Hypothesis

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

Eli Hatchwell

Abstract

Hypomelanosis of Ito (HI) is a sporadic multisystem disorder whose defining feature is a pigmented dysplasia. 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. The frequent presence of chromosomal mosaicism in HI makes sense of the wide variability in clinical phenotype. In a review of 70 published cases, the only consistent feature was the presence of hypopigmented skin without preceding vesicular or verrucous stages. A total of 74% of the patients, however, had one or more abnormalities of the central nervous system, eyes, hair, teeth, or musculoskeletal system. Such clinical variability is common to other mosaic genetic conditions (for example, Proteus syndrome) 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. 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. As a result of such analyses, familial 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. 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 autosomal or sex chromosome has been described. 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-
Table 1  Summary of females with IP1/HI in association with balanced X,autosome translocations

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<tbody>
<tr>
<td>46,X,t(X;9)</td>
<td>46,X,t(X;13)</td>
<td>46,X,t(X;17)</td>
<td>46,X,t(X;9)</td>
<td>46,X,t(X;10)</td>
<td>46,X,t(X;5)</td>
<td>46,X,t(X;10)</td>
<td>46,X,t(X;4)</td>
<td>46,X,t(X;22)</td>
<td>46,X,t(X;7)</td>
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</tr>
<tr>
<td>(p11.2p12)</td>
<td>(p11.2p12.3)</td>
<td>(p11.2p13.2)</td>
<td>(p11.2p13.2)</td>
<td>(p11.2p12.3)</td>
<td>(p11.2p13.2)</td>
<td>(p11.2p12.3)</td>
<td>(p11.2p13)</td>
<td>(p11.2p13.3)</td>
<td>(p11.2p13)</td>
<td></td>
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</tr>
</tbody>
</table>

Skin
- Hypopigmentation: +
- Hyperpigmentation: -
- Blistering: -
- GCS involvement: -
- Psychomotor delay: -
- Seizures: +
- EEG abnormalities: +
- Mental retardation: +
- Hypotonia: +
- Eye anomalies: -
- Hair anomalies: -
- Nail anomalies: -
- Cerebral anomalies: -
- Diagnosis made: -
- Skin biopsy: -
- Other features: Bilateral reinflationoma

X inactivation (blood): >90% Xn inactive
- >90% Xn inactive: 91% Xn inactive, 100% Xn inactive, 100% Xn inactive, 0, 0, 92% Xn inactive

X inactivation (skin): >90% Xn inactive
- >90% Xn inactive: 99% Xn inactive, 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 corticospinal 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. X normal, intact X. ** No mention of whether affected/unaffected skin was biopsied (all biopsies cultured and not assayed directly).

In addition to the evidence from ring (X) females of the effect of (mosaic) functional dosing 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-
Hypomelanosis of Ito and X;autosome translocations: a unifying hypothesis

Hypomelanosis

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 in-
activation analysis in peripheral blood lym-
phocytes 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 ran-
dom X inactivation in this female, it is im-
portant 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 mo-

cular 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.

(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 cen-

tromeric 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.9

(3) The phenotype results from interruption of
autosomal loci. This possibility is very dif-
ficult 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.4

(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, des-
pite 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 trans-
locations. 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 chro-
mosomal material, in a small number of cases
mosaic monosomy of autosomal sequences has
been found.1

Recent analysis of the female with a balanced
X;17 translocation and HI (case 1 of Hodgson
et al.) 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.67 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.68 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 fe-
males 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 IPI/HI
females not having classical
incontinentia pigmenti
The discovery of rare females manifesting X
linked phenotypes in association with a bal-
anced, 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 2).

<table>
<thead>
<tr>
<th></th>
<th>X17*</th>
<th>X9*</th>
<th>X13**</th>
<th>X10*</th>
<th>X8**</th>
<th>X18**+</th>
<th>X5*</th>
<th>X10*</th>
<th>X14*+</th>
<th>X22*</th>
<th>X17+</th>
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<tr>
<td>High arched palate (4/11)</td>
<td>+</td>
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<tr>
<td>Broad nasal bridge (3/11)</td>
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<td>HC&gt;95th centile (3/11)</td>
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<td>Abnormal ears (5/11)</td>
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<td>High forehead (3/11)</td>
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<td>Dental abnormalities (3/11)</td>
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<td>Flat face (2/11)</td>
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<td>Hypertelorism (2/11)</td>
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<td>Epicantthic folds (2/11)</td>
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<td>Small hands and feet (2/11)</td>
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<td>Brachycephaly (1/11)</td>
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<td>Prognathism (1/11)</td>
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<td>Polydactyly (3/11)</td>
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<td>Carpal fusion (1/11)</td>
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<td>Syndactyly (1/11)</td>
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<td>Short philtrum (1/11)</td>
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<td>Cleft soft palate (1/11)</td>
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<td>Hirsutism (1/11)</td>
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<td>Gum hypertrophy (1/11)</td>
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<td>Neonatal teeth (3/11)</td>
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<td>Alopecia (1/11)</td>
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* 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.46-50 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).57

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-

Table 3  Dysmorphic features reported in three females with a pigmented 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

<table>
<thead>
<tr>
<th></th>
<th>Case 1 of Dennis et al.</th>
<th>Case 2 of Dyke et al.</th>
<th>de Grouchy et al.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Xr(X)</td>
<td>Xr(X)</td>
<td>Xr(X)</td>
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<tr>
<td>Broad nasal bridge (3/3)</td>
<td>+</td>
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<tr>
<td>Hypertelorism (3/3)</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>High arched palate (2/3)</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Abnormal ears (2/3)</td>
<td>+</td>
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<tr>
<td>HC&gt;95th centile (1/3)</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Syndactyly (1/3)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Heart malformation (1/3)</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Polydactyly (1/3)</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Alopecia (1/3)</td>
<td>+</td>
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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 pericentric 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.
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todermal dysplasia, Menkes disease, and Goltz syndrome.\textsuperscript{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 "incontinencia 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.\textsuperscript{57} 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.\textsuperscript{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,XXX cells, 69, XXX cells may have two active X chromosomes.\textsuperscript{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.\textsuperscript{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 Sart\textsuperscript{77} 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 pigmented dysplasia, although a number have other abnormalities, including psychomotor retardation.\textsuperscript{19} 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.
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.26 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 related this with XLMR loci thought to map to this region.27

Functional disomy of Xp in cytotrogenically 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.24 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. This is obvious exceptions with 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.25 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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Hypomelanosis and X-autosomal translocations: a unifying hypothesis


