X-Chromosome Inactivation and Skin Disease

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X-chromosome inactivation (XCI) is the process in which females transcriptionally silence one of their two X chromosomes in early embryonic development, equalizing X chromosome gene expression between males and females. XCI depends on a gene called *XIST*, a functional RNA molecule that does not code for a protein. Recent studies indicate abundant intergenic transcription and nonprotein coding RNAs in the human genome, which are suspected to function in modulating gene expression. XCI may therefore serve as a useful model to learn and understand the potential function of these elements, as well as their effects on human disease. Here, we review the genetic and molecular basis of XCI and describe how the mechanistics of this process lead to the phenotypes of X-linked skin diseases, most notably in the pattern of lines, swirls, and whorls first noted by the dermatologist Alfred Blaschko. We suggest that XCI, and other epigenetic phenomena, will continue to impact our understanding of the genetic mechanisms of disease.

Journal of Investigative Dermatology (2008) **128,** 2753–2759;
doi:10.1038/jid.2008.145; published online 29 May 2008

THE IMPORTANCE OF DOSAGE COMPENSATION

Humans are sensitive to chromosomal dosage. In the majority of cases, developing fetuses that are either missing a chromosome or are carrying an extra chromosome do not survive to birth. Genetically, having an abnormal number of chromosomes is known as aneuploidy. In the uncommon cases where autosomal aneuploidies are viable, most notably in trisomies 13, 18, and 21 (respectively known as the Patau, Edwards, and Down syndromes), affected individuals display serious congenital malformations. By contrast, aneuploidies of the X chromosome are among the most common viable chromosomal abnormalities, and whose affected individuals can have relatively moderate phenotypes. The best known of these include Turner syndrome (XO females) and Klinefelter syndrome (XXY males). The reason that X chromosome aneuploidies are better tolerated than autosomal aneuploidies is due to the phenomenon of X-chromosome inactivation (XCI), in which all X chromosomes are transcriptionally silenced except for one. Thus, females of all sex karyotypes (XO, XX, XXX, or XXXX) will each have only one active X chromosome with all supernumerary X's being inactivated. The genetic region that controls XCI is located on the long arm of the X chromosome and is known as the X-inactivation center.

THE X FACTOR: *XIST* RNA AND THE MOLECULAR BASIS OF XCI

X-chromosome inactivation is initiated independently in each cell during the blastocyst stage. The key initiating event involves expression of a gene called the X-inactive specific transcript or *XIST* (pronounced ''exist'') (Brown *et al.*, 1992). *XIST* has several unconventional properties. First, it is activated only in cells with more than one X, and therefore it is not expressed in male cells. Second, *XIST* is expressed from only one of the two X's in females, randomly inactivating either the maternal or paternal X chromosome. Third, the *XIST* gene itself does not code for a protein, but instead appears to function entirely as an RNA molecule. Finally, *XIST* RNA has the characteristic of remaining exclusively nuclear, spreading from its site of transcription to ''coat'' the X chromosome from which it was produced. RNA fluorescence *in situ* hybridization using probes for *XIST* shows a ''cloud'' of *XIST* RNA that coats the inactive X chromosome (Figure 1a).

The expression and propagation of *XIST* RNA during early development is both necessary and sufficient to trigger long-range, chromosome-wide gene silencing across the X chromosome. The mechanistic details of the silencing cascade are not fully understood and are an area of intensive study (Chow *et al.*, 2005). The current evidence supports a model in which the structural domains within *XIST* RNA engage a variety of repressive transcriptional pathways (Figure 2a). Genetic studies have shown, for instance, that *XIST* RNA expression recruits the embryonic ectoderm development/enhancer of Zeste homolog 2 protein complex to the X-chromosome (Kohlmaier *et al.*, 2004). Embryonic ectoderm development/enhancer of Zeste homolog 2 is a component of the Polycomb group of proteins that are critical for setting up developmental patterns of gene expression (Schuettengruber *et al.*, 2007). They function in part by chemically modifying histones—the structural proteins around which DNA are spooled—making the associated DNA regions

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Abbreviations: NEMO, *NF-kappaB essential modulator; XCI, X-chromosome inactivation;* XIST, *X-inactive specific transcript*

Received 28 September 2007; revised 2 April 2008; accepted 6 April 2008; published online 29 May 2008

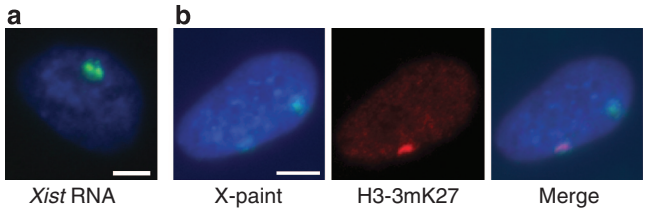

Figure 1. The inactivated X chromosome. (**a**) *XIST* RNA fluorescence *in situ* hybridization in a female somatic cell. RNA fluorescence *in situ* hybridization with a probe against *Xist* RNA (green) shows a cloud of *Xist* RNA covering the inactive X chromosome. The cell nucleus is counterstained with DAPI (blue). Bar = 5 μm. (**b**) The Barr body in a female XX cell. In the left panel, the X chromosomes of a female somatic cell are stained with a fluorescent ''X paint'' (green) and counterstained with DAPI (blue). In the middle panel, a fluorescent antibody against histone 3 trimethylated at lysine 27—a heterochromatic marker—selectively designates the inactive X chromosome, also known as the Barr body (red). In the right panel, both images are merged. Bar = 5 μm.

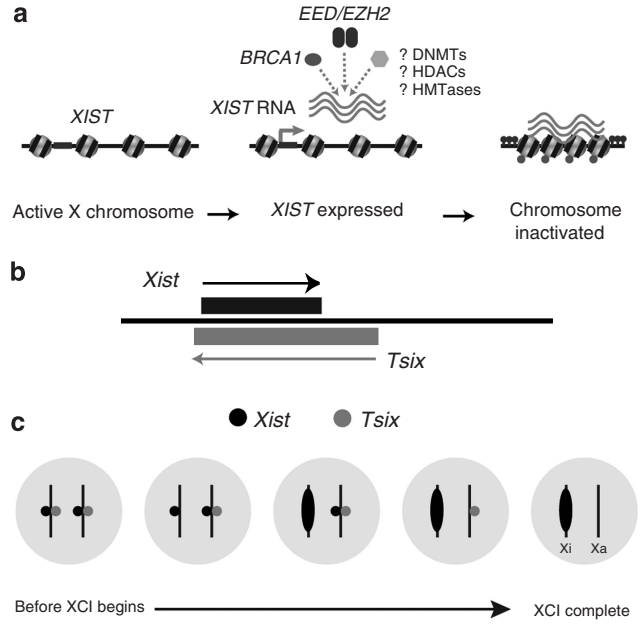

Figure 2. Molecular mechanism of XCI. (**a**) Schematic diagram of XCI. Before inactivation, *XIST* is not expressed and the genes on the chromosome are active. Upon expression of *XIST*, association of *XIST* RNA with cooperative and redundant transcriptional silencing pathways serves to silence the X chromosome in *cis*. After activation of *XIST* expression, the histones of the X chromosome are deacetylated (represented by compaction of the histone spheres), select histone lysine residues are methylated (represented by circles), and promoter CpG islands are methylated (represented by closed lollipops). Together, these factors lock the chromosome into an inactive state. (**b**) Schematic diagram of mouse *Xist/Tsix* locus. In the mouse, an antisense gene to *Xist* (black), named *Tsix* (gray), originates ~12 kb downstream of the end of *Xist* and is transcribed through the entire *Xist* locus in the opposite direction. *Tsix* functions to block *Xist* expression in *cis*. (**c**) Relationship of *Xist* and *Tsix* RNAs in mouse XCI. Before the onset of X-inactivation, both *Xist* (black dot) and *Tsix* (gray dot) are detectable at low levels on both X chromosomes using fluorescence *in situ* hybridization, which is schematized here in idealized form. At the onset of XCI, *Tsix* expression is turned off on one of the two X's, permitting the upregulation of *Xist* RNA from that chromosome (black oval). On the other X, *Tsix* expression persists until *Xist* is silenced. The chromosome expressing *Xist* becomes the inactive X (Xi), whereas the chromosome that was protected by *Tsix* becomes the active X (Xa).

less accessible to transcription in a way that can be maintained through future cell divisions.

The search continues to identify other factors that interact with *XIST* RNA. Some candidate-interacting pathways have not been formally proven but are thought to be likely. On the inactive X chromosome, the cytosine nucleotides at gene promoters are often methylated, an epigenetic process known as promoter CpG island methylation. This chemical modification has been associated with durable gene silencing (Jones and Takai, 2001). Along this line of reasoning, it is likely that *XIST* recruits DNA methyltransferase proteins, although the connection may be direct or indirect. Other possibilities include other histone-modifying proteins with gene-silencing activity, such as histone deacetylators and histone methyltransferases. Together, these higher-order gene control pathways cooperate to create multiple, redundant mechanisms to assure that the inactive X remains silent (Csankovszki *et al.*, 2001). In humans, the inactive X is recognized on the cytological level as the Barr body, which is a dense cellular element reflective of the tight chromatin packaging (Figure 1b).

There are several outstanding mysteries about XCI. It is still unknown how the structural domains of this long RNA, whose sequence is poorly conserved among mammals, is able to trigger such a potent chromosome-wide process and how it manages to only affect the chromosome from which it is transcribed. The location of the inactive X chromosome within the nucleus may be important: *XIST* appears capable of bringing the X chromosome to a nuclear location that is generally poor in RNA polymerases and transcription factors (Chaumeil *et al.*, 2006; Zhang *et al.*, 2007). Another logistical mystery is that of X-chromosome choice: how is a cell able to ''count'' chromosomes and ''choose'' to inactivate one chromosome but not the other? Recent developments provide clues to this question, including the discovery that the two X chromosomes seem to physically interact with each other just before the triggering of XCI (Bacher *et al.*, 2006; Xu *et al.*, 2006). This suggests, for example, that the two X chromosomes could transfer some mutually exclusive factor that coordinates the expression of *XIST* from one X but not the other.

Another exciting discovery, originally found in a mouse model of XCI, is the presence of an antisense gene to mouse *Xist* that is named *Tsix* (which is *Xist* spelled backward). As the name implies, this gene is produced from the antisense DNA strand from *Xist* and is transcribed through *Xist* in the opposite direction (Lee *et al.*, 1999) (Figure 2b). Genetic evidence from mouse models indicates that *Tsix* represses *Xist* expression in *cis* (Figure 2c). In a female cell, *Tsix* is initially expressed on both X's. During early development, *Tsix* becomes turned off on one of the two X's, which permits the upregulation of *Xist* from that locus and leads to inactivation of that chromosome. On the other X, *Tsix* expression persists and ''protects'' that X chromosome from expressing *Xist* and being inactivated. This sense–antisense interplay resembles a molecular switch that directs the two X chromosomes to opposite fates. Evidence suggests that *Tsix* functions both as an RNA molecule as well as by altering the

Xist chromatin (Sado *et al.*, 2005; Navarro *et al.*, 2006; Sun *et al.*, 2006). It is notable that antisense expression has also been detected downstream of human *XIST* and has been named *TSIX* (Chow *et al.*, 2003). It is tempting to speculate that the antisense gene in humans plays a similar role as it does in the mouse; however, this remains an area of debate within the field (Migeon *et al.*, 2002). Nonetheless, *TSIX* represents one of the many antisense genes in the human genome whose mechanism of action on gene expression and disease will be an area of great interest in the coming years.

THE EXCEPTIONS TO THE RULES OF XCI, AND THEIR CLINICAL IMPLICATIONS: SKEWED AND INCOMPLETE X-INACTIVATION

X-chromosome inactivation is random in human embryonic tissues, such that any given cell has a 50:50 chance of choosing to inactivate the mother's or father's X chromosome. As a result, every female is a mosaic of cells, each expressing exclusively her mother's or father's X-chromosome genes. However, several processes can occur that disturb this randomness and lead to a predominance of maternal or paternal expression, also known as ''skewed X-inactivation'' (Figure 3a and b). As XCI begins when the embryo consists of relatively few cells, it is stochastically possible that some embryos will choose to inactivate substantially more of the maternal or paternal X chromosome simply by chance. Another possible mechanism is that there may be genetic modifiers or polymorphisms that bias the cell to choose a particular chromosome (Plenge *et al.*, 1997). This bias is known as primary nonrandom X-inactivation, reflecting a disturbance to the process of randomness itself. Third, and probably most commonly, skewed X-inactivation can arise by a selection process: if one X chromosome contains a gene or genes that confer a growth advantage or disadvantage, then after many cell divisions, the overall ratio of cells may favor the expression of one or the other X. This is known as secondary nonrandom X-inactivation, reflecting the preserved randomness of the initial ''choice'' but with skewing because of downstream selective effects.

From a clinical standpoint, skewed X-inactivation can affect females who are heterozygous for X-linked gene mutations. Classically, X-linked traits have been classified as dominant or recessive, similar to autosomal traits. In practice, however, a significant proportion of female heterozygotes with X-linked recessive mutations display clinical features of disease in a spectrum of penetrance and severity (Dobyns *et al.*, 2004). The blurred distinction between dominant and recessive traits may stem from the difference between heterozygotes of X-linked and autosomal mutations. With the ''all-or-none'' molecular nature of X-inactivation, a female heterozygote with an X-linked mutation has ~50% of her cells producing only the mutant X-linked gene product and ~50% of her cells producing only the wild-type product although ''escape'' can occur (see below). By contrast, every cell in a female heterozygote with an autosomal mutation transcribes both chromosome copies, such that each cell will have a 50% dose of wild-type gene product. Despite the fact

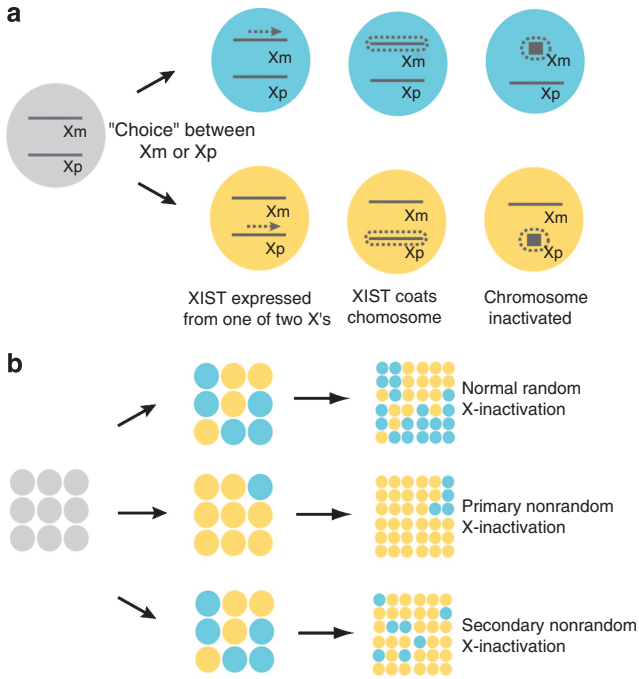

Figure 3. Skewed X chromosome inactivation. (**a**) Schematic of X-chromosome choice. In each female cell, the maternal X (Xm) or paternal X (Xp) may be ''chosen'' to be active. Before inactivation, both Xm and Xp are active. *XIST* RNA (dotted line) is randomly selected to be expressed from either the maternal X (top row, blue cells) or the paternal X (bottom row, orange cells). *XIST* coats the chromosome from which it is expressed and causes it to be transcriptionally silent and condensed. (**b**) Models of skewed X-chromosome choice. In female mammals, each cell independently chooses to inactivate either the maternal (blue) or paternal (orange) X chromosome. Before XCI begins, each cell has two active Xs (gray). In random XCI, cells choose either the maternal or paternal X in a ~50:50 ratio (top row). With further development and cell division, the same ratio is maintained. In primary nonrandom X-inactivation, some factor or modification alters the random choice, such that either the maternal or paternal X is preferentially chosen (middle row). In secondary nonrandom X-inactivation, the initial choice of X-inactivation is still random, but a gene on one or the other X chromosome favors the selection of the cells containing either the maternal or paternal X. With further cell divisions, the total number of cells is skewed toward those expressing the favored X chromosome (bottom row).

that about half of the cells of X-linked heterozygotes express only the mutant gene, female heterozygotes of X-chromosome mutations can display reduced disease penetrance and/or severity compared with hemizygous males, indicating that the cells expressing the wild-type gene can provide protection against the disease.

In this context, skewed X-inactivation can influence the appearance and severity of X-linked traits in heterozygous females if a higher proportion of cells choose to inactivate the wild-type X chromosome (Migeon, 2006). XCI skewing has been described in female heterozygotes with Duchenne muscular dystrophy and hemophilia A, who display aspects of muscle weakness or bleeding dysfunction that have been linked with preferential expression of the mutant X (Yoshioka *et al.*, 1998; Renault *et al.*, 2007). In these female heterozygotes, the X-inactivation skewing seems to cluster in

families, suggesting that there is an inherited locus that either disturbs X-chromosome randomness or provides a selective pressure against the other X chromosome. Therefore, if a female heterozygote manifests clinical features of X-linked disease that deviates in severity from what is expected, it is worthwhile to examine her X-inactivation pattern (as well as those of her female relatives) to determine if skewed X-inactivation is involved.

In addition to skewed X-inactivation, a second ''exception'' to the rules of XCI is that not all X-chromosome genes are silenced on the inactive X chromosome. A comprehensive survey indicates that ~85% of all human X-linked genes are silenced on the inactive X chromosome, but that the remaining genes are either partially or fully expressed (Carrel and Willard, 2005). These genes are referred to as ''escape'' genes, and are therefore expressed to at least some extent from both X's in female cells. One of the best-characterized examples is the steroid sulfatase gene that is mutated in X-linked ichthyosis (Hernandez-Martin *et al.*, 1999). In affected males, this disease results in a hyperkeratosis from a failure to properly shed senescent keratinocytes. If the steroid sulfatase gene was subject to XCI, female heterozygotes might be predicted to display a phenotype in areas of skin choosing to inactivate the wild-type X chromosome. However, as the steroid sulfatase gene ''escapes'' XCI and is expressed from both X chromosomes, the wild-type gene product is present in all cells, protecting against the clincal phenotype in female heterozygotes.

In summary, understanding the connection between X-chromosome disease genotype and phenotype depends on knowing the rules and exceptions of XCI.

BLASCHKO AND THE PATTERN OF X-LINKED MOSAICISM IN SKIN DISEASE

As XCI is complete after the blastocyst stage, the manifestation of X-linked phenotypes depends largely on the way in which these cells subsequently divide, mingle, and migrate to form the organs of the body. Knowledge about the clonality of different human organs is unfortunately incomplete; however, current understanding of select human tissues suggests significant variability: intestinal villi, for example, appear to be polyclonal—in other words, they consist of a heterogenous mixture of cells with either an active maternal or paternal X chromosome (Thomas *et al.*, 1988). Intestinal crypts, by contrast, appear to be monoclonal in nature, with large clusters of crypt cells expressing only the maternal or paternal X. Further analysis of tissue clonality will aid future understanding of X-linked disease on the molecular level (Bittel *et al.*, 2008).

Compared with many other tissues, the cutaneous manifestation of XCI mosaicism is better understood, thanks in part to the visual phenotype of individuals who carry X-linked mutations. These visual patterns are currently recognized as the archetypal pattern described by the dermatologist Alfred Blaschko, which has been subsequently updated by others (Figure 4a). Blaschko was a private dermatology practitioner who documented epidermal and sebaceous nevi with a characteristic linear appearance on the extremities, S-shaped curves on the trunk region, and V-shaped patterns on the back. He noted that the pattern of the affected regions were not the same as dermatomes, and were remarkably consistent between different affected individuals. He proposed that these lines might correspond to some sort of embryonic event, although it was uncertain what that event might be (Blaschko, 1901; Jackson, 1976). Many years later, Rudolf Happle hypothesized that skin disorders following Blaschko's lines could be explained by the mosaicism that results from XCI or early somatic mutations (Happle, 1985). Blaschko's lines therefore map out a migratory history of ectodermal skin cells as they have proliferated and traveled from embryonic

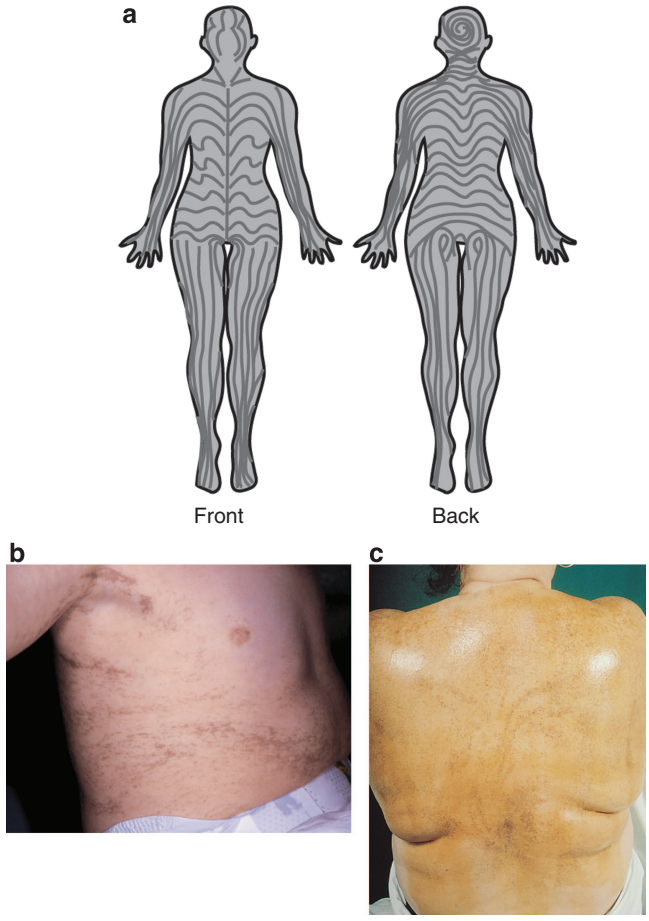

Figure 4. Patterns of X-linked skin disease. (**a**) Blaschko's lines. The visual appearance of X-linked skin disease can follow the pattern of lines described by the dermatologist Alfred Blaschko. The archetypal figure has been subsequently updated by others and is represented elsewhere with greater detail in regions such as the head and neck (see Happle and Assim, 2001). (**b**) Incontinentia pigmenti. The hyperpigmentation stage of incontinentia pigmenti shows the characteristic whorled pattern that follow Blaschko's lines. Image used with permission from Dermatology, Vol. 1, Bolognia, Jorizzo, and Rapini, Diseases of Hyperpigmentation, p. 996, Copyright 2003, Elsevier. (**c**) Iodine starch test in female carrier of anhidrotic ectodermal dysplasia. Application of starch in this female carrier shows a characteristic ''fountain pattern'' of dark areas with normal sweat glands as well as light areas that have no sweat glands. Image used with permission from Cambiaghi *et al.*, Copyright 2000, American Medical Association. All rights reserved.

development into the fully formed organism, with alternating affected and unaffected lines representing cells that have inactivated either the normal or mutant X chromosome.

One of the best-studied examples of an X-linked disease with a blaschkolinear pattern is incontinentia pigmenti (OMIM 308300). This disease is caused by mutations to the X-linked NF-κB essential modulator (*NEMO*) gene (Smahi *et al.*, 2000) and is lethal in males but has a variable phenotype in female heterozygotes. As its name implies, *NEMO* is a key regulator of the NF-κB signal transduction pathway, an important genetic mediator of immune and inflammatory responses. In female heterozygotes, vesicles and bullae form in the distribution of Blaschko's lines during very early life; these lesions later progress to a verrucous stage, which then give way to hyperpigmentation that develops in characteristic whirls and streaks on the trunk (Figure 4b). This hyperpigmentation often fades with time and is gone by adulthood. A fourth stage can occur, which is characterized by hypopigmented, atrophic lesions in a linear pattern. In addition to lesions on the skin, other dermatological manifestations of the disease include alopecia (which can result in swirls of hairlessness on the scalp) and nail dysplasias. Despite the varied skin changes that occur from incontinentia pigmenti, the morbidity from the disease is primarily due to effects of the *NEMO* mutation in the central nervous, ocular, and musculoskeletal systems.

Female heterozygotes with *NEMO* mutations have been observed to display variability in the severity of their phenotypes. One might predict that the relative ratios of mutant-to-normal X chromosome inactivation would correlate to the severity of disease. Consistent with this, skewed X-inactivation that favors inactivation of the mutant X chromosome has been observed in female heterozygotes, suggesting that secondary nonrandom X-inactivation can occur because of the presumptive growth advantage of the normal cell over the *NEMO*-mutant cell (Martinez-Pomar *et al.*, 2005). This secondary selection is also thought to be responsible for the resolution of skin lesions in later in the life of affected females (Nelson, 2006). Of the rare viable males with the disease, some have been shown to have Klinefelter syndrome (XXY) and are therefore protected from the lethal phenotype by the presence of a wild-type second X chromosome (Kenwrick *et al.*, 2001). In these observations, it is clear that the clinical presentation of incontinentia pigmenti illustrates the genetic principles of XCI.

Over a dozen other X-linked conditions have been described that follow the cutaneous patterns described by Blaschko (Table 1, footnote 1). These include anhidrotic ectodermal dysplasia (OMIM 305100), a disease caused by mutation in the X-linked ectodysplasin A (*EDA*) gene, which can result in patches of skin that contain no sweat glands. Use of an iodine starch test in female heterozygotes, which causes a violet-colored darkening of areas containing sweat glands, produces a striking visual demonstration of Blaschko's lines (Figure 4c), with a clear demarcation between affected and unaffected areas. Other X-linked cutaneous genetic diseases include oral–facial–digital syndrome type I, in which affected girls have spirals of hairlessness on the scalp; X-linked

Table 1. X-linked conditions with skin manifestations

Condition	OMIM no.
Adrenal hypoplasia, congenital	300200
Adrenoleukodystrophy	300100
Albinism–deafness syndrome	300700
Alport syndrome X-linked	301050
Amyloidosis, familial cutaneous (pigmentary disorder, reticulate with systemic manifestations)[1]	301220
Androgen insensitivity syndrome	300068
Angelman syndrome	105830
Angioma serpiginosum, X-linked[1]	300652
Bazex syndrome	301845
CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects)[1]	308050
Chondrodysplasia punctata (Conradi–Hunerman–Happle syndrome)[1]	302960
Chondrodysplasia punctata (XLR)	302950
Chronic granulomatous disease, X-linked	306400
Coffin–Lowry syndrome	303600
Craniofrontonasal syndrome	304110
Cutis laxa X-linked/Occipital Horn syndrome	304150
Dyskeratosis congenita, X-linked[1]	305000
Ectodermal dysplasia (anhidrotic)[1]	305100
Ectodermal dysplasia, hypohidrotic with immune deficiency[1]	300291
Ehlers–Danlos variant, heterotopia, periventricular	300537
Epidermolysis bullosa, macular type	302000
Fabry disease	301500
Fanconi pancytopaenia B	300514
Opitz-Kaveggia syndrome	305450
Goltz syndrome (focal dermal hypoplasia)[1]	305600
Ichthyosis, X-linked	308100
Ichthyosis follicularis, atrichia, and photophobia syndrome[1]	308205
Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked	304790
Incontinentia pigmenti[1]	308300
Keratosis follicularis spinulosa decalvans	308800
Lesch–Nyhan syndrome	300322
Lowe oculocerebrorenal-syndrome	309000
Melnick–Needles syndrome	309350
Menkes syndrome[1]	309400
Midas syndrome (microphthalmia, dermal aplasia, and sclerocornea)[1]	309801
Orofaciodigital syndrome I[1]	311200
Simpson–Golabi–Behmel syndrome type 1	312870
Simpson–Golabi–Behmel syndrome type 2	300209
Terminal osseous dysplasia and pigmentary defects	300244
Torticollis, keloids, cryptochidism, and renal dysplasia	314300
Wiskott–Aldrich syndrome	301000

[1]Condition manifests in Blaschko's lines.

chondrodysplasia punctata (Conradi–Hunerman–Happle syndrome), which results in linear and whorled patterns of pigmentary and atrophic lesions; and focal dermal hypoplasia, a disease that can also display linear patterns of hyperpigmentation and skin atrophy.

To date, over 300 X-chromosome genetic loci have been linked to disease (please refer to the National Center for Biotechnology Information's reference link to genes and disease at http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=gnd). A significant number of these X-linked conditions have skin manifestations as a significant or predominant component (Table 1).

HOW WILL EPIGENETIC MECHANISMS INFLUENCE OUR UNDERSTANDING OF DISEASE?

Although XCI has been known for over 50 years, the implications of this phenomenon on disease continues to emerge. Recently, the first tumor suppressor gene that resides on the X chromosome, *WTX*, was identified as a significant genetic cause of Wilm's tumor (Rivera *et al.*, 2007). In addition to the traditional genetic considerations, the location of this gene on the X chromosome immediately raised epigenetic questions as well. Tumor suppressor genes are thought to follow Knudson's two-hit hypothesis, which postulates that both tumor suppressor genes must be ''hit'' by mutation to lead to tumor formation. With one active X chromosome in both males and females, one would anticipate that both sexes can only sustain one *WTX* hit. On the other hand, one might speculate that females are better suited to tolerate *WTX* somatic mutations if the mutations ''hit'' the inactive *WTX* allele half of the time. Interestingly enough, however, no male bias for Wilm's tumor is seen in the data (Huff, 2007). The example of *WTX* illustrates how X-inactivation continues to impact our understanding and interpretation of new genetic discoveries.

The lessons learned from X-inactivation may soon extend beyond the realm of X chromosome genes. Until recently, genes that are active only on the maternally or paternally inherited chromosome—an expression pattern known as monoallelic expression—were thought to be limited to X-linked and imprinted genes, as well as specialized genes such as the odorant receptors. However, a recent genome-wide sample suggests that ~5% of autosomal genes may be monoallelically expressed (Gimelbrant *et al.*, 2007). The investigators extrapolate from their study to suggest that up to 1,000 human autosomal genes may feature monoallelic expression, with a cell-by-cell random choice of maternal or paternal expression. Some of the genes identified in the study are known to be connected with human disease, prompting important future questions to understand how this XCI-like expression pattern may influence disease phenotypes. The lessons learned from the paradigm of X-inactivation, including the concepts of all-or-none expression, random choice of expression between the two inherited chromosomes, as well as primary versus secondary selection effects, may soon prove to be applicable to the understanding of a significant subset of autosomal genes as well.

The recent sequencing of the human genome and continued discoveries from genome-wide analysis represent only the beginning of our understanding of genetic disease. The building blocks provided by the completed genome sequence will allow for the study of more complex, multifactorial, and epigenetic effects on disease phenotypes. The unique visual nature of skin disease provides a valuable stage where these genotypes and phenotypes will be directly seen and studied for years to come.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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