X-LINKED SEVERE COMBINED IMMUNODEFICIENCY

(X-SCID)

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Genomics and Medicine

What is X-SCID?

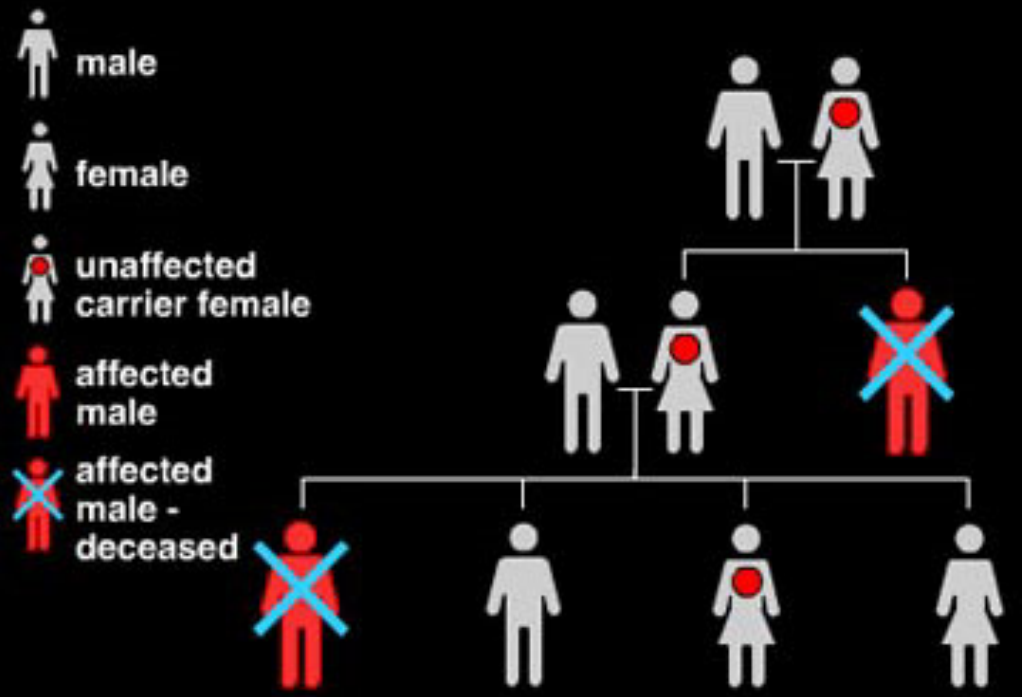
- X-Linked Recessive Trait
- Affects the immune system
- Usually affects only boys
- Symptoms include numerous infections before the person is three months old, pneumonitis, moniliasis, and eczema-like rashes

What does it do?

- Affects the B and T lymphocytes, specialized white blood cells that defend one from infection by viruses, bacteria, and fungi
- When one has X-SCID there is a lack of T and natural killer (NK) lymphocytes and non-functional B lymphocytes

Inheritance

- Females have two copies of the X –gene, and so they are usually only carriers of the disease
- Carrier women have a ¼ chance of having an affected son, and a ¼ chance of having a carrier daughter



Punnett Square of carrier female and unaffected male.

Blue- Carrier daughter

Red- Affected son

	X	Y
X	XX	XY
x	Xx	xY

Classical Diagnostic Methods

- Lymphocyte count
  - Very low number of T cells
  - Nonfunctional B cells present
  - NK cell number either low or nonexistent

Cell Type	Lymphocyte Counts			Control Values	
	Average	Range	% of Affected Individuals	Average	Range
Total lymphocytes	<2,000		70%	7,300 [1]	4,000-13,500 [1]
				5,500 [2]	>2,000 [2]
T cells	200	0-800	90-95%	5,500	>1,800
B cells	1,300	0->3,000	5%	800	700-1,300
NK cells	<100		88%	800	

More Classical Diagnostic Methods

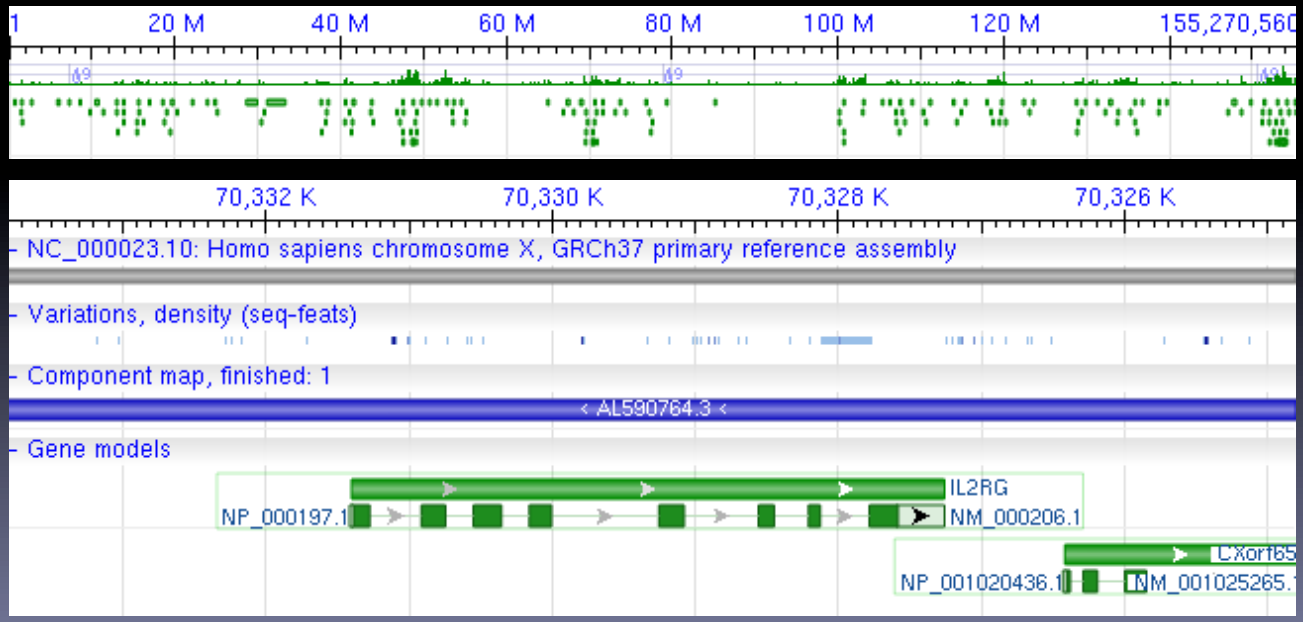
- Lymphocyte functional tests
  - No antibody response to vaccines and infectious agents
  - T cell responses to mitogens are lacking
- Immunoglobulin concentrations
  - Low serum concentrations of IgA and IgM
  - Normal amount of IgG at birth, but disappearance of IgG by three months of age
- Thymus
  - Absence of thymic shadow on chest X-ray

Classical Treatment

- Bone marrow transplantation
  - Try to use HLA-matched bone marrow transplantation from a relative
  - If that is not available, haploidentical parental bone marrow depleted of mature T cells is used
  - Matched, unrelated donor transplantation of bone marrow or cord blood stem cells can also be used, but GVHD is a significant problem
  - Finally, peripherally harvested hematopoietic stem cells can be used
- Administration of immunoglobulin

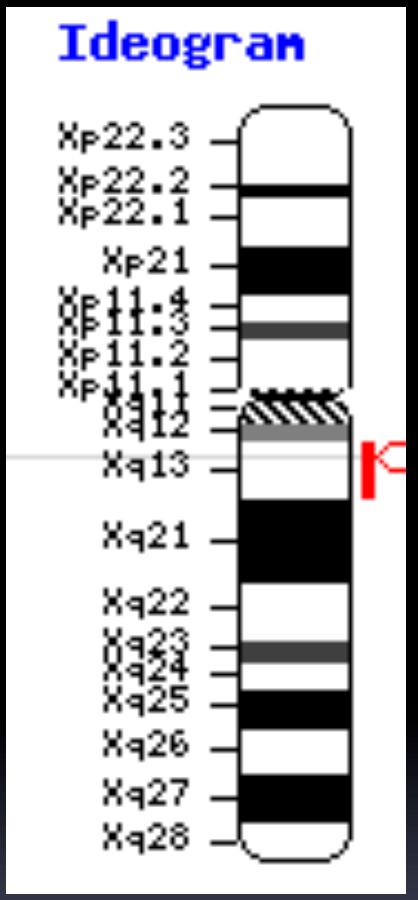
The Gene

- Chromosome X; Location Xq 13.1
- X-SCID results from a mutation in the interleukin 2 receptor gamma (IL2RG) gene
- Only known gene associated with X-SCID
- Prevents the proper development of T lymphocytes



Genetic Tests

- Diagnostic testing
  - Sequence analysis
    - Missense and nonsense mutations
    - Splice and regulatory regions
    - Insertions
  - Targeted mutation analysis
    - Large deletions
    - Complex mutations



Genetic Tests (cont.)

- Carrier testing
  - Testing for known family-specific IL2RG mutations
  - Sequence analysis of the IL2RG coding region and splice regions
  - Southern blot analysis
  - X-chromosome inactivation studies

Genetic Treatment

- Gene Therapy
  - Uses autologous bone marrow stem/progenitor cells retrovirally transduced with a therapeutic gene
  - Only considered for those who are not eligible for BMT or have failed BMT
  - Poses substantial cancer risk (leukemia), but at the same time has had success in curing the disease

References

Alexander Locke

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Wikipedia

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http://en.wikipedia.org/wiki/X-SCID