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Exclusion mapping of the X-linked dominant chondrodysplasia punctata/ichthyosis/cataract/short stature (Happle) syndrome: possible involvement of an unstable pre-mutation

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Summary. Homology with the mouse bare patches mutant suggests that the gene for the X-linked dominant chondrodysplasia punctata / ichthyosis / cataract / short stature syndrome (Happle syndrome) is located in the human Xq28 region. To test this hypothesis, we performed a linkage study in three families comprising a total of 12 informative meioses. Multiple recombinations appear to exclude the Xq28 region as the site of the gene. Surprisingly, multiple crossovers were also found with 26 other markers spread along the rest of the X chromosome. Two-point linkage analysis and analysis of recombination chromosomes seem to exclude the gene from the entire X chromosome. Three different mechanisms are discussed that could explain the apparent exclusion of an X-linked gene from the X chromosome by linkage analysis: (a) different mutations on the X chromosome disturbing X inactivation, (b) metabolic interference, i.e. allele incompatibility of an X-linked gene, and (c) an unstable pre-mutation that can become silent in males. We favour the last explanation, as it would account for the unexpected sex ratio (M:F) of 1.2:1 among surviving siblings, and for the striking clinical variability of the phenotype, including stepwise increases in disease expression in successive generations.

Introduction

Between 1977 and 1981, Happle fully delineated an X-linked gene defect characterized by chondrodysplasia punctata (CP), ichthyosis at birth evolving into streaky hyperkeratosis, patchy cicatricial alopecia, cataracts, and short stature (Happle et al. 1977; Happle 1979a, b, 1981). As in incontinentia pigmenti, the disease occurred exclusively in the female sex and the cutaneous lesions showed a mosaic distribution pattern following the lines of Blaschko (Blaschko 1901). Happle concluded that this was an X-linked dominant trait and suggested that the gene is lethal in males, but that it can be rescued in females because of X inactivation.

Familial occurrence of the syndrome is rare (Curth 1949; Manzke et al. 1980) and only three families with affected members in three generations have been described so far (Goerttler 1979; Mueller et al. 1985; Kalter et al. 1989). Most cases are sporadic and have been interpreted as *de novo* mutations (Happle 1979a; Mueller et al. 1985). Clinical expression is highly variable (Manzke et al. 1980; Kalter et al. 1989) and skeletal manifestations are not invariably present (Kalter et al. 1989; Prendiville et al. 1991). Thus, the often-used term "X-linked dominant chondrodysplasia punctata" is unsatisfactory. The designations "Conradi-Hünermann syndrome" or "Conradi disease" have been applied as an umbrella term for several genetically distinct forms of CP in the past (Spranger et al. 1971; O'Brien 1990) and therefore are ambigous. In this study, we will refer to the condition as "Happle syndrome".

The Happle syndrome can be classified within the heterogeneous group of conditions featuring CP (Spranger et al. 1971; O'Brien 1990) and can be distinguished (1) from the autosomal dominant type of CP, which has no obvious skin lesions and cataracts, (2) from the severe autosomal recessive rhizomelic type of CP, and (3) from X-linked recessive CP. The latter form of CP has been assigned to Xp22.3 by deletion mapping (Curry et al. 1984; Ballabio et al. 1988; Petit et al. 1990).

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In 1973, Philipps et al. reported a radiation-induced mouse mutant that they called bare patches (Bpa). They demonstrated an X-linked dominant mode of inheritance for the Bpa gene. This type of mouse exhibits skin lesions that include linear areas of hyperkeratosis, linear absence of hair and linear pigmentary disturbances, all analogous to the cutaneous manifestations of the Happle syndrome in humans. Morevover, Happle et al. (1983) have demonstrated similarities between the skeletal and ocular manifestations, and have suggested that the Bpa gene is homologous to the gene for the Happle syndrome.

The locus for Bpa has been mapped close to the murine X-linked visual pigment gene (Rsvp) (Philipps and Kaufman 1974; Herman and Walton 1990) and has recently been shown to be located between the alpha 3 subunit of the receptor for gamma amino butyric acid (Gabra 3) and Rsvp (Herman et al. 1991). In view of the evolutionary relationship between the murine and the human X chromosome, this strongly suggests a location of the human gene in the Xq28 region. To test this hypothesis, we performed linkage studies to localize the gene for the Happle syndrome.

Materials and methods

We studied the families described by Goerttler (1979) and Kalter et al. (1989), and a further eastern German family (D. Müller, unpublished). The three families comprised a total of 12 informative meioses (Fig. 1). The eastern German family contains a large side branch that could not be studied at the DNA level. However, this side branch adds valuable information on the transmission of the disease and therefore is also depicted.

Clinical examination

Visits to the three families were organized, and clinical re-examination confirmed the presence of the disease in the family members previously diagnosed as being affected. Disease expression was found to be highly variable both within and between the families. For example, in family 3, two of the three affected females showed the pathognomonic cutaneous signs and symptoms, but none of them exhibited recordable signs of CP, as had previously been pointed out by Kalter et al. (1989). Individual III-1 of this British family presented diagnostic difficulties and was finally classified as being mildly affected mainly because of a strikingly short stature. In the other two families, skeletal manifestations predominated, whereas the cutaneous involvement was mild. Individual III-4 of family 1 gave birth to a severely affected girl. This girl died immediately after birth and diagnosis was only made several years after her death on the basis of X-ray examinations (Dr. D. Müller, unpublished). No DNA was available from this child.

We noticed that all affected females were of short stature (height 155–165 cm). Short stature was considered to indicate the presence of the disease gene in the family, other members being of normal or above average height. Except for individual III-1 of family 3, all other affected females showed, in addition to short stature, one or more of the following: sectorial cataracts, patchy cicatricial alopecia, conspicuous coarse hair or scoliosis. In all three families, the grandmothers were mildly affected, the daughters showed more severe involvement and only the propositae exhibited the fully expressed disease.

DNA analysis

Genomic DNA was digested with restriction enzymes, separated on agarose gels and blotted on to a nylon membrane (Genescreen plus) using the alkali technique. A panel of 40 DNA markers was used, of which 26 were informative in the families (Table 1). Probes were 32P-labelled by random priming and hybridized to Southern blots by standard techniques. In addition to restriction fragment length polymorphism (RFLP) analysis, 4 dinucleotide repeat polymorphisms were employed: DXS453 (Weber et al. 1990), DXS456 and DXS424 (Luty et al. 1990) and a repeat at the coagulation factor 8 gene (Lalloz et al. 1991). The conditions used were essentially those described by Weber and May (1989). In short, for use in the polymerase chain reaction (PCR), one member of each pair of primers was 32P-labelled at its 5′ end by incubation with gamma 32P in the presence of polynucleotide kinase. After heating at 95°C for 5 min, the PCR products were put on ice for

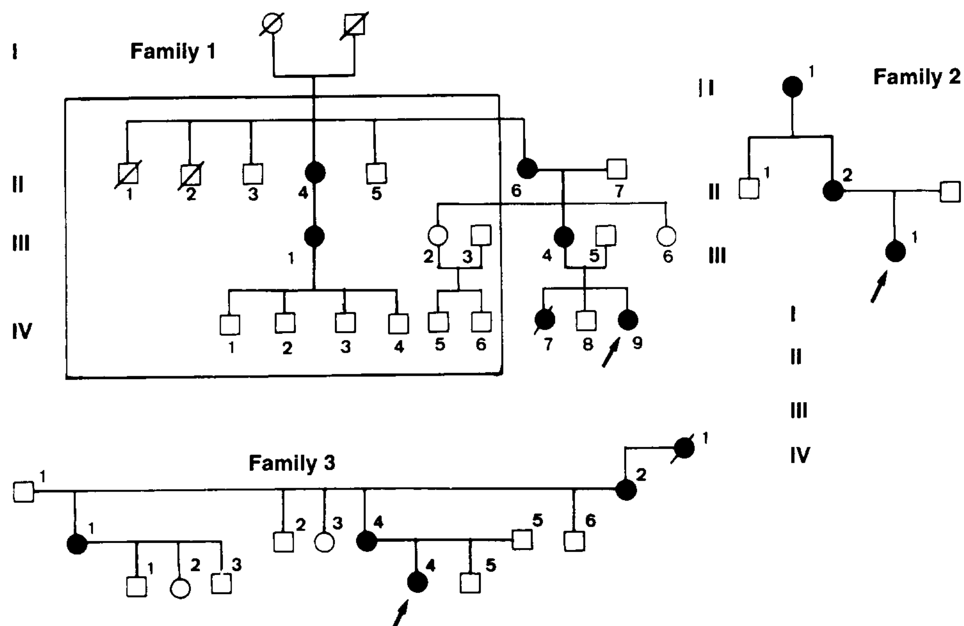

Fig. 1. Pedigrees of the three families studied. Family 1 contains a large side branch that could not be analysed at the DNA level. Note that, after Weinberg correction, the sex ratio (M:F) is 1.2:1, thus deviating from the expected 1:2

Table 1. DNA markers used

Locus	Probe name	RFLP enzyme	Alleles (kb)	Origin
DXYS20	p362A	*Taq*I	Many	J. Weissenbach
MIC2	p19b	*Taq*I	3.2/2.5	P. Goodfellow
MIC2	pSG1	*Msp*I	2.55/2.35	S. Darling
DXS143	pDic56	*Bcl*I	8.9/7.44	ATCC
DXS237	pGMGX9	*Hind*III	4/3.5+1.5	E. Gillard
DXS278	pCRI-S232	*Bgl*II	Many	Collab. Res.
DXS16	pXUT23	*Bcl*I	2.5/2.2	ATCC
DXS41	p99-6	*Pst*I	22/13	L. M. Kunkel
DXS84	p754	*Pst*I	12/9	P. L. Pearson
TIMP	EPAcDNA	*Bgl*II	12/9.5	H. F. Willard
DXS255	pM27β	*Eco*RI	Many	I. W. Craig
DXS14	p58-1	*Msp*I	4/2.5	ATCC
DXS453	Mfd66	CA-Repeat	Many	J. L. Weber
	pZAP169[a]	*Eco*RI	4.5/4.2	F. Cremers
DXYS1	pDP34	*Taq*I	11.8/10.6	D. C. Page
DXYS2	p7b	*Pst*I	12/9	J. Weissenbach
DXS94	pXG12	*Pst*I	7.2/6.5	P. Szabo
DXS287	pYNH3	*Rsa*I	3.2/2.8	ATCC
DXS456	pXG30B	CA-Repeat	Many	J. A. Luty
DXS42	p7F1	*Bcl*I	5.0/4.2	R. Nussbaum
DXS424	pXL5A	CA-Repeat	Many	J. A. Luty
DXS91	pXG17	*Msp*I	4.0/3.6	P. Szabo
DXS107	cpX234	*Taq*I	3.2/1.1	P. L. Pearson
DXS144	pC11	*Taq*I	4.3/3.0	J.-L. Mandel
DXS15	pDX13	*Bgl*I	5.8/2.8	K. E. Davies
F9	pTG397	*Taq*I	1.8/1.3	J. L. Mandel
DXS105	p55E	*Bgl*II	7.7/4.4	J. L. Mandel
DXS52	pST14-1	*Taq*I	Many	J.-L. Mandel
RCP	pHS7	*Sst*I	Many	J. Nathans
F8C		CA-Repeat	Many	E. G. D. Tuddenham
	F8-14	*Bcl*I	1.2/0.9	J. L. Mandel

[a] No DXS symbol assigned

another 5–10 min, and then resolved on a standard denaturing polyacrylamide DNA sequencing gel.

Genetic analysis

For those probes that were informative in at least two of the three families, two point linkage analysis was performed with the LINKAGE program MLINK (version 5.03; Lathrop and Lalouel 1984). Recombination chromosomes were drawn for individuals IV-8 and IV-9 of family 1, and for individuals IV-1, IV-3, IV-4 and IV-5 in family 3.

Results

Analysis of the segregation pattern (Fig. 2) revealed multiple recombination events widely scattered over the entire X chromosome. No region was found that showed consistent co-segregation between DNA markers and the disease locus. In particular, several informative markers in individuals IV-8 and IV-9 of family 1 gave recombinations in the Xq27–Xq28 region.

The results of linkage analysis are summarized in Table 2. Again, negative lod scores were obtained for loci spanning the entire X chromosome, including the Xq27–Xq28 region. The locus DXS52 (St14–1) gave a negative lod score of -2 at a recombination fraction of $\theta = 0.08$, thus firmly excluding a genetic region of 8 cM above and below this locus. A microsatellite repeat at the gene for coagulation factor VIII, which is the most distal locus used, yielded a negative lod score of -2, at a θ value of 0.17. At the loci DXS42 defined by probe p7F1 (Xq23–25) and DXS287 defined by probe YNH3, low positive lod scores of 1.5 ($\theta = 0.00$) and 0.60 ($\theta = 0.15$) were found. However, both probes were informative only in some of the family members. Two more informative neighbouring loci (DXS456 and DXS424) defined by dinucleotide polymorphisms gave negative lod scores of -2 ($\theta = 0.05$).

Discussion

At first glance, our data firmly exclude the gene for the Happle syndrome from the Xq28 region and would thus argue against the postulated homology between the human disease and the murine Bpa mutation. The gene for Bpa has been shown to be very close (within a segment of 3 million base pairs) to the locus DXPas8, which is the murine homologue of DXS52 (St14–1) (Faust and Herman 1991). DXS52 and the more distal coagulation factor 8 gave highly negative lod scores. Similarly multiple crossovers at four different loci from Xp22.3 appear firmly to exclude this region, which contains the gene for X-linked recessive CP.

Surprisingly, we also failed to find the gene for the Happle syndrome elsewhere on the X chromosome, even though we employed a battery of 22 additional DNA markers evenly spread along the remaining regions of the X chromosome. The apparent exclusion of an X-linked gene from the X chromosome is more than a flaw of beauty. This paradox gives rise to a number of questions.

How reliable is the exclusion mapping?

In addition to the lod scores, Table 2 also gives the relative map position (RMP) of the DNA markers. The scale used is that of Mandel et al. (1989) and comprises a range of 200 RMP units. By linkage analysis, the gene can definitely be excluded from Xp22.3 to Xp22.2, from Xp21.1 to Xq22, and from Xq25 to Xq28. The genetic distance between the locus DXS16 at Xp22.2 and DXS84 at Xp21.1 is still large (40 RMP units), but both loci give a negative lod score of -2 at O values of 0.11 and 0.12. As can be seen from the drawing of the six recombination chromosomes, it would require at least 3 additional double crossovers to place the gene between DXS16 and DXS84. This is improbable.

The lod score calculations do not firmly exclude the Xq22 to Xq25 region, which comprises a genetic distance of about 30 RMP units. Two loci from this region (DXS287 and DXS42) give low positive lod scores. As

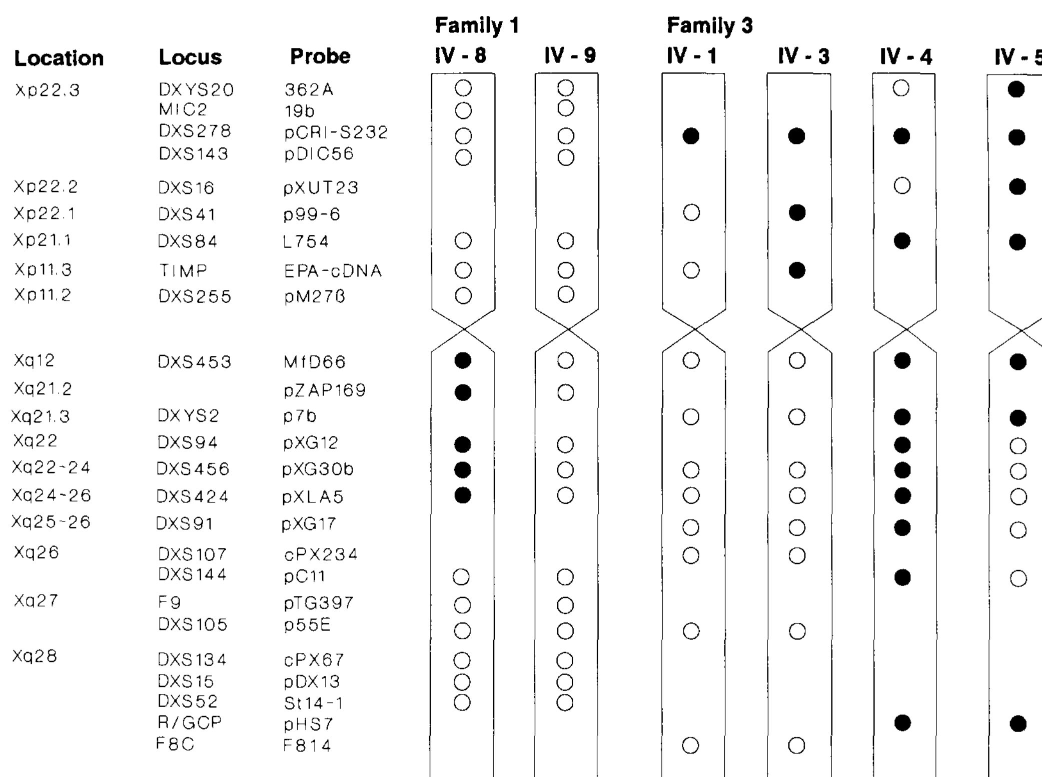

Fig. 2. Drawing of recombination chromosomes for which the full coupling phase is known (third generation chromosomes). *Open circle* indicates recombination; *closed circle* indicates co-segregation

has been pointed out above, the probes defining these loci were not informative in all family members, and more informative neighbouring markers score multiple recombinations. Examination of Fig. 2 shows that at least 4 double crossovers would be necessary to localize the gene here. Again, this is improbable.

Non-paternity is a trivial reason for not finding close linkage with any of the markers used. In our families, we can definitely rule out this possibility. We tested 30 informative markers, all of which were compatible with paternity. It could be argued that the clinical status of key individuals might have been wrongly assessed. We can only reply that great care was taken to classify the patients properly. Gene conversion has been demonstrated for the X-linked colour vision genes. The gene for the Happle syndrome could be shuffled to the "wrong" chromosome by this mechanism. Indeed, gene conversion could explain why, in individual IV-9 of family 1, all loci recombine. However, it is a rare event and thus unlikely to account for several independent recombination events in different families.

Table 2. Lod score calculations with the LINKAGE program MLINK. RMP, Relative map position according to Mandel et al. (1989)

Location	Locus	Lod score	θ	RMP units
Xp22.3	DXYS20	−2	0.12	+100
	DXS143	−2	0.11	+ 85
	DXS278	−2	0.07	
Xp22.2	DXS16	−2	0.12	+ 80
Xp21.1	DXS84	−2	0.11	+ 40
Xp11.3	TIMP	−2	0.06	
Xp11.2	DXS255	−2	0.12	+ 15
Xq12	DXS453	−2	0.14	− 15
Xq22	DXS94	−2	0.03	− 50
Xq22–24	DXS456	−2	0.05	
	DXS287	+0.6	0.13	
Xq23–25	DXS42	+1.5	0.0	− 70
Xq24–26	DXS424	−2	0.05	
Xq25–26	DXS91	−2	0.02	
Xq26	DXS144	−2	0.07	− 80
Xq27	DXS105	−2	0.17	− 89
Xq28	DXS52	−2	0.08	− 94
	F8C	−2	0.17	

Is the Happle syndrome not X-linked at all?

The data obtained in our study could also be taken as an indication that the Happle syndrome is not X-linked. Instead, a model involving autosomal dominant inheritance with sex-limited expression could be invoked. We regard this as a highly theoretical and remote possibility. In the past, such a model has been suggested for incontinentia pigmenti as an alternative to the X-linked dominant mode of inheritance. The gene for incontinentia pigmenti has now been mapped to Xq28 (Sefiani et al. 1989a).

Is the Happle syndrome genetically heterogeneous?

Genetic heterogeneity could possibly underlie our failure to localize the gene. The example of tuberous sclerosis (Sampson et al. 1989; Fahsold et al. 1991) shows that occasionally even *identical phenotypes* can be caused by mutations in different genes. However, biochemical and ultrastructural evidence argues against genetic heterogeneity. First, skin scales of patients with the Happle syndrome lack cathepsin B activity (Bergers et al. 1990). This defect has been found in scales only; stratum corneum from areas of unaffected skin appears to be normal (Bergers et al. 1990). Our patients were included in this study and also showed this cathepsin B deficiency. Although the etiological role of cathepsin B deficiency in the Happle syndrome is still unclear, these findings provide evidence against genetic heterogeneity. Secondly, the Happle syndrome is characterized by distinctive histological and ultrastructural features, for example calcium crystals within keratinocytes and Langerhans cell degeneration (Kolde and Happle 1985). We conclude that genetic heterogeneity of the Happle syndrome is improbable.

Is the Happle syndrome caused by mutations at different X-linked genes involved in X chromosome inactivation?

The mechanism implied in the above question can best be illustrated by the example of X/autosome translocations or ring formation of one X chromosome in hypomelanosis of Ito (HI). It is of note that some of these cases have been misclassified as incontinentia pigmenti. Surprisingly, three different breakpoints in Xp11 have been demonstrated (Crolla et al. 1989; Sefiani et al. 1989b) and a fourth breakpoint may involve Xq21. Sefiani et al. (1989b) have suggested that, in these cases, the HI phenotype could result from anomalous X-inactivation/reactivation in cells with a disturbed gene dosage.

Disturbed X-inactivation provides a mechanism reconciling X-linked inheritance and the apparent exclusion of the gene from the X chromosome. Applied to the Happle syndrome, it is a possible, but no very likely, disease mechanism, as it assumes mutations at several loci on the X chromosome.

Could metabolic interference play a role?

In 1980, Johnson proposed the concept of metabolic interference or the "+/− heterozygote". In this model, the heterozygote alone would be affected, whereas the homozygotes for both the normal and the abnormal allele would have the normal phenotype. In other words, the two alleles are not compatible and their interaction will produce a harmful effect. If an X-linked gene showed metabolic interference, the resulting formal genetics would be bizarre. The disease would become manifest only in females, and would segregate in a manner mimicking X-linked dominant transmission. Males could receive and transmit the abnormal gene, but could not exhibit the abnormal phenotpye. Such non-penetrant males would be scored as recombinants, and would preculde mapping of the disease locus on the X chromosome by linkage analysis. For an X-linked gene, the concept of metabolic interference predicts that *all* daughters of a non-penetrant male gene carrier will be affected. So far, transmission of the gene via an unaffected male has not yet been observed in the few families with Happle syndrome.

The concept of metabolic interference still needs to be firmly established and confirmed. We consider metabolic interference of an X-linked gene to be a possible, but not very likely, explanation.

Sex ratio and the Happle syndrome

When applying the concept of X-linked dominant transmission, a lethal gene effect for males is usually considered to account for a disease occurring in females only. For the genetic analysis in the families with the Happle syndrome, it was therefore assumed a priori that no male individual could have received the disease gene. After having excluded the gene from so much of the X chromosome, we wondered whether this assumption is supported by the sex ratio in the families studied.

For an X-linked dominant male-lethal gene, a sex ratio (M:F) of 1:2 is expected. As can be seem from Fig. 1, the sex ratio observed in our families is 1:1 (15 males, 9 affected and 6 healthy females). If the 3 propositae are subtracted (Weinberg correction), the sex ratio increases to 1.2:1 in favour of males.

Proposal of an unstable pre-mutation

In view of these sex ratio figures, we wish to challenge the notion that the gene is always lethal in males. Instead, we propose that mildly affected females carry an unstable pre-mutation that can become silent in males. Non-penetrant males would not be recognized as gene carriers and would be scored as recombinants, thus appearing to exclude the gene from its true location. Indeed, the apparent exclusion of the gene for the Happle syndrome from the X chromosome by means of linkage analysis can best be explained if one assumes that some male family members have received the mutant gene, but do not show any symptoms.

Intrauterine death of severely affected female embryos could be another mechanism accounting for the deviation from the expected sex ratio. Following this line of thinking, liveborn affected girls would represent "extreme lyonization" in favour of functionally normal cells. However, extreme lyonization does not explain how the gene can become silent in males. In this context, it may be of interest that, in family 3, the dinucleotide repeat polymorphisms pXG30B (DXS456, Xq21–q22) and XLA5 (DXS424, Xq24–26) and the probe pXG17 (DXS91, Xq25–26) detect recombinations always and only in the same 3 male family members (Fig. 3).

We suggest that the genetics of the Happle syndrome may be similar to that of the fragile X syndrome, which has become a model for hereditary unstable pre-muta-

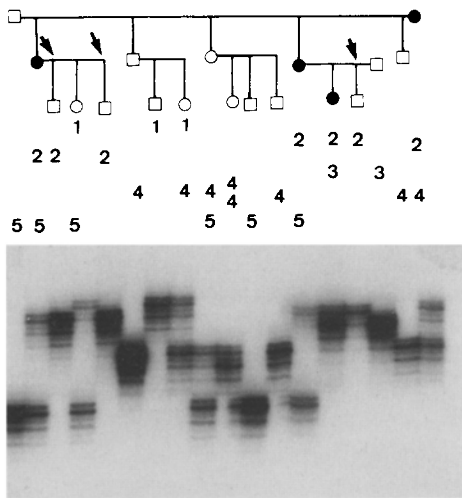

Fig. 3. In family 3, the micro-satellite repeat pXG30B (DXS456; Xq22–24) detects 3 recombinations *(arrows)* in male family members only. In this family, the same situation was found with more distal markers (loci DXS424 and DXS91)

tions (Oberlé et al. 1991; Verkerk et al. 1991; Yu et al. 1991). It has been shown that male and female fragile X carriers have 70 to 200 copies of a CGG repeat, whereas in normal individuals only about 40 copies are found (Sutherland et al. 1991). Once the repeat has been amplified beyond a critical size (about 200 copies), it becomes unstable and can reach different sizes in different tissues of the same patient. Sutherland et al. (1991) have pointed out that such an unstable pre-mutation could produce different phenotypic effects and could account for intrafamilial clinical variability.

Indeed, striking clinical variability is one of the hallmarks of the Happle syndrome. Moreover, in the three families, we observed a stepwise increase in the severity of disease expression from the grandmothers to the granddaughters. This phenomenon is reminiscent of anticipation, and could also be explained by the concept of a heritable unstable pre-mutation.

The proposed model of an unstable pre-mutation may also necessitate a re-examination of the formal genetics of the Bpa mouse. Philips et al. (1973) assumed that the gene was *always* lethal in males, but they did not follow the offspring of surviving males. The data obtained in single-factor segregations were not so clear-cut. In total, more than 3000 offspring were analysed. Crossing of Bpa+ females with normal male mice gave a significant over-representation of normal females and an unexpectedly high number of surviving males. The sex ratio (M:F) was 1:1.7. In view of the high number of animals analysed, the deviation from the expected sex ratio of 1:2 is striking and could in part be attributable to normal-appearing male mice that received a mutant, but silenced, gene.

Conclusion

The apparent exclusion of the X-linked gene for the Happle syndrome from the X chromosome is puzzling. Mutations interfering with X-inactivation could account for this paradox, but this leads to the assumption of several loci on the X chromosome being involved. Metabolic interference could mimic X-linked dominant transmission but, according to this model, *all* daughters of non-penetrant males should be affected. Our data can best be explained if one assumes that some males can receive the mutant gene without showing clinical symptoms. Hence, we propose an unstable pre-mutation that can become silent in "normal" males. Such an unstable pre-mutation is compatible with the unexpected sex ratio (M:F) of 1.2:1 and can explain the striking clinical variability of the syndrome and the stepwise increase in disease expression, observed in successive generations. Because of the limited number of available families, mapping of the locus for the Happle syndrome will have to rely on the candidate gene approach.

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