Hypomelanosis of Ito and X;autosome translocations: a unifying hypothesis

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Abstract

Hypomelanosis of Ito is a sporadic multi-system disorder known to be associated in many cases with chromosomal mosaicism. While no particular pattern is generally evident for the specific chromosomes involved in such patients, a subgroup of female patients exists in whom the common factor is the presence of a balanced, constitutional X;autosome translocation, with a cytogenetic breakpoint in the pericentromeric region of the X. It is argued here that the phenotype in these cases results not from the interruption of X linked genes but from the presence of mosaic functional disomy of X sequences above the breakpoint.

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Key words: hypomelanosis of Ito; X;autosome translocation; functional disomy Xp.

Hypomelanosis of Ito (HI) is a sporadic multi-system disorder whose defining feature is a pigmentary dysplasia.¹ It is now clear that the common factor in many cases of HI is the presence of chromosomal mosaicism, although this is not an invariable finding.²⁻³ The frequent presence of chromosomal mosaicism in HI makes sense of the wide variability in clinical phenotype. In a review of over 70 published cases, the only consistent feature was the presence of hypopigmented skin without preceding vesicular or verrucous stages.⁴ A total of 74% of the patients, however, had one or more abnormalities of the central nervous system, eyes, hair, teeth, or musculoskeletal system.⁴ Such clinical variability is common to other mosaic genetic conditions (for example, Proteus syndrome⁵) and presumably reflects the variable presence of the genetically abnormal cell line within different lineages.

The description of a number of females with balanced, constitutional X;autosome translocations in association with a phenotype designated incontinentia pigmenti (IP1, McKusick 308300) prompted the suggestion that a locus for incontinentia pigmenti exists at the common cytogenetic breakpoint in Xp11.⁶⁻¹⁰ Linkage analysis in familial cases of incontinentia pigmenti, however, failed to confirm this cytogenetic localisation and much evidence now exists for the presence of a locus at Xq28.¹¹⁻¹⁵ As a result of such analyses, fa-

miliar incontinentia pigmenti is now designated IP2 (McKusick 308310). A reappraisal of familial incontinentia pigmenti (IP2) and the phenotypes described in females with X;autosome translocations shows that there is very little overlap between the two; sporadic incontinentia pigmenti (IP1) does, however, resemble HI in the type and distribution of skin lesions, and in the occurrence of dysmorphic features, which are not present in IP2.^{16 17} Some of the confusion between HI and incontinentia pigmenti has resulted from the alternative name for HI, namely incontinentia pigmenti achromians. Given the clinical variability of HI alluded to above, there is little to distinguish cases of HI associated solely with autosomes from those related to X;autosome translocations.

This paper reviews all cases of HI described in association with a balanced X;autosome translocation and puts forward a unifying hypothesis to explain the presence of this subgroup of patients. Evidence is considered for functional disomy of X sequences as the main aetiological factor in the appearance of the phenotype in such patients. It is proposed that the term incontinentia pigmenti should now be reserved for the familial form which maps to Xq28.

HI and X;autosome translocations

In the rest of this review, females with "IP1" and X;autosome translocations are referred to as having HI. While HI is clearly heterogeneous in origin, the common factor is thought to be the presence of chromosomal mosaicism, although mosaic aneuploidy of almost any autosome or sex chromosome has been described.^{2 3 18 19} In addition, it is likely that mosaicism for single gene defects can also give rise to HI. The existence of a subgroup with balanced X;autosome translocations and similar cytogenetic breakpoints on the X requires explanation. Table 1 lists all the females described so far with HI in association with a balanced X;autosome translocation. A thorough search of published reports indicated that HI has not been reported with any of the many X;autosome translocations described with X breakpoints outside the interval Xq13-Xp11.21.

Examination of table 1 shows the following points. (1) All the breakpoints involve the peri-

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Table 1 Summary of females with IP1/HI in association with balanced X;autosome translocations

	Gilgenkrantz <i>et al</i> ^a	Kajii <i>et al</i> ¹⁰	Hodgson <i>et al</i> ^a	Hodgson <i>et al</i> ^a	Cannizzaro and Hecht <i>et al</i> ¹	Lungarotti <i>et al</i> ¹⁰	Bitoun <i>et al</i> ^b	Koiffmann <i>et al</i> ¹⁰	Penchaszadeh <i>et al</i> ¹⁰	Sybert <i>et al</i>	Steichen <i>et al</i> ¹
Karyotype	46,X,t(X;9) (p11;q34)	46,X,t(X;13) (p11.21;q12.3)	46,X,t(X;17) (p11.2;q11.2)	46,X,t(X;9) (p11.2;q33.2)	46,X,t(X;10) (p11;q22)	46,X,t(X;18) (p11;q23)	46,X,t(X;5) (p11.2;q35.2)	46,X,t(X;10) (p11;11)mat	46,X,t(X;14) (p11;q13)	46,X,t(X;22) (p11.2;q13.3)	46,X,t(X;17) (p13;q13)
<i>Skin</i>											
Hypopigmentation	+	0	+	+	0	+	0	+	+	+	+
Hyperpigmentation	?	+	0	0	+	0	+	—	0	—	0
Blistering	—	+	—	—	+	0	—	—	0	—	—
<i>CNS involvement</i>											
Psychomotor delay	+	+	+	+	+	—	+	+	+	+	+
Seizures	+	+	+	+	0	0	0	+	+	0	0
EEG abnormalities	+	+	+	0	0	—	+	+	0	0	0
Mental retardation	+	+	+	+	+	+	+	+	0	0	0
Hypotonia	0	+	0	+	+	0	+	+	+	0	0
Eye anomalies	0	+	+	+	0	0	—	+	0	0	+
Teeth anomalies	—	0	+	+	+	0	—	+	0	0	0
Hair anomalies	—	0	0	0	0	0	+	—	0	0	0
Nail anomalies	—	0	0	0	0	0	0	+	0	0	0
Cerebral anomalies	0	*	†	0	0	0	N	‡	0	0	1§
Diagnosis made	IP	IP	IP/Ito	IP Ito	IP	Ito	IP1	Ito	Ito	0	Ito
Skin biopsy	+	—	+	+	—	—	—	+	0	0	0
Other features/ information		Bilateral retinoblastoma						Maternally inherited translocation		Non- dysmorphic	Plexus papilloma
X inactivation (blood)	>90% Xn inactive	91% Xn inactive	100% Xn inactive	100% Xn inactive	0	0	92% Xn inactive	100% Xn inactive in both patient and mother	0	0	0
X inactivation (skin)**		>90% Xn inactive	99% Xn inactive	0	0	0	0	0	0	0	0

+ present, — absent, 0 not mentioned. N normal. * Moderate cortical atrophy, slight ventricular dilatation (CT scan). † Cerebral cortical atrophy (air encephalography). ‡ Diffuse corticosubcortical atrophy (CT scan). § Macrocephaly; huge plexus papilloma with enlargement of ventricular system. ¶ The patient's mother carried the same balanced translocation; the mother had seizures as a child but was well and had no pigmentary anomalies. Xn normal, intact X. ** No mention of whether affected/unaffected skin was biopsied (all biopsies cultured and not assayed directly).

centromeric region of the X; while in a majority it is Xp that is implicated, in three cases Xq is involved. It is thus unlikely that the same, single locus can be implicated in all these cases, unless the cytogenetic localisation is incorrect in a number of cases. (2) In one case, the X;autosome translocation was familial, being present in both mother and daughter. The mother, however, did not have the pigmentary dysplasia. If the breakpoint in this family were interrupting a critical locus, it might be expected that the mother and daughter would have an identical phenotype.

The effect of functional disomy of sequences on the X

Until recently, it has been difficult to gauge the phenotypic effect of functional disomy of the X in females. Females who harbour a duplication of material on one X chromosome are almost invariably normal phenotypically as they have a severely skewed X;inactivation pattern in favour of the intact X.^{20–22} Such females are, however, at 50% risk of passing on the duplicated chromosome to their sons who invariably have a severe phenotype. At least 15 cases of duplications of the X chromosome in a male karyotype have been reported with the duplications, when considered together, covering most of the X chromosome, with the exception of Xp11–Xq11 and Xq25–26.^{20–31} The reported cases have a wide range of differing phenotypic abnormalities, although facial dysmorphism, hypotonia, and mental retardation were common, albeit non-specific features. None of these subjects was reported as having a pigmentary dysplasia reminiscent of HI. This is perhaps unsurprising as such subjects are not mosaic. Six people with a duplication encompassing chromosomal region

Xp21 had sex reversal in addition to the other clinical features mentioned (that is, these were 46,XY females).^{26–28–30} Evidence now exists for the presence of a dosage sensitive sex reversal locus (DSS), adjacent to the locus for congenital adrenal hypoplasia at Xp21.^{29–32}

Cases of X chromosome duplication in males are thus instructive in that functional disomy of sequences on the X is tolerated, albeit with a severe phenotype, related to the presence of functional disomy of X chromosome sequences (there is evidence that the duplicated segment does not undergo X inactivation in such cases generally^{23–33}). These males, however, are not mosaic and do not easily allow for prediction of the effect of such disomy in a heterozygous female with random X inactivation.

The description of a subgroup of females with Turner's syndrome who have a severe phenotype (that is, compared to most Turner patients) in association with a (mosaic) cell that harbours a ring (X) chromosome is, however, instructive.^{34–38} There appears to be a good correlation between the presence of a severe phenotype in such females and the inability of the ring to inactivate, either because the X inactivation centre is absent, or because XIST expression is defective for reasons that are not entirely clear.^{35–39–40} It seems likely that the clinical severity in these cases is related to the presence of functional disomy of sequences present on the (active) ring. Of particular interest is the fact that a number of such females have been described as possessing a pigmentary dysplasia reminiscent of HI.^{34–37–41}

In addition to the evidence from ring (X) females of the effect of (mosaic) functional disomy of X sequences, another case of a female presenting with HI is instructive (J Hurst, personal communication). This female presented with seizures, developmental delay, hypo-

dontia, pigmented whorls on the back, and dysmorphism, including hypertelorism and flat nasal bridge with epicanthic folds. Cytogenetic analysis showed a de novo duplication at Xp11.2 of the region Xp11.4→p11.2. X inactivation analysis in peripheral blood lymphocytes showed random X inactivation with approximately a 50:50 pattern, rather than the expected skewing towards activity of the intact X. It is likely that the phenotype in this female results from the presence of functional disomy of sequences located in Xp11.2→11.4, in that proportion of cells that have the duplicated X active. The recognition of this female makes the existence of other females with submicroscopic duplications in the region likely (see below). While functional mosaicism results from random X inactivation in this female, it is important to note that in the case of ring(X) females it results from the physical presence or absence of the ring in different cell lineages.

Mosaic functional disomy of X specific sequences as the most likely mechanism for HI associated with balanced X;autosome translocations

What then is the mechanism whereby HI is manifested in the cases detailed in table 1? A number of possibilities are to be considered.

(1) *Interruption of a single locus by the breakpoint on the X chromosome can explain all the cases reported so far.* This explanation is unlikely to be true, not only because the reported breakpoints map on both sides of the centromere but molecular evidence also exists for heterogeneity of breakpoints that map to Xp11, implying that at least three of the breakpoints span a distance of 5 Mb, a distance greater than that spanned by the largest known human gene, dystrophin.^{42–45}

(2) *Each breakpoint defines a different locus (homologous in structure or function or both?) that can be implicated in the pathogenesis of HI in these females.* Again, this is unlikely. (A) The presence of a discordant phenotype in two females with the same breakpoint (X;10 translocation in table 1) implies that it is the functional status of the derived X that is important, rather than the precise site of interruption. (B) In the case of the other breakpoints, it is difficult to be certain that a specific locus interruption can be excluded. In the case of the X;17 translocation reported by Hodgson *et al.*,⁹ however, there is mounting evidence against a direct locus interruption. In situ hybridisation analysis has previously shown the X breakpoint to be centromeric and a recent reanalysis, in addition to confirming the centromeric nature of the X breakpoint, has shown the 17 breakpoints also to be centromeric, thus making involvement of a locus on 17 unlikely.⁴⁶

(3) *The phenotype results from interruption of autosomal loci.* This possibility is very difficult to exclude but would appear to be unlikely as a number of different autosomes have now been described in such cases, and in the case of the X;17 translocation, the 17 breakpoint is centromeric. In addition, no disruption of an autosomal gene has ever been diagnosed in association with a balanced X;autosome trans-

location, probably because most of the resulting phenotypes are recessive.⁴⁷

(4) *The phenotype results from an unusual pattern of X inactivation.* This seems the most likely explanation and is best exemplified by the case described above in which the phenotype is discordant between mother and daughter, despite identical karyotypes. In a female with a balanced X;autosome translocation, failure to eradicate cell lines bearing an inactive derived X will result in both mosaic functional disomy of X sequences and mosaic (variable) functional monosomy of autosomal sequences inactivated by spreading of X inactivation from the XIC of derived X. By comparison with the cases of ring (X) females, and the female described above with random X inactivation of a duplicated X chromosome, in both examples of which disomy of the X is the only possible mechanism, it would seem likely that it is the functional disomy that is the major factor in the females with HI and X;autosome translocations. Mosaic functional monosomy of autosomal sequences may, however, also be playing a role. While the majority of cases of mosaic aneuploidy described in association with HI involve the presence of extra chromosomal material, in a small number of cases mosaic monosomy of autosomal sequences has been found.³

Recent analysis of the female with a balanced X;17 translocation and HI (case 1 of Hodgson *et al.*⁹) showed random X inactivation in affected (hypopigmented) skin while X inactivation in normal skin and blood was skewed towards activity of the derived X as expected.⁴⁶ Such aberrant X inactivation in affected skin would result in functional disomy for all of Xp and a variable portion of 17p in those cells with an inactive derived X.

However, the phenotypic overlap between ring(X) females and those with HI associated with balanced X;autosome translocations makes disomy the most likely mechanism. Van Dyke *et al.*⁴⁷ found that pigmentary dysplasia was associated with the presence of a small ring (X) in females with a severe phenotype (in at least 19% of cases). Indeed, the female described by de Grouchy *et al.*⁴¹ was thought to have incontinentia pigmenti; Xp11 was again put forward as a region likely to contain the locus for incontinentia pigmenti as one of the breakpoints was in this region. It would seem preferable to reclassify this female as having HI associated with a small ring (X) chromosome that failed to inactivate (the ring (X) was found never to be late labelling).

Many of the dysmorphic features found in females with small ring (X) chromosomes are also frequent in females with HI associated with X;autosome translocations (tables 2 and 3).

X;autosome translocations and X linked disorders: theoretical reasons for IP1/H1 females not having classical incontinentia pigmenti

The discovery of rare females manifesting X linked phenotypes in association with a balanced, constitutional X;autosome trans-

Table 2 List of dysmorphic features reported in females with HI associated with balanced X;autosome translocations, graded according to frequency. Note overlap with ring (X) cases (see table 3).

	X;17 ⁹	X;9 ⁹	X;13 ¹⁰	X;10 ⁷	X;9 ^{8*}	X;18 ^{58†}	X;5 ⁶	X;10 ⁵⁹	X;14 ^{60†}	X;22 ^{3*}	X;17 ⁶¹
High arched palate (4/11)	+		+				+	+			
Broad nasal bridge (3/11)	+		+				+				
HC>95th centile (3/11)	+	+									+
Abnormal ears (3/11)	+		+	+							
High forehead (3/11)	+						+	+			
Dental abnormalities (3/11)		+						+			
Flat face (2/11)							+				
Hypertelorism (2/11)	+			+							
Epicanthic folds (2/11)	+			+							
Small hands and feet (2/11)	+							+			
Brachycephaly (1/11)		+									
Prognathism (1/11)		+									
Large tongue (1/11)		+									
Plagiocephaly (1/11)	+										
Carp shaped mouth (1/11)			+								
Syndactyly (1/11)				+							
Short philtrum (1/11)				+							
Cleft soft palate (1/11)				+							
Hirsutism (1/11)	+										
Gum hypertrophy (1/11)	+										
Neonatal teeth (1/11)				+							
Alopecia (1/11)							+				

* Dysmorphic features noted as being absent. † No mention made of dysmorphic features. With the exception of cases 5, 6, 9, and 10, a blank indicates that the relevant feature was not observed.

location has been of great benefit in the localisation and isolation of the loci involved in such disorders.^{48–50} The manifestation of the relevant X linked disorder in such females is thought to result from the severe skewing of X inactivation that is usually observed. While X inactivation in such females probably occurs randomly, subsequent selection against cells that have inactivated the derived X chromosome results in a uniform pattern of inactivation in which the intact X is almost invariably the inactive one. Interruption of the X linked locus under consideration on the derived X renders the female functionally nullisomic and the phenotype is therefore manifest. While it is usually assumed that cell selection is primarily directed against cells that have an inactive derived X because of spreading of inactivation onto the attached autosome, it is likely that functional disomy of X sequences is an equally potent abnormality against which selection occurs (fig 1).⁴⁷

Females with X linked phenotypes resulting from balanced X;autosome translocations manifest those phenotypes precisely because of the severe skewing that renders them “male-like”. Thus it would be surprising, a priori, to discover females manifesting an X linked dominant disorder with male lethality (such as IP2) in association with a balanced X;autosome

translocation. In addition, one would predict that females manifesting X linked disorders in association with X;autosome translocations would not have a mosaic pattern of expression. For example, the pattern of disease expression in IP2 is characterised by the presence of abnormal skin alongside normal skin, the demarcation being along Blaschko’s lines. Such “phenotypic mosaicism” is likely to arise because of random X inactivation during development; abnormal skin presumably contains large numbers of cells with the mutation bearing X active while normal skin has this chromosome inactivated. Such phenotypic mosaicism is known to occur in females who are obligate heterozygotes for a number of X linked disorders, including hypohidrotic ec-

XIC = X inactivation centre

Figure 1 This figure illustrates the situation in those cells that have failed to inactivate in the usual way. The intact X is active, while the derived X is inactive. Two functionally active copies of Xp (that is, of all sequences distal to the breakpoint in the pericentromeric region of the X) are therefore present, one on the intact X and one on the derived autosome. The latter Xp is presumed to remain functional as it has been physically disconnected from the XIC of the derived X. In addition to functional disomy of Xp, it is likely that there will be a (variable) monosomy of autosomal sequences owing to spreading of inactivation from the XIC of the inactive derived X.

Table 3 Dysmorphic features reported in three females with a pigmentary dysplasia associated with the presence of a ring(X) cell line, graded according to frequency. The most common features overlap with the most common features described in the X;autosome cases

	Case 3 of Dennis et al ³⁴	Case 5 of Van Dyke et al ³⁷	de Grouchy et al ⁴¹
	r(X)	r(X)	r(X)
Broad nasal bridge (3/3)	+	+	+
Hypertelorism (3/3)	+	+	+
High arched palate (2/3)		+	+
Abnormal ears (2/3)	+	+	
Epicanthic folds (2/3)		+	+
HC>95th centile (1/3)	+		
Syndactyly (1/3)	+		
Heart malformation (1/3)		+	
Polydactyly (1/3)		+	
Alopecia (1/3)			+

todermal dysplasia, Menkes disease, and Goltz syndrome.⁵¹ Thus, not only do significant differences exist between the phenotypes described in IP1 and those of "classical" IP (IP2) but there are more fundamental reasons why the females with IP1 are unlikely to have the same locus implicated as those with IP2. This argument predicts that no female will be described who has "incontinentia pigmenti" in association with an X;autosome translocation involving the IP2 locus at Xq28. In addition, it argues against the likelihood that *any* of the X breakpoints in females with HI associated with a balanced X;autosome translocation involve a locus that defines a familial disorder.

Specific reasons for IP1/HI breakpoints not being related to incontinentia pigmenti

It would now seem clear that the phenotypic differences between IP1/HI and IP2 are sufficient to warrant the designation IP1 redundant.¹⁷ In addition to the differences in evolution of skin abnormalities between the two conditions, most of the females with IP1/HI have been noted to be dysmorphic (table 2), a feature not present in classical familial incontinentia pigmenti.¹⁶

Functional disomy of X sequences in diploid/triploid mixoploidy as a mechanism for HI?

HI has been described in association with diploid/triploid mixoploidy. It is tempting to speculate that functional disomy of X sequences may also be implicated in the pathogenesis here. In cells that have more than one X chromosome, it is invariably the case that one X remains active, while all others are inactivated. This is true for diploid cells, irrespective of the number of X chromosomes present. Triploid cells, however, appear able to support the activity of more than one X chromosome. Thus, while only one X is active in 47,XXY cells, 69,XXY cells may have two active X chromosomes.⁵²

It seems likely that it is the ratio of autosomes to X that determines the number of X chromosomes that will remain active, with a usual diploid complement of 44 autosomes ensuring that only one X remains active. In the case of 69,XXX or 69,XXY triploidy, a proportion of cells will harbour more than one active X chromosome, with the result that these cells will be functionally disomic for the whole of the X, a situation that is likely to be deleterious to the cell line under consideration. Clearly, however, the presence of an extra set of autosomes cannot be ruled out as being implicated in the pathogenesis of HI in these people.

Can specific X linked loci be defined which are necessary for development of HI resulting from functional disomy of the X?

It is probable that the females ascertained as having HI in association with X;autosome translocations with breakpoints in Xq13-Xp11 represent a small minority of all females with such translocations. In a recent review of 122 published cases of balanced X;autosome translocations in females, the breakpoints in 57 were listed as lying above XIC.⁴⁷ Of these, 20 were said to be phenotypically normal and it is to be expected that the true proportion is even higher as such phenotypically normal females are much less likely to be ascertained. In the majority of cases, the breakpoints are unlikely to interrupt specific loci and skewed X inactivation will result in a normal phenotype. There is unlikely to be a specific reason for ineffective selection against cells bearing an inactive derived X. In their review, Schmidt and Du Sart⁴⁷ reported that inactivation of the derived X, in at least some tissues, occurs in 23% of females with balanced X;autosome translocations.

However, no females have been described with HI where the X breakpoint lies outside Xq13-Xp11. It is noteworthy that, of 24 females known to manifest Duchenne muscular dystrophy in association with a balanced X;autosome translocation that disrupts the DMD locus, none has been described as having a pigmentary dysplasia, although a number have other abnormalities, including psychomotor retardation.⁵³ Thus it seems likely that if specific loci are to be implicated in the pathogenesis of HI, when present in a functionally disomic state, then such loci must be located proximal to Xp21. In addition, the presence of HI in females with small ring (X) chromosomes, in whom functional disomy is almost certainly the aetiological mechanism, argues for the presence of the implicated locus (loci) within the ring.

Thus, the locus (loci) in question may be mapped by considering the smallest ring (X) found to cause HI and the most distal X breakpoint that also gives rise to the phenotype (fig 2). However, although such analysis may define a minimum region within which such a locus (loci) must reside, it is conceivable that different loci may be responsible in different cases.

Figure 2 Diagram illustrating the possible location of a locus/loci that causes the HI phenotype when present in a functionally disomic form. Given that quite a number of females have now been described who manifest a severe phenotype in association with a small ring X chromosome, it should be possible to define this region more precisely. Any such locus, according to the hypothesis, should map distal to the most "telomeric" IP1 X;autosome translocation breakpoint, and proximal to the most "centromeric" of all the Xp ring X breakpoints.

Why are no X breakpoints described below Xq13?

Inactivation of the derived X in a cell bearing an X;autosome translocation with a breakpoint below Xq13 will result in functional disomy of Xq sequences. The absence of X breakpoints below Xq13 argues against functional disomy of Xq sequences as being important in production of the HI phenotype. If a locus (loci) on Xp is particularly important in the production of the HI phenotype (that is, in a functionally disomic state), then only breakpoints above the XIC will be ascertained in this way.

X;autosome translocations and mapping XLMR genes

Failure to eradicate cell lines bearing an inactive derived X may happen in some tissues and not others. Thus, it is likely that some females with mental retardation associated with balanced X;autosome translocations, in whom a pigmentary dysplasia is absent, may still be manifesting their phenotype as a result of the mechanism outlined above (that is, in those cases where the breakpoint lies above XIC). In such females, eradication of cell lines bearing an inactive derived X may have been successful in skin but not in other tissues, such as CNS. It is possible that such females will be erroneously interpreted as possessing a translocation that results in the interruption of a locus for X linked mental retardation (XLMR). This is likely to be a potential hazard in the mapping and isolation of genes implicated in XLMR, particularly where this is non-syndromic. The case described by Hodgson *et al*⁵⁴ illustrates the point. A female with a balanced, de novo, constitutional X;13 translocation was described as developmentally delayed and dysmorphic. No pigmentary dysplasia was noted but her dysmorphic features, albeit relatively non-specific, were consistent with those seen in the females described above. Others have noted an increased incidence of breakpoints at Xp11 in females with mental retardation and X;autosome translocations and correlated this with XLMR loci thought to map to this region.⁵⁵

Functional disomy of Xp in cytogenetically normal females with HI?

It is likely that females exist with submicroscopic duplications in Xp, who manifest the phenotype of HI. Indeed, this may be one possible mechanism to explain the rare reported cases of familial HI.⁵⁶ The presence of a submicroscopic duplication on one X may result in a variety of phenotypes depending on the pattern of X inactivation in relevant tissues. A phenotypically normal mother (or one who simply had a pigmentary dysplasia) might have a severely affected daughter with HI and CNS abnormalities. It is harder to explain familial occurrences of HI by implicating submicroscopic autosomal abnormalities, as there is not as much scope for phenotypic variability as is afforded by differential X inactivation. It is suggested that a search for submicroscopic

duplications in proximal Xp may be fruitful in female cases of HI where cytogenetic analysis is normal, particularly if there are indications that the HI may be familial, albeit with variable severity.

Conclusion

This review has presented evidence for the role of functional disomy of Xp in the pathogenesis of HI associated with X;autosome translocations with breakpoints in the pericentromeric region of the X. Previous ideas about such X breakpoints defining specific loci are likely to be false for reasons stated above.

Further work to map minimal regions of overlap found in (A) ring (X) cases and (B) translocation cases may define a locus (loci) that is implicated in the pathogenesis of HI and may lead to the discovery of patients with HI resulting from submicroscopic duplications.

In addition, caution is required when interpreting the pathogenesis of mental retardation in females with balanced X;autosome translocations and it should not be assumed that the X breakpoint necessarily defines a locus implicated in XLMR. The obvious exceptions will include females who manifest a well defined phenotype in association with a balanced X;autosome translocation (for example, Menkes syndrome, see above).

Implications for genetic counselling

While the majority of females with balanced X;autosome translocations with breakpoints above XIC are likely to be phenotypically normal, accurate prediction of the phenotype of any daughters with an identical translocation cannot be made with certainty, as "unfortunate" X inactivation may result in a severe phenotype as illustrated by the maternally inherited X;10 translocation detailed in table 1. Conversely, where a phenotypically normal mother with a balanced X;autosome translocation has a son with the same balanced translocation, reassurance can be given that the child will be phenotypically normal although male infertility would be expected.⁵⁷ In this situation the presence of a normal phenotype in the mother makes interruption of a specific locus on either the X or the autosome unlikely, so that there is no specific reason why male offspring should have an abnormal phenotype.

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