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X-inactivation and human disease: X-linked dominant male-lethal disorders

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X chromosome inactivation (XCI) is the process by which the dosage imbalance of X-linked genes between XX females and XY males is functionally equalized. XCI modulates the phenotype of females carrying mutations in X-linked genes, as observed in X-linked dominant male-lethal disorders such as oral-facial-digital type I (OFDI) and microphthalmia with linear skin-defects syndromes. The remarkable degree of heterogeneity in the XCI pattern among female individuals, as revealed by the recently reported XCI profile of the human X chromosome, could account for the phenotypic variability observed in these diseases. Furthermore, the recent characterization of a murine model for OFDI shows how interspecies differences in the XCI pattern between *Homo sapiens* and *Mus musculus* result in discrepancies between the phenotypes observed in patients and mice.

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Introduction

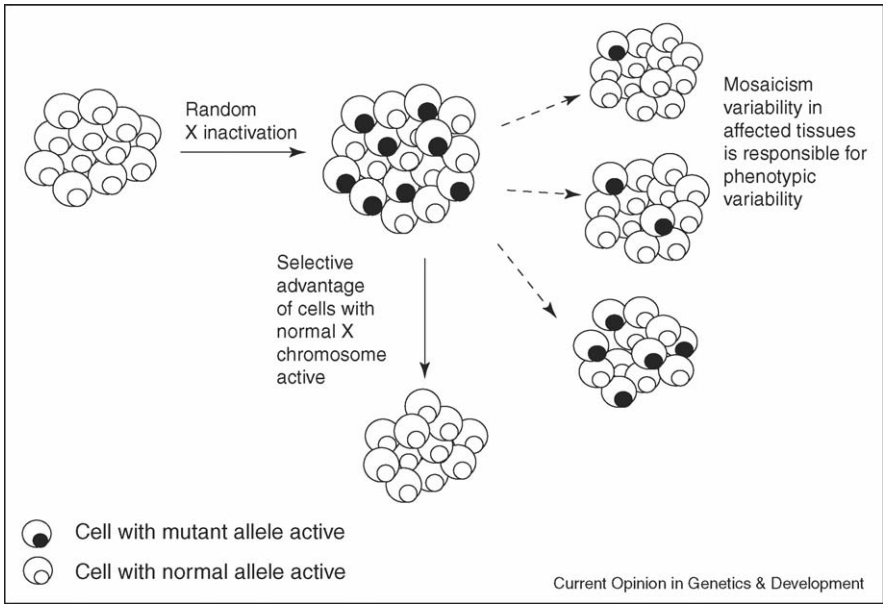
X chromosome inactivation (XCI) is the process by which one of the two X chromosomes becomes transcriptionally inactive in each somatic cell of mammalian females. The purpose of this dosage compensation mechanism is to functionally equalize the gene dosage imbalance of X-linked genes between XX females and XY males. Interestingly, some genes (approximately 15%) escape XCI, and are expressed from both the active and the inactive X chromosomes in females [1••]. The XCI pattern of genes (i.e. monoallelic as apposed to biallelic expression) might vary in various respects: among individuals within the same species [1••] (see also the review by CM Valley and HF Willard [2], this issue); among different species, such as human and mouse (see the example of the *OFD1* gene, below); or among different tissues — although this has not been formally demonstrated. The choice of which of the two X chromosomes becomes inactive is completely random in a normal situation and, once initiated, is stably propagated to all daughter cells. This process has important implications for the effects seen in diseases that are due either to mutations in X-linked genes or to numerical or structural anomalies of the X chromosome. An important consequence of XCI is that heterozygous females are a mosaic of two populations of cells that have either the wild type or the disease allele active. In principle, in heterozygous female individuals carrying mutations in X-linked genes, the ratio of the two types of cells should be approximately 50:50; however, skewing of XCI can occur, thereby altering this ratio. Skewed XCI can be due to either positive or negative cell selection mechanisms. This can modulate the expression of disease manifestations of X-linked recessive disorders in females. Different degrees of skewing can also be responsible for the variable severity of the phenotypes in women carrying X-linked dominant mutations. Familial skewing of XCI has also being described [3]. A schematic representation of the effects of cell selection that lead to skewed XCI is depicted in Figure 1.

In this review, we focus on the influence that XCI has on the phenotypic expression of X chromosome mutations in female individuals. To illustrate this, we use the example of X-linked dominant male-lethal disorders, such as oral–facial–digital type I (OFDI) and microphthalmia with linear skin-defects (MLS) syndromes, in which XCI might play a role in the variability of expression of the disease phenotypes. In addition, we discuss how differences between *Homo sapiens* and *Mus musculus* in the X-inactivation status could account for discrepancies between the phenotypes observed in the patients and those of the corresponding murine models.

X-linked dominant male-lethal disorders

An X-linked disorder is described as dominant if it is expressed in heterozygotes. A subgroup of X-linked dominant disorders includes those characterized by male lethality or reduced male-viability. Table 1 lists all the disorders that fit into this category, including those recognized more recently, and summarizes their main features, as well as the pattern of XCI typically observed in patients. The corresponding gene has been identified for six of these disorders. According to studies performed in cultured cells, two of these genes appear to escape and four appear to be subject to XCI. Murine models are available for some of these diseases. A summary of the information available on these genes is reported in

Figure 1



Schematic representation of XCI in female somatic cells. In normal conditions, the ratio of the two cell types (carrying the active and the inactive X chromosomes) is approximately 50:50, but in females with X-linked dominant disorders this ratio can be different because of a disadvantage for cells expressing a mutant X-linked allele. Divergence from the 50:50 ratio, known as skewing of XCI, can be different in various tissues and in different developmental stages, and can vary among individuals, causing a variable severity of the phenotype observed. For disorders such as MLS, OFCD, ODPD and IP, affected females usually have totally skewed patterns of XCI, in favour of an active wild type X chromosome. Cell selection usually affects only those cell lines in which the disease gene is expressed [43]. Abbreviations: IP, Incontinentia pigmenti; ODPD, terminal osseous dysplasia and pigmentary defects; OFCD, oculo-facio-cardio-dental syndrome.

Table 2. In some cases, the disease phenotype is clearly related to the function of the corresponding gene (e.g. *OFD1*). In other cases, no obvious relationship could be observed. For example, there are situations in which the gene is ubiquitously expressed and appears to be important in all cells, despite the disease having a highly 'tissue-specific' phenotype. This apparent discrepancy might be related to the different ability of each tissue to cope with the presence of dying or suffering cells in which the X chromosome carrying the wild type allele is inactivated.

It is likely that XCI plays a major role in modulating the severity of the phenotypes of all these diseases.

Oral–facial–digital type I syndrome

The oral–facial–digital syndromes are a heterogeneous group of disorders characterized by defects in the face, oral cavity and digits. OFD type I (Online Mendelian Inheritance in Man (OMIM) 311200) can be recognized by X-linked dominant inheritance with embryonic male lethality [4,5] and by the presence of polycystic kidney, which has not been found in the other types of OFD syndromes [6,7]. The central nervous system is involved in 40% of OFDI individuals, who display mental retardation, hydrocephalus and morphological anomalies [8–10]. A high degree of phenotypic variability, even within the same family, has been described for this disease.

Only a few exceptional OFDI male cases have been described to date: a patient with Klinefelter syndrome [11]; a 34-week live-born male — who, however, developed cardiac failure and died 21 hours after delivery — from a family displaying a clear X-linked dominant inheritance of the disease [12]; and a newborn male born at term, but who died 4 hours after birth with typical signs of OFDI, including cystic kidneys [13].

The *OFD1* gene encodes a 1011 amino acid protein, which is expressed during development and in adult tissues in all the structures affected in this syndrome [14,15]. Experiments performed in somatic cell hybrids suggest that the human gene escapes XCI [1••,14], whereas there is evidence that the *Ofd1* gene is subject to XCI in mouse [16]. *OFD1* is thus an example of a gene that shows interspecies differences in its pattern of XCI. We hypothesize that the evidence obtained in somatic cell hybrids demonstrating that *OFD1* escapes XCI does not reflect the situation of all other tissues, in which *OFD1* might undergo XCI, at least partially.

Most of the *OFD1* mutations identified to date in patients [15,17,18,19•] lead to a premature truncation of the protein in its N-terminal region and are therefore predicted to act with a loss-of-function mechanism. However, the possibility that truncated OFD1 protein has a dominant–

Table 1

X-linked dominant male-lethal disorders.

Disease	Locus name	OMIM	Clinical description	XCI in patients
Chondrodysplasia punctata 2	*CDPX2*	302960	Skin defects and skeletal abnormalities, including short stature, rhizomelic shortening of the limbs, epiphyseal stippling, and craniofacial defects	Random
Congenital hemidysplasia with ichthyosiform erythroderma and limb defects[a]	*CHILD*[a]	308050	Inflammatory nevus with striking lateralization and strict midline demarcation, as well as ipsilateral hypoplasia of the body	Random in one patient analyzed
Oculo-facio-cardio-dental	*OFCD*	300166	Facial abnormality, cataract, microphthalmia, teeth abnormalities, and cardiac septal defects	Skewed
Terminal osseous dysplasia and pigmentary defects	*ODPD*	300244	Abnormal and delayed ossification of bones of hands and feet, brachydactyly, camptodactyly and clinodactyly. Digital fibromatosis. Pigmentary skin-lesions on the face and scalp, dysmorphic features including hypertelorism, and multiple frenula.	Skewed
Rett[a]	*RTT*[a]	312750	Autism, dementia, ataxia, and loss of purposeful hand-use	Random
Incontinentia Pigmenti[a]	*IP*[a]	308300	Abnormality of skin pigmentation associated with a variety of malformations of the eye, teeth, skeleton and heart etc.	Skewed
Oral–facial–digital type I	*OFD1*	311200	Orofaciodigital abnormalities and cystic kidneys	Nonrandom in 30%
Microphthalmia with linear skin-defects	*MLS*	309801	Irregular linear areas of erythematous skin hypoplasia, involving the head and neck, microphthalmia, corneal opacities. Also associated cardiac defects and central nervous system abnormalities	Skewed
Aicardi	*AIC*	304050	Agenesis of the corpus callosum, with flexion spasms and coriorethinal abnormalities	Preferentially random
Goltz	*FDH*	305600	Atrophy and linear pigmentation of the skin, herniation of fat through the dermal defects, and multiple papillomas of the mucous membranes or skin. Digital, oral and ocular anomalies and mental retardation can be present	Skewed in two patients analyzed

[a] Can be present with reduced male viability. Abbreviations: AIC, Aicardi; CDPX2, chondrodysplasia punctata 2; CHILD, congenital hemidysplasia with ichthyosiform erythroderma and limb defects; FDH, focal dermal hypoplasia; IP, incontinentia pigmenti; MLS, microphthalmia with linear skin-defects; ODPD, terminal osseous dysplasia and pigmentary defects; OFCD, oculo-facio-cardio-dental; OFDI, oral–facial–digital type I; RTT, Rett syndrome.

negative effect on the wild type protein has not been formally ruled out. In the case of genes escaping XCI, it has been shown that the allele located on the inactive X chromosome has a lower level of expression compared with that of the gene located on the active one. Therefore, for most of these genes, the 'escape' from XCI is not complete [20••]. This is due to the generally lower levels of expression of the inactive X-alleles compared with those of the corresponding active X-alleles. In addition, there might be sex-specific effects — such as hormonal

Table 2

Features of genes responsible for X-linked dominant male-lethal disorders.

Gene	Locus name	Gene features	XCI in humans[a]	XCI in the mouse	Mouse model
OFD1 [15]	*OFDI*	Required for primary cilia formation and left–right symmetry	Escaping	Inactivated [16]	[22••]
MECP2 [32]	*RTT*	Methyl-CpG-binding protein 2, possibly involved in DNA methylation	Inactivated	Inactivated [33]	[34]
EBP [35,36]	*CDPX2*	Emopamil-binding protein involved in cholesterol biosynthesis	Inactivated	Inactivated [35]	Td [35]
NEMO [37]	*IP*	Inhibitor of nuclear factor κB kinase β subunit.	Escape	Presumably inactivated	[38,39]
BCOR [40•]	*OFCD*	BCL-6-interacting co-repressor. Functions as transcriptional co-repressor	Inactivated	NA	NA
NSDHL [41]	*CHILD*	NAD(P)H steroid dehydrogenase-like protein involved in cholesterol biosynthesis	Inactivated	NA	Bpa, Str [42]

[a] Analyzed using somatic cell hybrids [1••]. Abbreviations: BCOR, BCL6 co-repressor; EBP, emopamil-binding protein; MECP2, methyl-CpG-binding protein 2; NA, not available; NEMO, NF-κB essential modulator; NSDHL, NAD(P)H steroid dehydrogenase-like protein.

effects — on gene expression. The high degree of phenotypic variability observed in OFDI patients could be related to the variable level of expression from inactive X-chromosomes of the *OFD1* gene in females. Alternatively, phenotypic heterogeneity among females might result from a variable pattern of XCI [19•] (B Franco, unpublished).

Previous studies have shown that the protein encoded by *OFD1* is centrosomal and is located at the basal body of primary cilia [18,21]. A mouse model for this genetic disorder has recently been generated and reveals that complete absence of *Ofd1* in hemizygous males causes early developmental defects, mainly neural tube, heart and laterality defects, the latter owing to absence of cilia in the embryonic node. Heterozygous females die at birth, displaying defects of the head, the oral cavity and the skeleton [22••]. They also develop kidney cysts in which cilia were found to be absent. These data identified Ofd1 as a factor required for cilia formation, and definitively place OFDI in the group of genetic disorders associated to ciliary dysfunction.

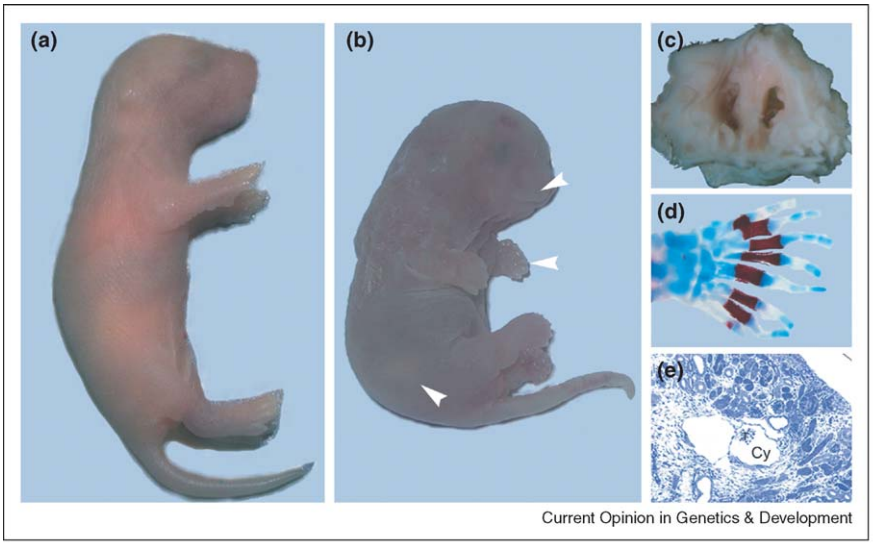
Interestingly, the effect of Ofd1 disruption in the mouse was revealed to be more severe than in humans: newborn females do not survive beyond birth, they display cystic kidney in 100% of cases and have additional features (e.g. skeletal and vascular defects) not observed in OFD type I patients. Moreover, polydactyly is invariably present, whereas in humans it is less frequent than brachydactyly or syndactyly. Figure 2 displays examples of the phenotypic abnormalities observed in 100% of the $Ofd1^{\Delta 4-5/+}$ female mutants analyzed to date.

Obvious differences between *H. sapiens* and *M. musculus* could account for this discrepancy, although a possible explanation could be related to the difference of the XCI status for the *OFD1* and *Ofd1* genes in the two respective species. In humans, the 'escape' of *OFD1*, at least partially, from XCI results in biallelic expression, with human females retaining half a dosage of the functional gene in each cell. We postulate that the XCI pattern can vary among the various human tissues, with some tissues existing in which *OFD1* escapes XCI and others existing in which *OFD1* undergoes XCI at variable degrees. In mice, the gene undergoes XCI; therefore, female mice are mosaics, with half of the cells completely devoid of Ofd1. In mice, the severity of the phenotype, in addition to the presence of phenotypic features not observed in humans, could be caused by an absolute requirement in these tissues for at least one functional copy of the gene within each cell. Cystic kidney is observed in 100% of the cases in mutant mice but in only 15% of patients. Owing to the escape from XCI, human females might have sufficient OFD1 protein for cilium assembly. It is possible that cystogenesis results from a second somatic mutation in kidney cells, in a similar manner to the model proposed for autosomal dominant polycystic kidney [23].

Microphthalmia with linear skin-defects syndrome

The microphthalmia with linear skin defects syndrome (MLS), also known as MIDAS, is a rare disorder described

Figure 2



Phenotypic abnormalities observed at P0 in $Ofd1^{\Delta 4-5/+}$ females. **(a)** A newborn wild type and **(b)** an $Ofd1^{\Delta 4-5/+}$ female showing shortened skull and facial region, shortened, polydactylous limbs and enlarged cystic kidneys. Abnormal structures are indicated by arrowheads in (b). **(c)** Freshly dissected palates from heterozygous mutant mice always show palatoschisis. **(d)** Alizarin red (bone) and alcian blue (cartilage) staining reveals the presence of supernumerary digits (polydactyly). **(e)** Kidney semithin sections of a mutant animal stained with toluidine blue indicate the presence of cystic kidneys. Abbreviations: Cy, cyst; T, tuft indicating the glomerular origin of cysts. This figure was adapted with permission from Macmillan Publisher Ltd; Nature Genetics [22••].

in the early 1990s. It is characterized by variable degrees of microphthalmia and by linear skin defects that are usually located on the face and neck, and which are areas of aplastic skin that subsequently heal to form hyperpigmented areas. Additional features include sclerocornea, corneal opacities, agenesis of the corpus callosum, ventriculomegaly, microcephaly, mental retardation, infantile seizures and, more rarely, cardiac anomalies. MLS is predominantly observed in patients with deletions and unbalanced translocations that involve the Xp22.3 region and that result in monosomy for this region [24]. Aicardi and Goltz syndromes share some similarities with MLS syndrome, and a few reports have described MLS patients with Xp22 deletions as possibly having Aicardi or Goltz syndromes. However, they are now considered as distinct disorders [25].

The molecular defect underlying MLS has not yet been identified, although the *holocytochrome c-type synthetase* (*HCCS*) transcript, a candidate gene contained within the MLS critical-interval, has been recently implicated in the male-lethality trait of MLS syndrome [26]. It has been suggested that the pattern of X inactivation could play a crucial role in the development of MLS [3] and in the extreme intrafamilial variability of the phenotype observed among sporadic cases [27–30]. The majority of patients carrying Xp22.3 deletions show skewed XCI [31], and the same holds true also for cases in which no chromosomal abnormalities were found (B Franco, unpublished). The observation that skewed XCI occurs in rapidly dividing cells, such as blood cells, suggests that there is a selective disadvantage for cells carrying the mutated allele on their active X chromosomes. We hypothesize that in heterozygous females, once the XCI process initiates, cells that have inactivated the normal X-chromosome would either die or suffer severe problems. Therefore, the developmental problems that are found in the MLS syndrome might be the result of the different ability of the various tissues and organs to remove these 'suffering' cells by cell-selection mechanisms. The extreme variability of phenotypes observed in MLS is probably caused by differing degrees of XCI skewing. Therefore, a milder phenotype might be caused by complete skewing of X inactivation not only in blood cells but also in tissues such as eye and skin.

Conclusions

Although the past four decades have witnessed major advances in the understanding of the processes underlying dosage compensation between sexes in mammals, the mechanism of XCI continues to puzzle investigators. There is clear evidence that the expression of X-linked mutations in females is regulated and highly influenced by these processes. X-linked dominant male-lethal disorders represent a paradigmatic example of such influences. The observations reviewed here emphasize the importance of studying such diseases to understand the mechanisms by which XCI and cell selection modulate the phenotypes resulting from mutations of X-linked genes in female mammals.

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- •• of outstanding interest

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