Turner syndrome is caused by loss of all or part of an X chromosome in females. A series of recent studies has characterized phenotypic differences between Turner females retaining the intact maternally inherited versus paternally inherited X chromosome, which have been interpreted as evidence for effects of X-linked imprinted genes. In this study I demonstrate that the differences between Turner females with a paternal X and a maternal X broadly parallel the differences between males and normal females for a large suite of traits, including lipid profile and visceral fat, response to growth hormone, sensorineurial hearing loss, congenital heart and kidney malformations, neuroanatomy (sizes of the cerebellum, hippocampus, caudate nuclei and superior temporal gyrus), and aspects of cognition. This pattern indicates that diverse aspects of human sex differences are mediated in part by X-linked genes, via genomic imprinting of such genes, higher rates of mosaicism in Turner females with an intact X chromosome of paternal origin, karyotypic differences between Turner females with a maternal versus paternal X chromosome, or some combination of these phenomena. Determining the relative contributions of genomic imprinting, karyotype and mosaicism to variation in Turner syndrome phenotypes has important implications for both clinical treatment of individuals with this syndrome, and hypotheses for the evolution and development of human sexual dimorphism.
because the X chromosome evolves relatively rapidly and bears a concentration of genes related to reproduction and cognition (Vallender and Lahn 2004; Nielsen et al. 2005). Phenotypes related to reproduction and cognition are indeed notably altered in Turner and Klinefelter syndromes, with both syndromes involving dysregulation of gonadal development and alterations to neurocognitive profiles of verbal versus visual-spatial skills (Money 1993; Simpson et al. 2003; Bondy 2006; Kesler 2007). These findings indicate that studies of Turner and Klinefelter syndromes that integrate approaches from evolutionary biology and medical genetics should provide useful insights into both the developmental-genomic aetiologies of these conditions, and how X-linked genes have been involved in the evolution of modern humans.

In this paper I focus on the causes of phenotypic variation among individuals with Turner syndrome, and between Turner syndrome females, normal females and normal males. Turner syndrome is characterized phenotypically by short stature, gonadal dysgenesis, a range of anatomical stigmata, and a neurocognitive profile of spared or enhanced verbal abilities but impaired visual-spatial and social skills (Sybert and McCauley 2004; Bondy 2006; Kesler 2007). The syndrome is caused by partial or complete loss of one of the two X chromosomes in most or all cells, due to a range of cytogenetic alterations, with most cases associated with either: (i) the absence of one entire X (45,X), resulting in monosomy, (ii) deletion of part of the short, Xp, arm of the X chromosome (46,XdelXp), or (iii) formation of an Xq iso-chromosome (46,XiXq, with two identical arms of Xq and an Xp deletion) (see Bondy 2006 for more detail on karyotypic variation).

Turner females may also be mosaics of 45,X with 46,XX cells, or mosaics of 45,X cells with cells bearing 46,XdelXp, 46,XiXq, 46,XY, or other karyotypes. Estimates of the frequency of mosaicism range from 67% to 90% (Held et al. 1992; Fernández-García et al. 2000), but the presence and degree of mosaicism has been difficult to establish because multiple tissues must be studied and PCR-based methods must be used for accurate quantification, but most studies have relied on karyotype data from single tissues (Fernández-García et al. 2000). Chromosomal mosaicism of the forms 45,X with 46,XX, or 45,X with 46,XdelXp or 46,XiXq, notably mitigates the severity of Turner syndrome phenotypes (e.g. Murphy et al. 1997; El-Mansoury et al. 2007). Turner phenotypes are also mediated in part by preferential inactivation of structurally abnormal X chromosomes, or in some cases by failed or partial X-inactivation (Migeon et al. 1996; Wolff et al. 2000; Leppig and Disteche 2001).

Determining the nature and causes of karyotype–phenotype correlations in Turner syndrome is important both for clinical treatment of this condition, and for understanding the roles of sex-linked genes in human evolution and development. The primary genetic consequences of Turner syndrome aneuploidies, deletions and mosaicism, that may contribute to phenotypic variation between Turner syndrome females and 46,XX females, and among females with this syndrome, are twofold: (i) full or partial haploinsufficiency of noninactivated X-linked genes in pseudautosomal region 1 (at the terminus of the Xp arm) or elsewhere on this chromosome; and (ii) the presence of a full or fragmentary Y chromosomal in some or all cells (Bondy 2006; Lynn and Davies 2007).

A third source of potential variation in Turner syndrome phenotypes is epigenetic. Given that the intact chromosome in Turner syndrome is inherited from either the father or the mother, imprinting (silencing by parent of origin) of genes may also influence gene expression on the X (Skuse et al. 1997; Skuse 1999, 2000, 2005, 2006; Davies et al. 2006), as it does for many autosomal imprinted genes. A series of studies has tested for phenotypic differences between Turner females with the intact X inherited either maternally or paternally (Hamelin et al. 2006; Bondy et al. 2007; Sagi et al. 2007). Some of these studies have employed small sample sizes, but more-recent and larger studies have demonstrated statistically significant differences for diverse traits, with important implications for genetic diagnosis and clinical treatment.

Skuse (1999) has suggested that X-linked imprinting may serve as a mechanism for the evolution of sexual dimorphism in humans, given that gene dosages of X-linked imprinted genes are expected to differ between the sexes, and a basis in population-genetic theory has been provided for this hypothesis by Iwasa and Pomiankowski (1999) and Mills and Moore (2006). In accordance with these ideas, Skuse et al. (1997) has shown that Turner-syndrome individuals with the maternally inherited X intact (the only X present in normal XY males) differ from paternal-X females in exhibiting a set of relatively male-typical cognitive traits including higher liability to autism.

Do other traits exhibit a similar pattern, of normal sex differences mirroring differences between Turner females with an intact maternal X (Xmat) versus an intact paternal X (Xpat)? If so, can these differences be ascribed to effects of X-linked imprinting, or to correlates of the parental origin of the X chromosome such as mosaicism or karyotype, given that dosages of noninactivated X-linked genes may also mediate human sexual dimorphism? Sufficient data are available to evaluate these patterns for seven categories of phenotype.
Phenotypic differences between Xmat and Xpat females with Turner syndrome

In comparing the results from multiple studies that assess the same phenotypic trait in Turner syndrome females with an intact maternal versus paternal X chromosome (Table 1), it is important to recognize that the different studies have used different clinical populations; for example, Tsezou et al. (1999) and Bondy et al. (2007) included 45X/46,XX mosaics, whereas Hamelin et al. (2006) and Sagi et al. (2007) excluded them, and Sagi et al. (2007) included only females with 45,X or isodicentric karyotypes. This source of among-study variation, in conjunction with variation between and within studies in sample sizes and methods of quantifying phenotypes (e.g. Sagi et al. 2007), means that it is difficult to interpret failures of replication in terms of the presence or absence of biological effects. For each trait, data are compiled on patterns of concordance between differences between Xmat versus Xpat Turner females, differences between 45,X and other Turner females, and differences between males and females in normal populations (Table 1).

Response to growth hormone

Females with Turner syndrome exhibit reduced adult stature that can be prevented in part via treatment with growth hormone (Sybert and McCauley 2004; Bondy 2006). Tsezou et al. (1999) found no significant difference between Xmat and Xpat Turner females in growth-hormone-stimulated height gain over 2 years, but Hamelin et al. (2006) reported significantly greater gain in height among Xmat than Xpat Turner females, over 5–6 years between ages 10 and 20, with parental origin explaining 36–53% of the response to growth hormone. Sagi et al. (2007) found a mean height gain per year in response to growth hormone treatment that was 28% greater in Xmat than Xpat females, but this difference was not statistically significant. Males are substantially and significantly more responsive to growth hormone treatment than females (Burman et al. 1997; Thangavel and Shapiro 2007).

Lipid profiles and visceral fat

Turner syndrome females exhibit an atherogenic lipid profile (a distribution of serum fatty acid levels associated with high risk of atherosclerosis) and high levels of visceral fat compared to normal 46,XX females (Van et al. 2006a). Van et al. (2006b) reported significantly higher levels of visceral fat, and higher levels of total cholesterol, LDL cholesterol, and triglycerides, in Xmat than Xpat Turner females aged 27–31 years on average, and they note that this difference directly parallels the difference between normal males and females. By contrast, in a population of Turner females with a mean age of 15 years, Sagi et al. (2007) found lower total and low-density lipoprotein levels in the Xmat than Xpat group.

Among normal middle-aged populations, males exhibit higher levels of visceral fat, and higher LDL levels, than do females (Freedman et al. 2004; Van et al. 2006a,b). However, such sex differences in LDL levels are absent or much less pronounced in children and adolescents (Freedman et al. 2000; Joliffe and Janssen 2006).

Compared to 45,X/46,XX mosaics, levels of LDL, triglycerides, and body fat were higher in 45,X females by 10%, 26% and 18% respectively in the study of El-Mansoury et al. (2007), but these differences were not statistically significant. By contrast, levels of total cholesterol were significantly higher in 45,X than 45,X/46,XX mosaics, by 15% ($P < 0.01$ in El-Mansoury et al. 2007). This population exhibited a mean age of 31, comparable with that of Van et al. (2006b).

Sensorineural hearing loss

Turner syndrome females exhibit high rates of early-onset hearing loss, due to otitis media (middle-ear infections), auricular anomalies, and other causes (King et al. 2007), with symptoms notably more severe in cases with monosomy 45,X than in cases with mosaicism or structural X-chromosome defects (Barrenäs et al. 1999, 2000; Morimoto et al. 2006). Otitis media and aging-related hearing loss are also more common and severe in males than 46,XX females (see Barrenäs et al. 2000; Henry 2004), but early-onset hearing loss is very rare in such populations. In mouse models of hearing loss, females lose hearing earlier than males in a strain with early-onset hearing loss comparable in timing to that in Turner syndrome females, but males lose hearing earlier in strains with the late-onset, age-related loss that corresponds to the usual situation in humans (Henry 2004). These findings suggest that early-onset and late-onset hearing loss involve different mechanisms, that are mediated differently by sex.

Hamelin et al. (2006) found significantly less early-onset sensorineural hearing loss among Xmat (34% of patients) than Xpat (67%) females with Turner syndrome. This difference corresponds to the sex difference between normal male and female humans to the extent that mechanisms of early hearing loss are similar between females with Turner syndrome and mouse strains with early-onset hearing loss. El-Mansoury et al. (2007) reported a 51% incidence of impaired hearing in 45,X Turner females, compared to 26% in 45,X/46,XX mosaic females ($P = 0.07$).
Table 1. The differences in phenotype between Turner syndrome females with a maternal versus paternal X chromosome are broadly consistent with the differences between normal males and females, and the differences between monosomic 45,X Turner females versus Turner females with other karyotypes. These parallel patterns may be caused by X-linked imprinting mediating the development of sexual dimorphism, by lower levels of mosaicism and higher rates of 45,X monosomy in Turner females with a maternal X chromosome, or by both processes (See text for details).

| Trait                          | Xmat/Xpat difference | Sex difference | 45,X/other difference | Comments                                      |
|--------------------------------|----------------------|----------------|-----------------------|-----------------------------------------------|
| Response to growth hormone     | Greater response in Xmat females (1) or no difference (2,3) | Males show larger response than females (4,5) | No data | Height in Turner syndrome affected by X-linked and autosomal genes (6) |
| Lipid profile and visceral fat | Higher cholesterol, LDL, and visceral fat in Xmat females, in middle age (7); lower total and LDL LDL cholesterol in Xmat females in adolescence (3) | Males have higher LDL and visceral fat than females across middle age; sexes similar in adolescence (7–11) | 45,X females have higher cholesterol than 45,X/46,XX females (12) | In (7), females were age 27–31 on average; in (3), they were age 15 on average |
| Sensorineural hearing loss     | Xmat females show lower levels of early-onset hearing loss (1) | Males show more overall hearing loss is rare (13,14); in mouse models, males have less early-onset hearing loss (14) | 45,X females may have more hearing loss than 45,X/46,XX females (P = 0.07) (12) | Turner syndrome cardiac defects are found differentially in males (16–21) |
| Congenital heart defects      | Xmat females exhibit more cardiac anomalies (15), or no difference (2,3,6) | Higher rates of aortic cardiac anomalies at birth in males (16,17) | Higher rates of aortic cardiac anomalies in 45,X than mosaic females (18,19) | |
| Congenital kidney defects     | Xmat females have higher rate of renal anomalies (3), or no difference (6) | Higher rates of renal anomalies at birth in males (16) or no difference (17) | No difference in rates of ‘urinary track malformations’ between 45,X and 45,X/46,XX females (12) | |
| Neuroanatomy                  | Larger cerebellum in Xmat than 46,XX females (22); larger superior temporal gyrus in Xmat than Xpat females (23); larger hippocampus and smaller caudate nuclei in Xmat than Xpat females (24); no differences (25,26) | Males have larger cerebellum, larger left anterior superior temporal gyrus, and larger amygdala-hippocampus, but smaller caudate nuclei (27–29) | 45X/46,XX females exhibit intermediacy between 45,X and 46,XX females for some neuroanatomical and neurological-function traits (30–32) | |
| Psychological traits          | Xmat females show impaired social cognition, lower verbal skills, more attention, thought and aggression problems, higher rate of autism (33–35); Xmat females have better visual-spatial memory (35); twofold higher rate of ADHD in Xmat females but difference not significant (36) | Males exhibit poorer social and verbal skills than females, higher rates of autism and ADHD, and better visual-spatial skills (37–39) | Larger difference between high verbal and low performance skills in 45,X than 45,X/46,XX females (40) | |

(1) Hamelin et al. 2006 (2) Tsezou et al. 1999 (3) Sagi et al. 2007 (4) Burman et al. 1997 (5) Thangavel and Shapiro 2007; (6) Bondy et al. 2007 (7) Van et al. 2006b (8) Van et al. 2006a (9) Freedman et al. 2000 (10) Freedman et al. 2000 (11) Jolliffe and Janssen 2006 (12) El-Mansoury et al. 2007 (13) Barrena et al. 2000 (14) Henry 2004 (15) Chu et al. 1994 (16) Lary and Paulozzi 2001 (17) Shaw et al. 2003 (18) Gettsche et al. 1994 (19) Prandstraller et al. 1999 (20) Geodakian and Sherman 1970 (21) Geodakian and Sherman 1971 (22) Brown et al. 2002 (23) Kesler et al. 2003 (24) Cutter et al. 2006 (25) Good et al. 2003 (26) Kesler et al. 2004 (27) Good et al. 2001 (28) Chen et al. 2007 (29) Wilke et al. 2007 (30) Murphy et al. 1997 (31) Murphy et al. 1993 (32) Murphy et al. 1994 (33) Skuse et al. 1997 (34) Skuse 1999 (35) Bishop et al. 2000 (36) Russell et al. 2006 (37) Geary 1998 (38) Baron-Cohen 2003 (39) Hermens et al. 2005 (40) Temple and Carney 1993.
Congenital heart defects

Chu et al. (1994) reported a significantly higher incidence of cardiac anomalies in Turner females with an intact Xmat (34, 38% of 34, Fisher’s exact test, \( P = 0.0026 \)) than an intact Xpat (4, 11% of 34, Fisher’s exact test, \( P = 0.0026 \)), based on pooling of published data from four studies that individually yielded Fisher’s exact values of 0.005 (Ross et al. 1991), 0.088 (Lorda-Sanchez et al. 1992), 0.15 (Chu et al. 1994) and 0.70 (Mathur et al. 1991). By contrast, three other studies have reported similar rates of cardiac anomalies between groups (Tsezou et al. 1999; Bondy et al. 2007; Sagi et al. 2007). Overall, using Fisher’s combining test of probabilities, the difference between these two groups was not significant (\( \chi^2 = 20.3, 14 \) d.f., \( P = 0.13 \)). Differences between studies may be due to the sensitivity of diagnostic methods (Bondy et al. 2007), and variation in the karyotypes present or the degrees of mosaicism, given substantially higher rates of cardiac anomalies in monosomic 45,X females than mosaic females (Götzsche et al. 1994; Prandstraller et al. 1999; El-Mansoury et al. 2007).

The cardiac defects most common in Turner syndrome include anomalies of the aorta, especially aortic coarctation and stenosis. These heart defects exhibit 20–50% higher rates in males (Geodakian and Sherman 1971; Lary and Paulozzi 2001; Shaw et al. 2003), and they have been considered as the most well-defined ‘male’ heart defects (Geodakian and Sherman 1970, 1971).

Congenital kidney defects

Sagi et al. (2007) found a higher incidence of renal anomalies in Xmat Turner females (12/60) than in Xpat females (0/20; \( P = 0.03 \), Fisher’s exact test). By contrast, a recent analysis with large samples sizes found no such difference (33/133 vs 12/50 respectively, \( P > 0.50 \)) (Bondy et al. 2007), as did earlier studies with small samples (reviewed in Sagi et al. 2007), including Chu et al. (1994). Fisher’s combining test of the data from the seven studies to date showed a lack of overall significance (\( P > 0.50 \)). Congenital renal anomalies show a lack of sex bias (ratio 1:1) in one epidemiological study (Shaw et al. 2003), but a significant male bias (1.74:1) in another study (Lary and Paulozzi 2001).

Neuroanatomy

For each of the three studies showing X-chromosome parent of origin effects on neuroanatomy in Turner syndrome (Brown et al. 2002; Kesler et al. 2003; Cutter et al. 2006), the observed parental-origin differences parallel the differences between males and 46,XX females (Good et al. 2001; Chen et al. 2007; Wilke et al. 2007), given the information available (Table 1).

Psychological traits

Skuse et al. (1997) and Skuse (1999) reported that Xmat females exhibited higher levels of verbal, social, emotional and behavioural problems than Xpat females (Table 1); by contrast, Bishop et al. (2000) describe evidence that Xmat Turner females exhibit better visual-spatial memory, but worse verbal memory, than Xpat females, with females also better than males at this verbal-memory task. Russell et al. (2006) found that seven (35%) of 20 Xmat Turner females, and one (14%) of seven Xpat females were diagnosed with ADHD, but this difference was not statistically significant (Fisher’s exact, \( P = 0.30 \)), nor was the difference significant between 45,X females (8, 30% of 27) and mosaic females (4, 17% of 23) (Fisher’s exact test, \( P = 0.25 \)). Similarly, Sagi et al. (2007) reported that five of seven Xpat females, but only four of eleven Xmat females, had academic skills or degrees (Fisher’s exact test, \( P = 0.17 \)).

The verbal versus visual-spatial differences between Turner syndrome females and 46,XX females contrast with the differences between males and 46,XX females, given that on average, males exhibit relatively better visual-spatial skills compared to verbal skills than do females (Geary 1998; Baron-Cohen 2003). However, as described by Skuse et al. (1997) and Skuse (1999), some of the neurocognitive differences between Xmat and Xpat Turner females, such as lower verbal, attentional, emotional and social skills in the Xmat genotype, notably parallel the differences between males and 46,XX females.

The effects of karyotype and mosaicism on cognitive functions in Turner syndrome have yet to be investigated in detail, but Temple and Carney (1993) reported that the differences between verbal IQ scores and performance IQ scores were larger in monosomic 45,X than in mosaic 45,X/46,XX Turner females, and Murphy et al. (1993, 1994, 1997) describes evidence from neuroimaging and cognitive studies for X-chromosome dosage effects on verbal versus visual-spatial/performance skills. Genetic evidence for such effects has been provided by Vawter et al. (2007), who found strong correlations of gene-expression levels with verbal skills, for several X-linked genes, in individuals with Klinefelter syndrome (usually XXY in males).

Pleiotropic effects of growth

Of the traits in Table 1 that show evidence of differences between Xmat and Xpat Turner females, one trait, response to growth hormone, is a direct correlate of
growth parameters, and three additional traits, sensorineural hearing loss, lipid profile and body composition, and neuroanatomy, are also known to be growth-related. Thus, in females with Turner syndrome females, the extent of hearing loss is positively associated with reduced height (and lower IGF1 levels) (Barrenas et al. 2000; Morimoto et al. 2006), and growth hormone treatment is associated with both reduced truncal (visceral) obesity (Gravholt et al. 2005) and increased levels of grey matter in the temporal, parietal and occipital lobes of the brain (Cutter et al. 2006). Taller females with Turner syndrome also bear a reduced number of anatomical stigmata (El-Mansoury et al. 2007), but there is no apparent effect of GH treatment or height on cognitive function in Turner syndrome (Ross 2005; Messina et al. 2007). Barrenas et al. (2000) describe evidence that growth-related phenotypes in Turner syndrome (and other aneuploidies) are mediated by effects of aneuploidy on rates of cell turnover, which in Turner syndrome differentially modulate growth of SHOX-regulated mesodermal tissues with the shortest cell cycle time and highest cell cycle rate. This hypothesis of aneuploidy effects on cell cycle times is also supported by evidence for altered temporal control of cell replication in Turner syndrome (Reish et al. 2002), and changes in the proportions of 45,X vs 46,XX cell lines over time in vivo (Nielsen 1976; Held et al. 1992; Devi et al. 1998).

Despite patterns in covariation of clinical phenotype with height in Turner syndrome, Turner females clearly do not differ in height by parental origin of the X chromosome (Mathur et al. 1991; Bondy et al. 2007; Kochi et al. 2007; Sagi et al. 2007). Instead, the height of Turner syndrome females shows a strong, positive, highly significant correlation with their mother’s height (regardless of parental origin of the X), but the association with father’s height is smaller or nonexistent (Salerno and Job 1987; Chu et al. 1994; Tsezou et al. 1999; Hamelin et al. 2006; Bondy et al. 2007; Kochi et al. 2007). The simplest explanation for this remarkable, well-replicated finding is that haploinsufficiency of some X-linked, noninactivated gene or genes (such as SHOX) results in altered transactivation of one or more autosomal imprinted genes that regulate growth. The imprinted gene DLK1 represents a notable functional and positional candidate for such effects due to its roles in regulating growth, adiposity, and bone development (Abdallah et al. 2004, 2007; Ansell et al. 2007), its location at 14q32.2 where apparent imprinting effects on human height have been described (Mukhopadhya and Weeks 2003), and the phenotypic effects of reduced or absent DLK1 expression, which include low birth weight, short stature, high palate, micrognathia (small teeth), small hands, hypotonia (weak muscle tone), scoliosis, recurrent otitis media, high cholesterol and obesity (Kotzot 2004; Temple et al. 2007), all of which are relatively common in Turner syndrome. Comparable interactions between X-linked genes and autosomal imprinted genes affecting growth have been described in mice (Vrana et al. 2000; Loschiavo et al. 2007), and Pan et al. (2007) describe sex-specific X-chromosome effects on height and triglyceride levels that are consistent with an important role for sex linkage in phenotypic variation for these traits. Taken together, these findings suggest that growth-related phenotypes in Turner syndrome are mediated in part by one or more autosomal imprinted genes, as well as by X-linked genes.

Alternative hypotheses for differences between Xmat and Xpat Turner females

Most studies of phenotypic differences between Xmat and Xpat Turner females have interpreted their results in terms of hypothesized effects of one or more X-linked, imprinted genes (e.g. Skuse et al. 1997; Sagi et al. 2007). However there is, as yet, no conclusive evidence for the presence of imprinted genes on the human X-chromosome, despite the discovery of several such genes in mice (Davies et al. 2005; Raefski and O’Neill 2005) and the inferred presence of X-linked imprinted genes in humans from mapping of sex-differential effects on prenatal lethality (Naumova et al. 1998; Green and Keverne 2000).

An alternative, though nonexclusive, hypothesis for differences between Xmat and Xpat Turner females is confounding of parental origin of the X chromosome with the form of the karyotype and the degree of mosaicism in Turner syndrome, such that Xmat and Xpat females tend to exhibit a different karyotype, a differing degree of mosaicism, or both (Box 1). By this hypothesis, Turner females with the Xmat intact, which tend to exhibit a more male-typical Turner-syndrome phenotype for some traits (Table 1), are presumed to have developed under a lower degree of cryptic or documented mosaicism (which leads to a relatively female-typical phenotype) (e.g. Henn and Zang 1997; Havercamp et al. 1999; Hanson et al. 2001; El-Mansoury et al. 2007), or under the influence of specific karyotypes that produce a more female-typical phenotype, such as karyotypes that lack Y-chromosome material. Data on the frequency of different karyotypes and mosaicism in Turner females with an intact Xmat versus Xpat are now available from four studies, which allows such alternative hypotheses to be evaluated.

First, in Bondy et al. (2007) (Table 1), 61 (46%) of 133 Xmat females were not pure 45,X karyotypes or mosaics (for diverse karyotypes including 46,XX), compared to 33 (66%) of 50 Xpat females (Fisher’s exact test, \( P = 0.011 \)). Considering monosomic and mosaic females only, 44 (38%) of 116 Xmat females were mosaics.
Box 1. Alternative, nonexclusive hypotheses for the presence of differences between Xmat and Xpat females that parallel the differences between males and females.

(1) Genomic imprinting. For X-linked imprinted genes, gene dosages are expected to differ between males and females, with the nature of the difference depending upon the direction of imprinting and whether or not the gene is X-inactivated (Skuse 1999). Males exclusively bear the maternally inherited X, so Turner females with an intact maternally inherited X are expected to exhibit relatively male-typical phenotypes for traits mediated by X-linked imprinted genes. By contrast, females bear one paternally inherited X, and one maternally inherited X.

(2) Mosaicism and karyotype. For X-linked genes that are not inactivated, males express one copy, and 46,XX females express two copies. To the extent that human sexual dimorphism is mediated by dosages of such X-linked genes, Turner females are expected to exhibit some degree of male-typical traits. Turner females with a monosomic 45,X karyotype are thus expected to bear traits relatively more typical of males than Turner females with other karyotypes. To the extent that the 45,X karyotype differentially involves the maternally inherited X, due to the nature of the cytogenetic mechanisms whereby it becomes the sole or primary cell line (e.g. Fig. 1), Turner females with an intact maternal X are expected to be more likely to exhibit relatively male-typical traits, compared to Turner females with an intact paternal X. Females with a maternally inherited X are also more likely to bear Y-chromosomal material, but there is no evidence that Y-linked genes mediate the phenotype in Turner syndrome except in some cases of 45,X/46,XY mosaicism, which is rare.

compared to 28 (62%) of 45 Xpat females (Fisher’s exact test, \( P = 0.0046 \)). A lower level of mosaicism in Xmat than Xpat Turner females is also suggested by some hypotheses for the generation of Turner syndrome chromosomal anomalies, which posit that deletions (and some other alterations) of all or part of the X chromosome are relatively frequent in the rapidly replicating paternal germ line (Kelly et al. 1992; Jacobs et al. 1997; Uematsu et al. 2002), that mosaicism or a karyotype other than 45,X early in development may be a prerequisite for viable embryonic development (Hecht and Macfarlane 1969; Hook and Warburton 1983), and that abnormal X chromosomes may be differentially lost in development, such that all or most females karyotyped after birth as 45,X are either cryptic mosaics (with a second cell line present but undetected), or exhibited a mosaic karyotype, or a partial second X, earlier in development (Held et al. 1992; Amiel et al. 1996) (Fig. 1).

For example, Kelly et al. (1992) provide experimental evidence that mosaicism may be present in fetuses with Turner syndrome, but be lost prior to birth, resulting in 45,X. Mosaicism involving 45,X/46,XX can also be generated via postzygotic nondisjunction, a mechanism that can also explain the presence of mosaicism of the form 45,X/47,XXX in some Turner females.

Second, Sagi et al. (2007) found that 83% (55 of 66) of monosomic 45,X females were Xmat rather than Xpat, whereas 36% (five of 14) females with the isodicentric karyotype 46 XiXq bore Xmat as their intact X chromosome (Fisher’s exact test, \( P = 0.0007 \)). These authors did not find significant differences in any phenotypic trait between females with monosomic 45,X versus isodicentric 46,XiXq karyotypes, but evidence for differences between these two karyotypes has been reported in other studies for IQ (Messina et al. 2007) and height (Cohen et al. 1995).

Third, the study population of Hamelin et al. (2006) (Fig. 1) included 7 (20%) of 35 Xmat females that were
either not pure 45,X or mosaics (with 46,XX mosaics not included), and 8 (42%) of 19 Xpat females mosaic or otherwise not 45,X (Fisher’s exact test, \( P = 0.080 \)). However, this marginally nonsignificant difference was due to a significantly higher incidence of the nonmosaic 46,XiXq karyotype in Xpat females; when this karyotype category is excluded, the frequency of mosaics is essentially the same in both Xmat (15%) and Xpat (18%) females for their sample.

Fourth, Uematsu et al. (2002), Table III) assembled data from 21 earlier studies, and found that most (459, 75% of 614) pure 45,X females bore an X of maternal origin, while the 46,XiXq karyotype was about equally distributed between Xmat (\( n = 60 \)) and Xpat (\( n = 71 \)) females. Thus, considering these two karyotypes, pure 45,X karyotypes were significantly more frequent in Xmat females (88%) than in Xpat females (69%) (Fisher’s exact test, \( P < 0.001 \)). These results are consistent with the data from Sagi et al. (2007) described above, with data from Hamelin et al. (2006) who found a higher incidence of isodicentric chromosomes in Xpat females, and with the results of Bondy et al. (2007) given that in their sample, the karyotype 45,X/46,XY comprised 13% of the Xmat females, but 26% of the Xpat females.

Uematsu et al. (2002) also showed that 19 of 20 females with Y-chromosome material bore an intact maternal X, which is consistent with simple expectations from Mendelian inheritance. Overall, Y-chromosomal material has been reported in about 10–20% of Turner syndrome cases (Gravholt et al. 2000; Hanson et al. 2001; Alvarez-Nava et al. 2003). In 45,X/46,XY mosaics, the phenotype can vary from Turner-like female, to intermediate in sexual development, to male, depending upon the presence or absence of the male-determining SRY gene and the degree of mosaicism (Robinson et al. 1999; Telvi et al. 1999). However, in Turner syndrome cases, the presence and form of Y material is apparently not associated with phenotype (Telvi et al. 1999).

Taken together, these data indicate that parental origin of the X chromosome can be confounded with karyotype in three ways: (i) females with an isodicentric karyotype (46,XiXq or 45,X/46,XiXq) are relatively more likely, or similarly likely, to bear an intact paternal than maternal X chromosome, (ii) Xmat females appear less likely than Xpat females to exhibit mosaicism when karyotyped and (iii) Xmat females are more likely than Xpat females to bear Y-chromosomal material. Based on available evidence from karyotype-phenotype correlations, the second difference may parsimoniously account, at least in part, for parallel patterns in phenotypic variation between Xmat versus Xpat Turner females, compared to males versus 46,XX females. However, it is important to note that these parallel patterns are by no means consistently supported for each phenotype examined, and that more data are needed on mosaicism in relation to parental origin of the X for robust evaluation of this hypothesis.

Most generally, separating the confounded effects of parental origin of the X, karyotype and mosaicism requires fine-scale genotype-phenotype correlations with larger samples than have been used thus far in most studies. Similar considerations should also apply to Klinefelter syndrome, for which phenotypic differences between XmatXmatY and XmatXpatY males have been described (Stemkens et al. 2006; Wikström et al. 2006). Thus, about 8–20% of Klinefelter patients are 46,XY/47,XXY mosaics with relatively moderate phenotypes (Ratcliffe et al. 1986; Bojesen et al. 2003; Abdelmoula et al. 2004), and only XmatXmatY males may develop as a result of postzygotic errors in mitosis (Thomas and Hassold 2003). Future studies of the causes of phenotypic variation among and between individuals with different sex chromosome aneuploidies might usefully focus on traits, such as fingerprint ridge counts (Penrose 1968) and enamel and dentin thickness (Alvesalo 1997; Lähdesmäki and Alvesalo 2006), for which male–female differences appear to mirror differences between Turner females and Klinefelter males, and for which effects of parental origin of the X have yet to be investigated.

Conclusions

The development of human sexual dimorphism is mediated by four main causes: (i) hormonal differences that follow from activation of the SRY male-determining gene, (ii) other effects of genes on the Y, (iii) dosage effects of the 15–20% of X-linked genes that are not inactivated (Carrel and Willard 2005), and (iv) hypothetically, by genes that are X-linked and imprinted (Skuse 1999, 2000, 2005; Arnold et al. 2004; Davies and Wilkinson 2006; Xu and Distefo 2006; Blecher and Erickson 2007). I have shown in this paper that the differences between Turner syndrome females with an intact maternally inherited versus paternally inherited X chromosome broadly parallel the differences between females who are monosomic 45,X versus other karyotypes, and the differences between normal XY males and XX females. A simple explanation for these patterns, which is supported by data showing relatively severe and relatively male-typical phenotypes in pure X monosomy, is that in Turner syndrome the maternally inherited X is more-frequently monosomic than the paternally inherited X. To the extent that noninactivated X-linked genes, differentially expressed between XY males and XX females, explain variation in Turner syndrome phenotypes, they are also implicated in the development and evolution of human sex differences;
similarly, to the extent that X-linked imprinted genes exist and influence Turner syndrome phenotypes, the patterns described here would strongly implicate such genes as an important mechanism of sexual differentiation. Determining the roles of X-linked imprinting, karyotype, and mosaicism in Turner syndrome may thus help in deciphering not just the genetic aetiology of this condition, but also the genetic and epigenetic basis of human sexual dimorphism (Davies and Wilkinson 2006; Skuse 2006).

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