Manifesting Carriers: Skewed X Chromosome Inactivation.

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(revised)

Introduction

- In the past, it was thought that genetic defects on the X chromosome could only affect males.
- Assumption: because females inherit two X chromosomes, if one X is defective, chances are the other X is normal and will compensate.
- Advances in genetics now show that this is not always the case and that sometimes females do manifest X chromosome (chrm) diseases.
- This presentation explains how this happens in females who display symptoms of X-linked neuromuscular diseases.

Chromosomes

- Sequences of 4 chemicals form “words” that control protein synthesis: basis of living things.
- Each “coding” sequence represents a gene.
- Chromosomes: long strings of 1000s of genes.
- Humans have 46 chrms, found in 23 pairs:
  - 22 “ordinary” pairs (called autosomes):
    - Chrms (genes) in each pair show variations, but, overall, they match like a pair of candlesticks.
  - Plus one special pair of sex chromosomes:
    - There are 2 sex chrms in humans: X & Y.
    - X and Y always pair together (XX or XY).

Sex Chromosomes

- The two sex chrms are different and special:
  - X resembles most chrms, has many genes.
  - Y is far smaller, has few genes, main role: starts a cascade of events that makes embryo into a male.
- The sex chrm pairing determines the gender:
  - An XX (+ the other 22 autosomal pairs) is a female.
  - An XY (+ the other 22 pairs) becomes a male.
- In a female (XX), one X chrm comes from mom's egg & the other X, from dad's sperm.
- In a male (XY), the X chrm comes from mom's egg & the Y chrm from dad's sperm.

X - Linked Traits

- Almost every gene on the X chrm is unique to it – they are not found paired on the Y chrm.
- Because males (XY) have only one X chrm, they only have one copy of these genes.
- If a son inherits an X with a mutated gene (from mom), he usually shows disease symptoms.
- This holds even if the trait involved is recessive.
- Genes on the X chrm are called X-linked.
- Certain types of muscular dystrophy (e.g. Duchenne & Becker) are X-linked recessive.

X Chromosome Inactivation

- Female's cells all start with 2 X chrms.
- Two Xs would double the dosage of X genes & would disrupt the normal functions of the cell.
  - To avoid this, early in embryo growth, in each cell, one X is randomly selected & inactivated.
- The inactive X appears as a twisted ball called a Barr body: it is still reproduced in cell division.
- As cells are reproduced, they carry on with the same X inactivated and the same X functional.
- We see a patchwork of different Xs functioning in different cells – we call this a mosaic.

Mosaic Patterns

- Examples of mosaic patterns:

  - A tile floor.

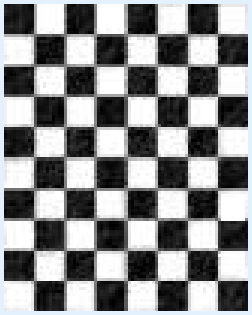
- Calico cat: Essentially, a white female cat that also carries X chrm genes for orange fur and for black fur. Random X inactivation yields some orange fur cells and some black fur cells randomly distributed over the white fur.

X Dosage Compensation

- In cases where a female has a gene mutation on one of her Xs, the other X copy is usually healthy. *Usually*, the healthy gene works normally & can "make-up" for the mutated gene.
- Because inactivation is random, some healthy Xs are tuned off and so are some of the mutated Xs. About 50% of healthy Xs are left active along with 50% of the mutated copies.
- Normally, a female who carries an X-linked defect on one X will not manifest the disease because enough healthy X chrms are left functional to compensate for the defect.

Mosaicism in Muscular Dystrophy

- Duchenne & Becker muscular dystrophy are caused by mutations in a gene on the X chrm:

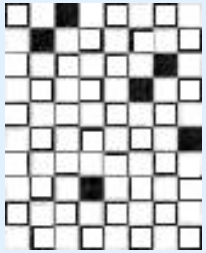


Normal random pattern.

- Females who inherit a mutated dystrophin gene (on the X chrm) will display a mosaic pattern:
- In females, some cells (white squares) will have the mutated X inherited from dad left active
- In females, some cells (black squares) will have the healthy X inherited from mom left active
- Normally, the ratio is 50 – 50 healthy to unhealthy active cells. This allows for enough normal protein production to minimize any symptoms of the disorder and she is an asymptomatic carrier.

Skewed X Inactivation

- Skewed means tilted to one side: not random.
- If the inactivation is skewed towards the healthy X chrm, then many healthy Xs (black squares) will be inactivated, leaving many defective Xs active.



Skewed pattern.

- When this happens, there may not be enough healthy Xs left to support normal function and the female may show symptoms of the illness.
- In some females, >90% of the healthy X chrms are inactivated (random would be 50%).

Carriers or Manifesting Carriers

- Females who have one normal X and one mutated X are carriers (usually asymptomatic).
- If skewed X inactivation knocks out >50% of the healthy Xs and leaves the defective X gene active in the majority of her cells, the female may show symptoms of the disorder, in some cases, as severe as an afflicted male. She is a manifesting carrier:
  - Degree of impact correlated to degree of skewing.
- Research questions: What causes a skew? Is it genetically controlled? Does it 'run in families'?

A Clinical Illustration

The gene linked to EDA became the first gene mapped to the X chromosome

- Typical patchwork pattern of affected tissues seen in a case of X-linked mosaicism in Ectodermal anhidrotic dysplasia (EDA):
  - Abnormal development of the skin and associated structures (hair, nails and teeth, and sweat glands).
- Muscle pathology and weakness may show a similar “patchy” presentation depending on the number of cells with a normal X chrm active and making correct protein in given muscle tissues.

Illustration: http://www.people.virginia.edu/~rjh9u/andysp.html

Another Clinical Illustration

Some cases are linked to X inactivation

- This illustration depicts the patchwork pattern seen in a rare disorder: Hypomelanosis of Ito.
- White patchy skin is often seen with other symptoms, including intellectual and developmental retardation, seizures & other neurological problems along with skeletal and dental problems. Linked to chromosomal mosaicism & sporadic mutations.

http://flatrock.org.nz/topics/science/dual_identities.htm

Manifesting Carriers

- Summary: normally, a female has enough healthy X chrms left active to protect her from symptoms of X-linked recessive disorders.
- A mom with a defective X chrm may pass it on to her children, thus she is called a carrier.
- If a female shows (manifests) symptoms herself, then she is called a manifesting carrier.
- A female can manifest symptoms at any age and whether or not she has children, if she:

  1). Carries a defective X gene and

  2). Has had skewed X inactivation occur.

Background Information.

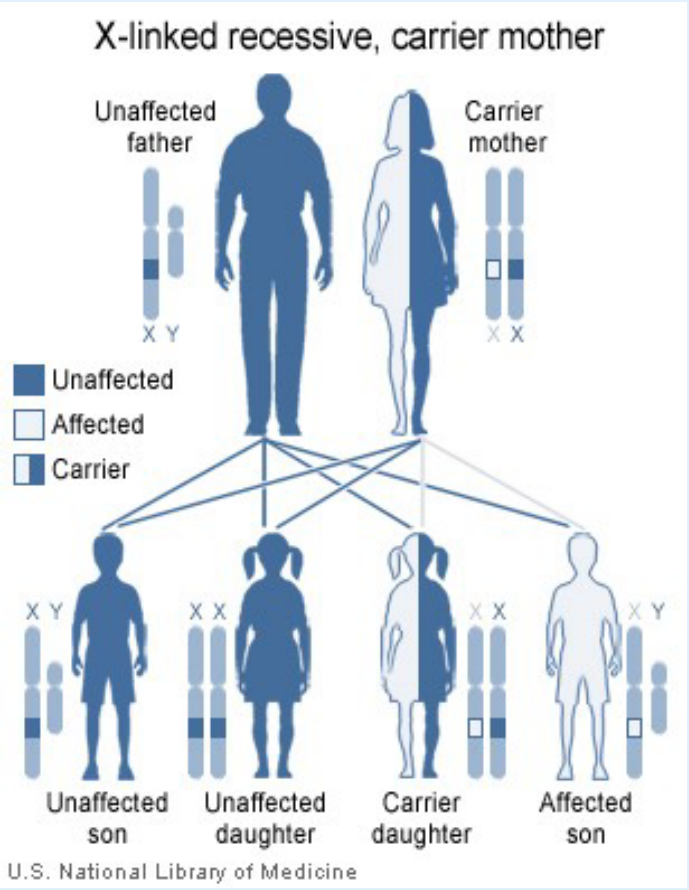
Gametes (Eggs & Sperm)

- Normal cells each have 46 chrms (in 23 pairs).
- When an egg & a sperm join, the first new cell formed must also have 46 chrms (23 pairs).
  - To achieve this, when egg & sperm cells are formed, they reduce their 46 chrms to 23.
  - An egg has 22 chrms + 1 X (1 of the female's 2 Xs).
  - A sperm cell has 22 chrms + either an X or a Y.
    - Child gets 23 chrms from each parent = 46 (23 pairs).
- In this step, a mixing of chrms / genes occurs.
- The "new" chrms create a unique offspring.

What Is Passed On

- Mothers (XX) can only pass on an X chrm.
- Half of the father's sperm contains an X, the other half, a Y, so he can pass on either.
- To be passed on, a defect must occur in the genetic code of genes in egg or in sperm cells:
  - The genetic code carried in egg & sperm cells is the only genetic material passed on.
- We call all other cells in the body somatic cells.
- Mutations of genes in somatic cells may lead to disease (e.g. cancer), but are not passed on.

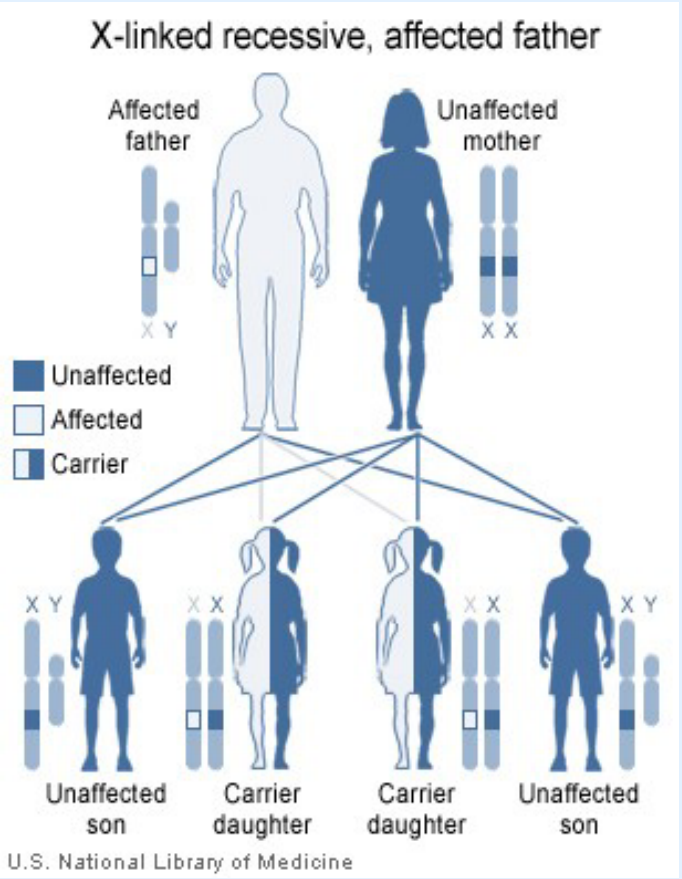
Recessive X Gene Inheritance – 1



- This illustration depicts a healthy father and a carrier mother.
  - Each daughter (XX) has a 50-50 chance of inheriting the defective X chrm from mom (and being a carrier).
  - Each son (XY) has a 50-50 chance of inheriting the defective X chrm from mom (and manifesting the disorder).

http://ghr.nlm.nih.gov/info=inheritance/show/risk_assessment

Recessive X Gene Inheritance – 2

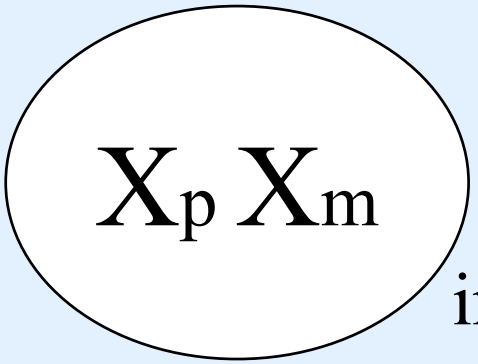


- This illustration depicts an afflicted father and a normal mother.
- If dad has an X-linked defect, he passes it on to all daughters but not to his sons (sons only get his Y):
  - Daughters are usually unaffected carriers.

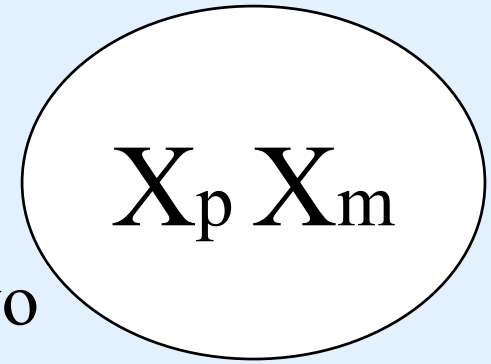
http://ghr.nlm.nih.gov/info=inheritance/show/risk_assessment

Female Cells (only sex chromosomes shown)

Xm = maternal X (from mom) Xp = paternal X (from dad)

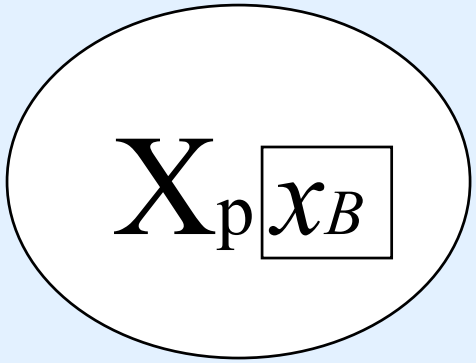


First few cells in the embryo

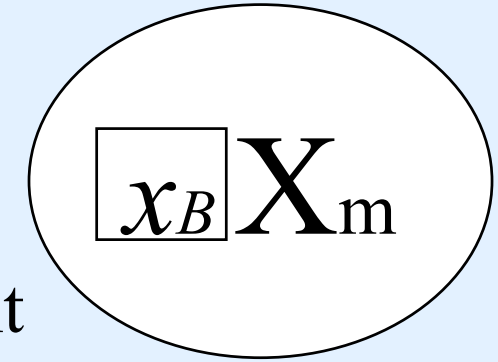


Both Xs active in each cell

↓ X inactivation occurs very early in embryo formation ↓



Mosaic pattern in all subsequent cells



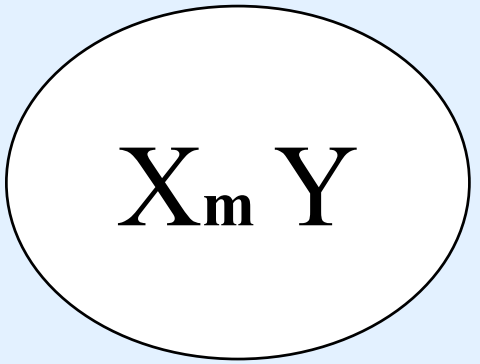
Only 1 X active per cell

Some cells have the Xp active, some, Xm

[Xb] = **Barr body: Inactive X**

Male Cells (only sex chromosomes shown)

Male Cells: Son always inherits the Y from dad and his X from mom (Xm). This X is derived from one of mom's two Xs, (either her Xp or her Xm).

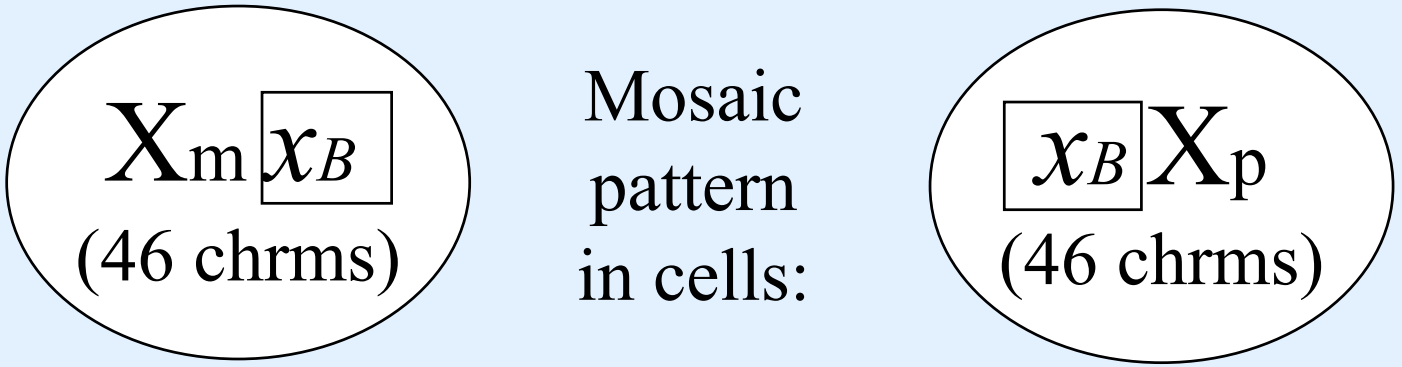


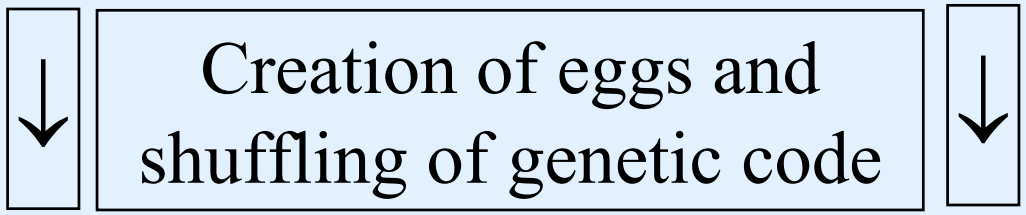
As a son only receives one X (always from his mother), X-linked disorders are passed from mothers to sons. If mom has a defective X and son inherits this X, then he will always display the disorder. Son can't get dad's X.

A daughter receives one of her Xs from dad. If this X carries a defective gene, she becomes a carrier and may pass it on, but normally, she does not manifest the disease (usually, her other X is healthy and compensates).

Creation of Eggs

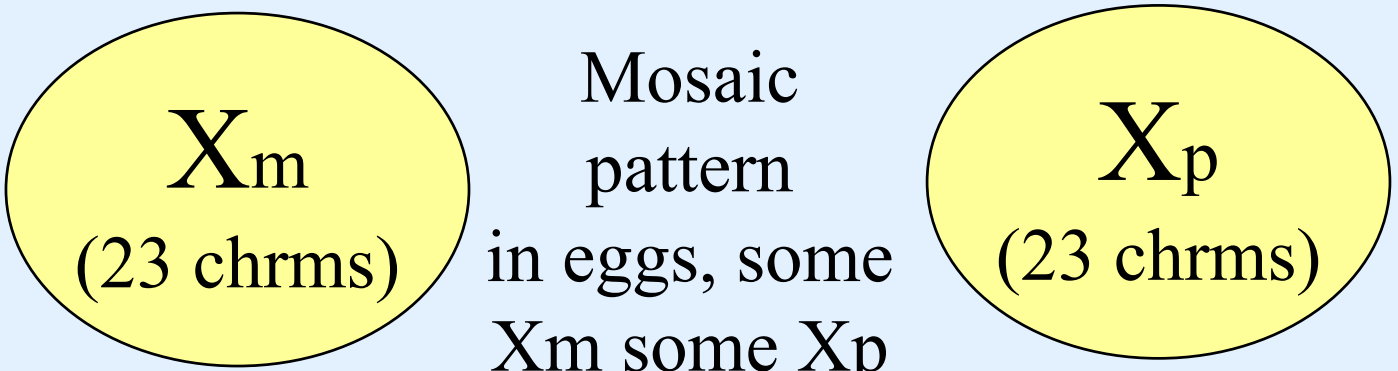
Some female cells carry an active Xm and some carry the Xp





m = maternal: X from her mother

p = paternal: X from her father



Creation of Sperm Cells

No mosaic pattern seen in cells: all cells are →

$X_m\ Y_p$ (46 chrms)

Male Cells

Creation of sperm and shuffling of genetic code

↓

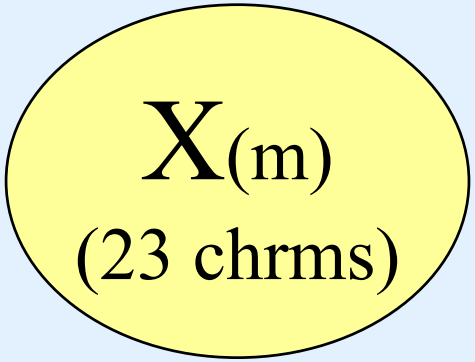
All male cells carry an X from mom and a Y from dad

X_m (23 chrms) OR Y_p (23 chrms)

Sperm

Sperm cells: Receive either the X or the Y (in equal numbers)

Fertilization



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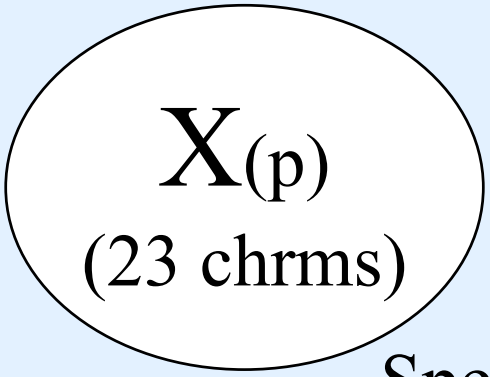

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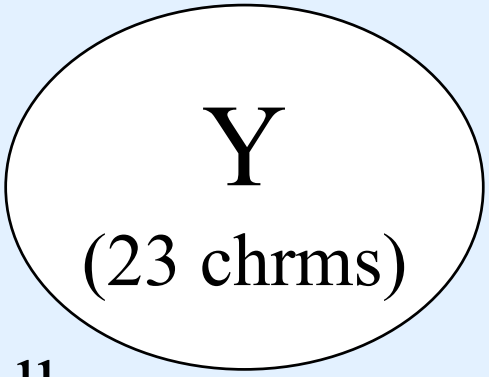
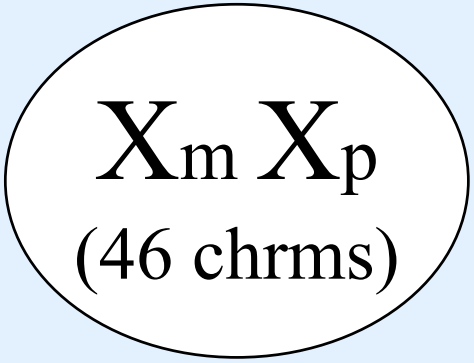


Egg
(always has an X)

Sperm cells
(gives either an X or a Y)

One egg (X) joins with one sperm (X or Y) to yield:

Female Child



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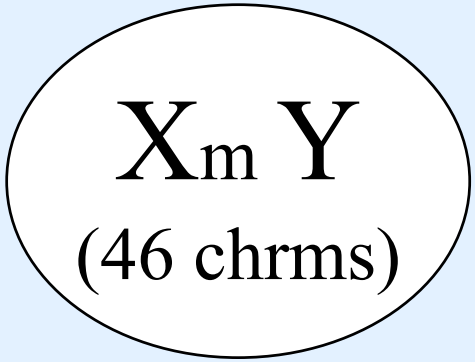

Male Child

Sex Chromosome Lineage – 1

- Sons (XY):
  - The lone X always comes from mom:
    - 50-50 chance this X is derived from mom's dad (MGF).
    - 50-50 chance this X is derived from mom's mom (MGM).
  - Y always from dad: (always from dad's dad: son's PGF).
- Daughters (XX):
  - One X comes from mom:
    - 50-50 chance this X is derived from mom's dad (MGF).
    - 50-50 chance this X is derived from mom's mom (MGM).
  - Other X comes from dad:
    - This X must be derived from dad's mom (PGM).
    - (Because dad's father gave him his Y).

Sex Chromosome Lineage – 2

Maternal Great Grandparents		Paternal Great Grandparents
MGGM + MGGF | MGGM + MGGF	||	PGGM + PGGF | PGGM + PGGF
XX + XY | XX + XY	||	XX + XY | XX + XY

Child's genetic relationship to each of 8 great grandparents (above): 1/ 8.

Maternal Grandparents		Paternal Grandparents
1 of mom's Xs | 1 of mom's Xs	||	1 of mom's Xs | 1 of mom's Xs
& dad's X | & dad's Y	||	& dad's X | & dad's Y
XX (MGM) + XY (MGF)	||	XX (PGM) + XY (PGF)

Child's genetic relationship to each of 4 grandparents (above): 1/ 4 (.25)

Mom		Dad
1 of mom's Xs & dad's X	||	1 of mom's Xs & dad's Y
XX	||	XY

Child's genetic relationship to each of his or her parents (above): 1/ 2 (.5)

1 of mom's 2 Xs	+	dad's Y
Male Child:	= XY	

Sex Chromosome Lineage – 3

Maternal Great Grandparents		Paternal Great Grandparents	
MGGM + MGGF	MGGM + MGGF	PGGM + PGGF	PGGM + PGGF
XX + XY	XX + XY	XX + XY	XX + XY

Child's genetic relationship to each of 8 great grandparents (above): 1/ 8.

Maternal Grandparents		Paternal Grandparents	
1 of mom's Xs & dad's X	1 of mom's Xs & dad's Y	1 of mom's Xs & dad's X	1 of mom's Xs & dad's Y
XX (MGM) +	XY (MGF)	XX (PGM) +	XY (PGF)

Child's genetic relationship to each of 4 grandparents (above): 1/ 4 (.25)

Mom	Dad
1 of mom's Xs & dad's X	1 of mom's Xs & dad's Y
XX	XY

Child's genetic relationship to each of his or her parents (above): 1/ 2 (.5)

1 of mom's 2 Xs + dad's X

Female Child: = XX