCGACTCT | FRAME_SHIFT | L199*PT? | ENST00000251607 | NA | 24 | NA | NA | 35 |
| TRNT1 | 3 | 3186382 | . | T | G | FRAME_SHIFT | L199FSS? | ENST00000251607 | NA | 24 | NA | NA | 46 |
| PRF1 | 10 | 72358365 | . | C | G | MISSENSE | R371T | ENST00000373209 | NA | 416 | deleterious | possibly_damaging | 19,81 |
| ZNF341 | 20 | 32357987 | . | G | T | MISSENSE | R504L | ENST00000375200 | NA | 269 | deleterious | probably_damaging | 32 |
| IL2RG | X | 70330010 | . | C | G | MISSENSE | W197S | ENST00000374202 | NA | 95 | deleterious | probably_damaging | 29,3 |
| IL2RG | X | 70330011 | . | A | G | MISSENSE | W197R | ENST00000374202 | NA | 95 | deleterious | probably_damaging | 28 |

# Investigations

Family Sanger Segregation



# Twins with NOVEL X-LINKED VARIANT IN *IL2RG* GENE Suspected to Early Onset Inflammatory Bowel Disease

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# Conclusion & Significance

- X-linked severe combined immunodeficiency (SCID) is caused by the *IL2RG* gene which encodes a protein called the common gamma chain.
- Several variations have been identified in the *IL2RG* gene, which potentially are able to prevent the production of proteins or lead to producing nonfunctional versions.

- In this report, twins with a novel *IL2RG* gene variant were described.
- Based on genetic analysis both parents were wild type and symptom-free.

HOW THIS COULD BE POSSIBLE?

# Conclusion & Significance

- Bowel inflammatory symptoms were the very early disease manifestations.
- X-linked SCID was established as the final diagnosis.
- The *IL2RG* gene variant was the only responsible change in the patients' genome and in spite of other patients reported with X-linked SCID, the early clinical presentations were significantly different.

Various SCID manifestations could be a result of different mutation sites,

even in the same gene defect.


# Questions?