David's Case	NOTES
Phenotype This is the true story of David Vetter ("Boy in the Bubble"), although his specific genetic variant is not known. Due to a brother who had previously died of SCIDS at 7 months, David was placed in sterile-isolation at birth and based on bloodwork was diagnosed with SCIDs.	He lived in a "bubble" at home or in the hospital his whole life, due to the lack of an exact match for a bone marrow transplantation – to prevent what was considered inevitable contraction of a deadly infection. Eventually, as his condition began to seriously deteriorate, he received a bone marrow transplant which inadvertently infected him with Epstein Barr Virus. He died of Burkitt's Lymphoma. Now, new gene therapy-based treatment protocols are being developed – so the exact gene/variant cause of the disorder could provide a new potential therapeutic option.
Preliminary Diagnosis	Severe Combined Immunodeficiency Syndrome (SCIDS) with low T- and B-cell numbers
Genetic Variation(s)	IL2RG: c.343T>C, p.Cys115Arg
Laboratory Assertion(s)	pathogenic
Variant Information: • Asserted interpretation listed in **ClinVar**	pathogenic
• HGVS names from **ClinVar**	NG_009088.1:g.5939T>C NP_000197.1:p.Cys115Arg
• Is population data available in **dbSNP**?	rs111033622 Exceedingly low variant levels seen.
Gene Information in NCBI Gene: • Symbol and Name	IL2RG & Interleukin 2 Receptor subunit Gamma
• Gene Summary • Tissue Expression information	IL2RG: The protein encoded by this gene is an important signaling component of many interleukin receptors, helping to coordinate the structure and the function of interleukin -2, -4, -7 and -21 complexes, and is thus referred to as the common gamma chain. Mutations in this gene cause X-linked severe combined immunodeficiency (XSCID), as well as X-linked combined immunodeficiency (XCID) - a less severe immunodeficiency disorder.
• Gene Ontology information	Expressed in the lymph node, thymus, appendix, spleen, and a few other tissues such as intestine, bone marrow and bladder.
	Contributes to IL2, IL4, IL7 and IL15 Receptor activities Involved in T- and B-cell differentiation Involved in immune response
Ultimate Impacted Biomolecule based on: • **GDV** to view the chromosome and gene region	Located in the coding region within exon 3.
• **RefSeqGene Graphics** view of gene region and transcript(s)	Located in the coding region within exon 3.
• **RefSeq Protein Graphics** view of protein and domains	This variation replaces a Cysteine with an Arginine.
• **CDD or iCn3D** to view a structure*, as needed*	This wildtype encoded Cysteine is normally involved in a disulfide bond. Loss of the Cysteine not only disrupts the disulfide bond-held structural stabilization, but the charged and hydrophilic Arginine further unfolds the protein due to interactions with the aqueous environment.
Proposed Molecular Mechanism of Variant Impact	Loss of the disulfide bond prevents proper folding of the IL2RG protein, which is recognized by the cell's "unfolded protein response" and targets the protein for degradation.
How does this relate back to the phenotype (symptoms/clinical features & diagnosis)?	The degradation of the IL2RG protein prevents proper formation of a number of interleukin complexes, thus drastically disrupts the signaling and coordination of T-cells and B-cells – rendering virtually the entire immune system non-functional. This causes the patient to be dangerously susceptible to infections and eventually death.