

X/Y chromosome variations & Immune System Health

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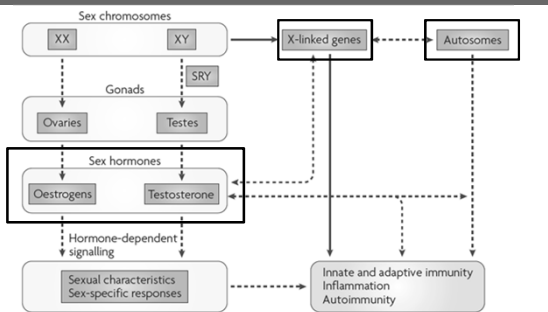
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Division of Endocrinology, LA
Children's Hospital
Mitchell Geffner, MD

Overview

- Why this presentation?
What is the Rationale for our Research?
- Introduction to the Immune System
- What we have found in our Research - Preliminary

Different mechanisms regulating immunity are triggered by the sex chromosome



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Libert et al (2010), Nature Review

X Chromosome contains many genes that control our immune system:

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The X chromosome in immune functions: when a chromosome makes the difference

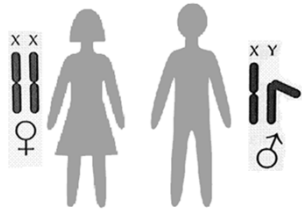
Libert et al (2010), *Nature Review*

Abstract | In response to various immune challenges, females show better survival than males; the X chromosome has an important role in this immunological advantage.
X chromosome-linked diseases are usually restricted to males, who have only one copy of the X chromosome; however, females are more prone to autoimmune diseases, and the X chromosome may be involved in the breakdown of self tolerance. Several hypotheses have been proposed in recent years that support a role for the X chromosome in shaping autoimmune responses. Here, we review the main mechanisms responsible for increased immune activity in females. This provides a survival advantage in the face of pathogenic insult but can also enhance the susceptibility of females to autoimmunity.

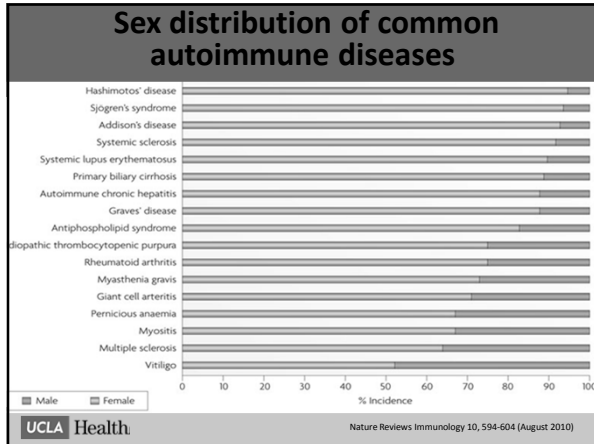
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The strongest genetic factor predisposing to autoimmunity is being female

Female : Male Odds Ratio = 3-10 : 1

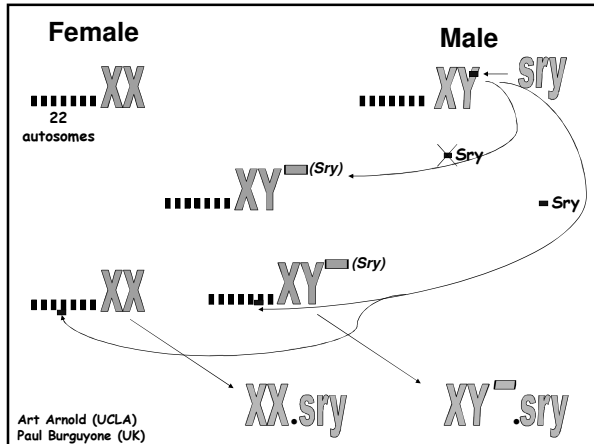


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Does Sex Chromosome genotype play a role that is independent of sex hormones?

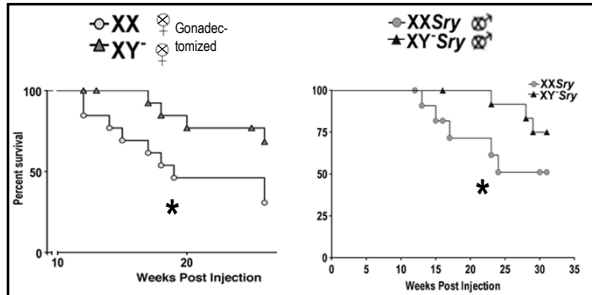
Dosage effect: XX vs. X:
0 vs. Y



Four Core Sex Chromosome Complement Model

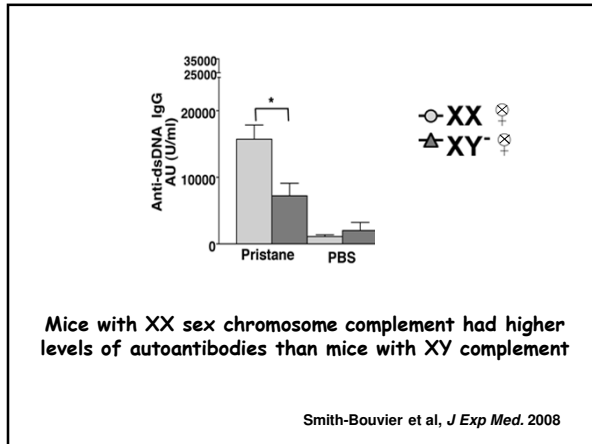
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Paul Burguyone (UK), Art Arnold (UCLA Department of Physiology)



Regardless of their gender or gonadal sex, mice that have XX chromosome have less survival from autoimmune disease than mice with XY chromosome

Smith-Bouvier et al, *J Exp Med*. 2008



Mice with XX sex chromosome complement had higher levels of autoantibodies than mice with XY complement

Smith-Bouvier et al, *J Exp Med*. 2008

**Regardless of their gender or gonadal sex,
XX mice developed more autoimmune
disease than XY mice**

Hypothesis

***Sex chromosome dosage, rather than the
sex itself, imparts gender dimorphism in
autoimmune diseases.***

**Translate murine findings onto
Human disease**

Approaches:

- 1. Study immune system in X/Y variation disorders**
- 2. Candidate X/Y gene approach**

BOY SCOUTS OF AMERICA

LOOKING TO THE FUTURE
for X&Y Chromosome Variations

2013 Conference • July 26-28 • Denver, Colorado

GENETIC.ORG KS-A TSSIS

Turner Syndrome Society of the United States

How X/Y chromosome variations affect the Immune System Health

Subjects enrolled thus far	Numbers
XX males	
47, XXY	48
47, XXY/XY Mosaic	2
48, XYY	1
46, XY/46,XX Mosaic	1
XYY males: 47, XYY	2
XY males: 46, XY	119
X0 females: 45, X0	40
XX females: 46,XX	150
XXX females 47,XXX	3

Analyze and Compare

- immune system components,
- immune system function, &
- immune mediated disorders:

XXXY vs. **XXY** vs. **XY** vs. **XYY** vs ...

- Age 7 years and older
- Questionnaire [website] and Blood

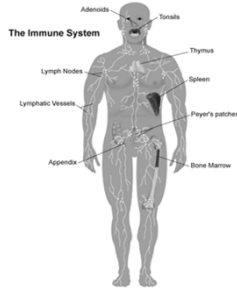
XXX vs. **XX** vs. **X0**

Overview

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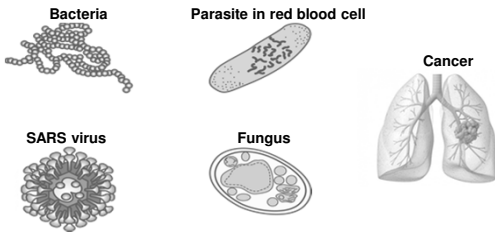
What is the immune system?

The immune system is a network of cells, tissues, and organs that work together to defend the body against attacks by "foreign" invaders.



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Immune system fights against the invaders in the body



to protect against disease or other potentially damaging foreign bodies.

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Architecture of the immune system

It is the 2nd largest organ in the body

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• **Bone Marrow:** The yellow tissue in the center the bones produces white blood cells.

Thymus (two lobes in front of the trachea behind the breast bone)

• **Spleen:** The largest lymphatic organ in the body contains white blood cells that fight infection or disease.

Lymph nodes (small organs shaped like beans, which are located throughout the body & connect via the lymphatic vessels)

Adenoids (two glands located at the back of the nasal passage)

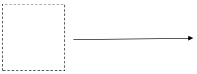
Appendix (a small tube that is connected to the large intestine)

Blood vessels (arteries, veins, & capillaries through which blood flows)

Lymphatic vessels (a network of channels throughout the body that carries lymphocytes to the lymphoid organs & bloodstream)

Peyer's patches (in the small intestine) **Tonsils** (in the back of throat)

Network of cells in various organs - Skin



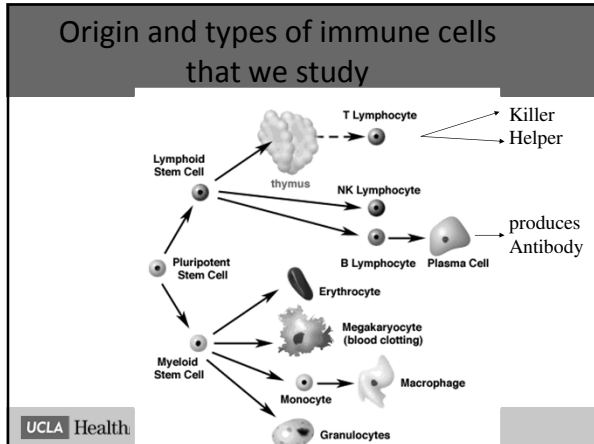
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The Immune system is a network of many immune cells and molecules

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What are lymphocytes?

- These small white blood cells play a large role in defending the body against disease.
- The two types of lymphocytes are
 - B-cells, which make antibodies that attack bacteria and toxins, and
 - T-cells, which help destroy infected or cancerous cells.
 - Killer T-cells kill cells that are infected with viruses and other pathogens or are otherwise damaged.
 - Helper T-cells help determine which immune responses the body makes to a particular pathogen.

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CD8+ T cells

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Ability to proliferate

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Memory in immune system

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Naïve and Memory T cells

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Immune phenotyping of PBMCs

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Cytokines

Immune cells release chemicals, called Cytokines, which trigger an immune response to combat cancer or a virus

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IL-4 producing cells

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Other immune cells

- **White blood cells, such as**
 - **phagocytes (engulfing cells) and**
 - **cytotoxic cells (natural killer cells),****actually kill the infectious microorganism by "devouring" it.**

http://www.youtube.com/watch?v=skPtWocTKdU&feature=player_embedded&t=1

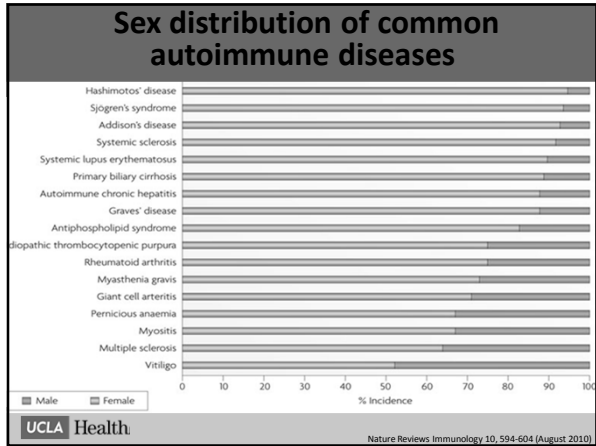
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What are disorders of the immune system?

- **Immunodeficiency** occurs when the immune system is not as strong as normal, resulting in severe infections.
 - **Gene defects**, such as severe combined immunodeficiency,
 - **acquired** conditions such as HIV/AIDS, or through the use of immunosuppressive medication.
- **Cancer** of the Immune system – Lymphoma
- **Autoimmunity** results from a hyperactive immune system attacking normal tissues as if they were foreign bodies.
- **Asthma and allergies.** A normally harmless material such as grass pollen, food particles, mold or pet dander is mistaken for a severe threat and attacked.

The immune system identify a variety of threats, including viruses, bacteria and parasites, and distinguishes them from the body's own healthy tissue.

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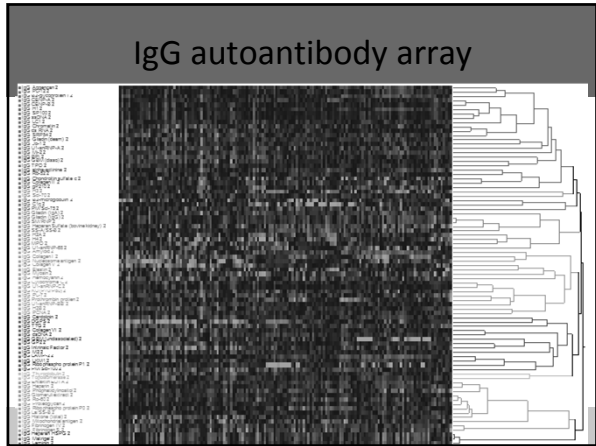


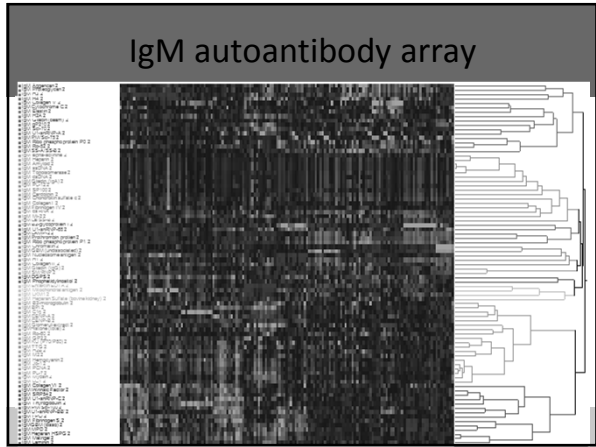
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X0 females	
45, X0	40
XX females	
46, XX	150
XXX females	
47, XXX	3

Increased levels of certain IgG autoantibodies in XX ♂ as compared to XY ♂

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Increased levels of certain IgG autoantibodies in XX ♂ as compared to XY ♂

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Some autoantibodies were lower in XX ♂ than in XY ♂

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IgM Autoantibodies in X0 females and XX females

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We have found many immune changes in relation to X/Y variation

- **Alterations in**
 - memory T cells
 - Killer T cells
 - Cytokine producing cells
- **More production of undesirable 'auto'antibodies, but no overt disease [or you are not telling me the full story]**

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Implications

- The altered proliferating and naive CD8⁺ T cells in X/Y variations might affect protection against certain infections where rapid CD8⁺ T cell expansion is needed.
- However, altered memory CD8⁺ T cell responses might pose difficulty in chronic infections and other conditions where long-term memory T cell responses are protective.

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Pitfalls with our study and how you can help

- We need more people to enroll in the study, so we can be confident about the results.
- Control participants: We also need samples from XY and XX individuals who are, ideally, 'matched' for ethnicity and age+/- 5 years.
- Follow up study: If you gave blood sample previously, we need your sample again.

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Implications of our study and Future Directions

- Might provide explanation for unexplained symptoms that you may have.
- Might help in
 - early diagnosis of immune related conditions,
 - proper use of vaccination against pathogens,
 - screening for autoimmune diseases, and
 - use of preventive strategies.

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X/Y chromosome variations & Immune System Health

You can enroll for this study, provide consent, & complete the Questionnaires at <https://ctq.ctrl.ucla.edu/ctq/login/>

We will then arrange for a blood sample to be drawn at your physician's office or at the next meeting. You may contact us at:

**uclastudies@yahoo.com
310-206-1883**

Thank You!!
