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Review

X-chromosomal markers: Past, present and future

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Abstract

Experience gained in clinical genetics led to the fundamental idea of using X-chromosomal markers in a wide range of forensic applications. To date more than 30 STRs have been established as forensic markers. Joint typing of very tightly linked STRs yields stable haplotypes, and can be used for establishing the relationship between distant relatives, such as aunt–niece pairs and cousins. For such applications the new ChrX typing kit Argus X-8® which is commercially available now is a powerful tool. This paper is aimed at presenting a brief survey of historical developments and discussing present and future aspects of forensic X-chomosomal testing.
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Keywords: X-chromosomal STRs; Kinship testing; Trace analysis; Linkage; Haplotyping

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1. History of forensic utilisation of the X chromosome

Regarding X-chromosomal markers the first significant achievement was done when the Xga blood group was detected by the team of Race and Sanger. A review referring to this was given by Tippett and Ellis [1]. During the era of PCR technology, many short tandem repeats (STRs) were established. Some of them are located on the X chromosome (ChrX). The fundamental idea of making wide use of X-chromosomal markers in forensic practice developed from the experiences made during the second half of the last century in the field of the clinical genetics. There are a great many well-known diseases and traits, such as haemophilia, Duchenne muscular dystrophy, G6PD deficiency, red–green blindness, etc., following an X-chromosomal mode of inheritance. If a male patient is fertile, all his daughters possess the defective paternal X chromosome and carry it to half of the next generation. Half of all such daughters again are gene carriers and also half of their sons inherit the defective allele and exhibit the trait due to the hemizygote state of their ChrX. Furthermore, if a male exhibits two or more ChrX-linked traits, it is obvious that alleles of all relevant loci are unified to one haplotype. This explains why ChrX-linkage analysis is fairly easy. Knowledge of such simple contexts is valuable not only for clinical genetics, but also for kinship testing.

The first two ChrX microsatellites, which played a significant role, were HPRTB [3,4] and ARA [4,5]. Kishida

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et al. [6] and Desmarais et al. [5], almost at the same time, developed formulas for calculating useful parameters, such as the mean exclusion chance (MEC), etc., which consider the unique inheritance of ChrX. Thirty years earlier Krüger et al. [7] had developed the MEC for autosomal markers. The formulas are reviewed earlier [8].

One of the challenges in kinship testing is to establish techniques, which can bridge large pedigree gaps. From observations in clinical genetics, we know that persons, who share a very rare genetic feature, can be combined in a common pedigree. The approach of substituting single STRs by haplotypes consisting of clustered STRs can also provide highly indicative tools, and can be systematically applied to kinship testing. This paper is aimed at demonstrating the potentials of ChrX markers in solving forensic cases.

2. Special features of the X chromosome

The gonosomes X and Y (ChrY) are unique and differ in several aspects from the autosomes (AS). In the cells of human males not affected by chromosomal aberrations, gonosomes do not normally occur in pairs but comprise one X and one Y chromosome. Hence, most of the ChrX and ChrY regions are hemizygous in males. In females, ChrX is present as a homologous pair, and resembles autosomes in this respect. However, even individuals with more than one ChrX possess only one active ChrX per cell. Additional copies are inactivated according to the Lyon-hypothesis [9], explaining why ChrX monosomies, trisomies and polysomies are compatible with life. For parental generations such gonosomal irregularities can usually be excluded since they would be associated with infertility. Unexpected and undetected aberrant gonosomal karyotypes in an offspring may, however, occur and affect the accuracy of kinship testing by means of ChrX markers. Gonosomal genotype X0, for example, which is associated with the Ullrich–Turner syndrome, occurs at an incidence of one in 2500 female life-births [10]. Both complete and partial monosomies have been observed. Another aberrant female karyotype is XY, which occurs in association with androgen insensitivity and consequent testicular feminisation. Testicular feminisation causes genetic males to exhibit an unobtrusive female phenotype [11] although the underlying condition can easily be confirmed by an amelogenin test. The posterior probability of full or partial ChrX monosomy, or an XY female, increases when several closely linked ChrX markers appear to be homozygous. In the way they perturb kinship testing, karyotypes XO and female XY are formally equivalent to autosomal uniparental disomy [12,13]. Similar to AS markers, paternity exclusion based on ChrX marker homozygosity requires independent analytical verification.

A gonosomale aberrant male karyotype with XXY (or XXXY, etc.) develops the Klinefelter syndrome and shows a prevalence of about 1:500 males [14]. The Klinefelter syndrome can be detected in kinship testing when ChrX markers reveal heterocygocity. If gonosomal aberrations or testicular feminisation are detected, ChrX typing is no longer a valid means of kinship testing.

3. ChrX short tandem repeats

STRs located on autosomes had been used in the forensics science long before the Y chromosome [15,16] and ChrX STR markers were applied. Although the existence of ChrX STRs, i.e. HPRTB [3,4], ARA [4,5] and DXS981 [17] were reported rather early, the intention to use such markers as a tool for special applications developed late. Table 1 and Fig. 1 show most of the forensic ChrX repeat markers known to date. The majority of them do not exhibit any peculiarities in terms of their handling and some of them are routinely used by our own group and many others. Notwithstanding the fact that HumARA is one of the forensically best established STR markers [5] our group has announced recently that we for ethical reasons do not longer consider HumARA a suitable forensic marker [18]. This CAG repeat codes for a polyglycine tract and discloses bulbar muscular atrophy (SBMA) [19] and numerous health risks.

In general, mutation rates of ChrX STRs do not seem to differ from microsatellites of the other chromosomes. STRs with long homogenous repeat structures, such as DXS10011 and DXS8377, are prone to instability. The latter show mutation rates of $\mu = 0.037$ [20] and $\mu = 0.025$ (unpublished data), respectively. For example: the pedigree shown in Fig. 2 consists of 12 members and involves 14 meioses. If we attempted to use such STRs, there would be a high probability for the total of mutations to cumulate to an unacceptable level. Therefore, we should avoid highly mutable STRs when typing large pedigrees.

4. ChrX markers in trace analysis

With a few exceptions, ChrX markers in stain analyses are neither more or less useful than AS markers. The power of discrimination (PD) value of ChrX markers varies depending on the sex. If female traces are to be assigned to female individuals, ChrX markers yield the same results as AS. For matching male traces to male suspects, the PD value of ChrX markers is generally lower than that of AS markers. This is due to the fact that for male ChrX analysis only one allele per STR is used. In a mixed female/male stain, the chance of having all male alleles included in the female component is higher for ChrX than for AS markers. Therefore, it is not advisable to use ChrX markers for testing male traces in a female background. In order to identify female traces in male contamination, however, ChrX markers are more efficient than AS markers since the female alleles can only be completely included in the male component if the female coincidentally happens to be homozygous at all loci. Demonstration of female skin debris under male finger nails or vaginal cell at a penis, etc. may be an issue for application of an X-chromosomal STR amplification kit.

Table 1
Characteristics of ChrX STRs in forensic use

Locus and repeat length (bp)	Localisation (distance from Xp-tel)		Het	MEC	MEC	Reference
	bp	cM		(Trio case)	(Duo case)	
DXS6807 (4)	4,603,118	4.39	0.608	0.709	0.471	[34]
DXS9895 (4)	7,236,843	8.76	0.694	0.704	0.554	[35]
DXS10135 (4)	9,116,057	No report	0.9251	0.9159	0.8499	Szibor, up.
DXS8378 (4)	9,179,962	No report	0.658	0.714	0.532	[21,35]
DXS9902 (4)	15,083,273	22.04	0.636	0.743	0.490	[35]
DXS10076 (4)	48,065,558	No report	0.784	0.751	0.620	[27]
DXS10077 (3)	48,073,264	No report	0.518	0.468	0.322	[27]
DXS10078 (4)	48,078,442	No report	0.825	0.799	0.681	[27]
DXS7132 (4)	64,438,357	83.30	0.687	0.883	0.557	[35]
DXS10074 (4)	66,760,138	No report	0.833	0.811	0.7059	[23]
DXS981 (4)	67,980,377	No report	0.8426	0.8171	0.7055	[30]
DXS6800 (4)	7,486,555	93.17	0.690	0.694	0.548	[35]
DXS9898 (4)	87,602,564	No report	0.731	0.745	0.596	[36]
DXS6801 (4)	92,317,317	99.73	0.6472	0.582	0.4535	[21,37]
DXS6809 (4)	94,744,298	102.28	0.808	0.815	0.7033	[38]
DXS6789 (4)	95,255,559	103.56	0.746	0.702	0.5677	[21,39]
DXS7424 (3)	100,424,961	No report	0.764	0.836	0.639	[21,25]
DXS101 (3)	101,219,161	No report	0.78	0.885	0.794	[40]
DXS6797 (4)	107,287,210	112.89	0.754	0.712	0.575	[41]
DXS7133 (4)	108,847,688	No report	0.575	0.658	0.422	[21,35]
GATA172D05 (4)	112,980,738	116.17	0.775	0.804	0.654	[35]
HPRTB (4)	133,341,004	No report	0.737	0.919	0.610	[42]
DXS10101 (4)	133,379,963	No report	0.9015	0.8933	0.8146	[24]
DXS9908 (4)	142,666,846	165.11	0.760	0.720	0.586	[43]
DXS8377 (3)	149,237,039	No report	0.916	0.922	0.855	[21,35]
DXS10134 (4)	149,320,642	No report	0.859	0.842	0.741	Edelmann, up.
DXS7423 (4)	149,381,471	No report	0.688	0.734	0.548	[44]
DXS10011 (4)	150,858,594	No report	0.964	0.944	0.827	[20]

Physical and genetic mapping data obtained from Human Genome Browser (http://www.genome.ucsc.edu/cgi-bin/hgGateway) and from the Marshfield database (http://www.marshfieldclinic.org/), respectively. Expected heterozygosity (Het) mean exclusion chance (MEC) and power of discrimination (PD) were calculated as reviewed earlier [8]. All calculations are based on the allele distribution of the European population referenced here. Up.: unpublished.

5. ChrX markers in kinship testing

Gonosomal markers are especially efficient for solving deficiency cases. A specific demand for kinship tests in which only remote relatives are available for testing can be expected to arise, particularly from the need to rejoin families in the context of war and world-wide migration. Furthermore, skeleton and corpse identification of the victims of wars and mass disasters require a combination of sophisticated methods. In this context mention should be made that in some instances ChrX markers are more efficient than AS markers. This fact is reflected by the formulas for calculating the mean exclusion chance (MEC) for AS markers and ChrX markers. If markers have a comparable PIC, the MEC for ChrX markers is higher than for AS markers [5–7].

6. Kinship testing in trios and duos

Paternity cases involving the common trio constellation of mother, offspring and alleged father can usually be solved with AS STRs alone, and do not seem to require any additional or alternative markers. If a father/son relationship is to be tested, ChrX markers are not useful at all. However, if a father/daughter parentage is in question, it may be worthwhile using also ChrX markers for testing. This is especially the case if difficult-to-analyse template materials are involved, such as DNA from exhumed skeletons, etc. For testing mother–daughter relationships, ChrX markers are similar to AS markers and do not provide any specific advantage. Testing mother–son kinship, however, is more efficiently performed using ChrX markers. The exclusion chance in such cases is identical to that of ChrX STRs in father/daughter tests. The option for ChrX marker typing utilising short amplicons [21] should be considered, especially if skeletal human remains or other difficult samples are to be analysed. In such instances, sufficient statistical power has to come from a small number of low size STRs. Due to their higher MEC, ChrX markers may be superior to autosomal markers in such contexts.

7. Deficiency paternity cases

Deficiency paternity testing and other complex kinship testing are the main fields of ChrX marker application. ChrX markers typing can assign pedigree members over long distances with respect to X-chromosomal tracks. However, they fail if X-chromosomal lines are interrupted by a father–son relationship. If female individuals have the same father, they always share the same paternal ChrX. An investigation of ChrX markers of two sisters or stepsisters can thus exclude paternity, even if DNA of the parents is not available. AS markers cannot

provide such qualitative information. A positive proof of paternity is also possible with lacking maternal genotype information, but is generally less reliable. This is due to the fact that sisters usually inherit partially matching haplotypes from their mother. The co-inheritance of two identical maternal ChrX without recombination is possible, but rare. If ChrX markers are investigated in a deficiency case, the mother of the unavailable putative father (i.e. the putative grandmother) is the key figure. Strictly speaking, instances in which she is available for typing do not represent deficiency cases. All ChrX alleles of the putative father can be determined by investigating her, and the MEC can be calculated using the relevant formula for AS markers [7]. The ChrX marker genotype of the putative grandmother can also be reconstructed, to some extent, from her children. If she has several daughters, it is possible to determine the parental origin of most of their ChrX alleles and thus the grandmaternal genotype. If brothers of the putative father are available, the situation is even more informative. Then, the grandmaternal genotype must be heterozygous for all ChrX loci for which brothers of the putative father carry different alleles. If they carry identical alleles, the constellation is only semi-informative: the mother can be either homozygous or heterozygous at the corresponding locus. If closely linked loci have already been clearly identified at being either homozygous or heterozygous, the probability of homozygosity at the original locus can be assessed by haplotyping. This

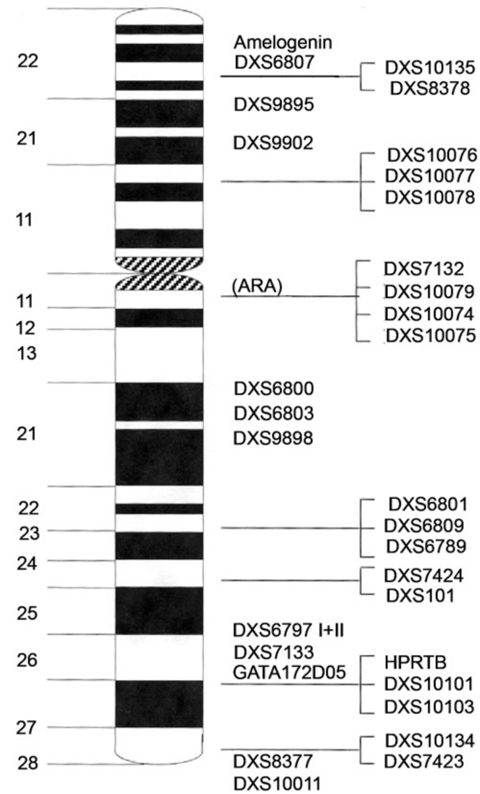

Fig. 1. Distribution of 30 forensic STR markers at the X chromosome.

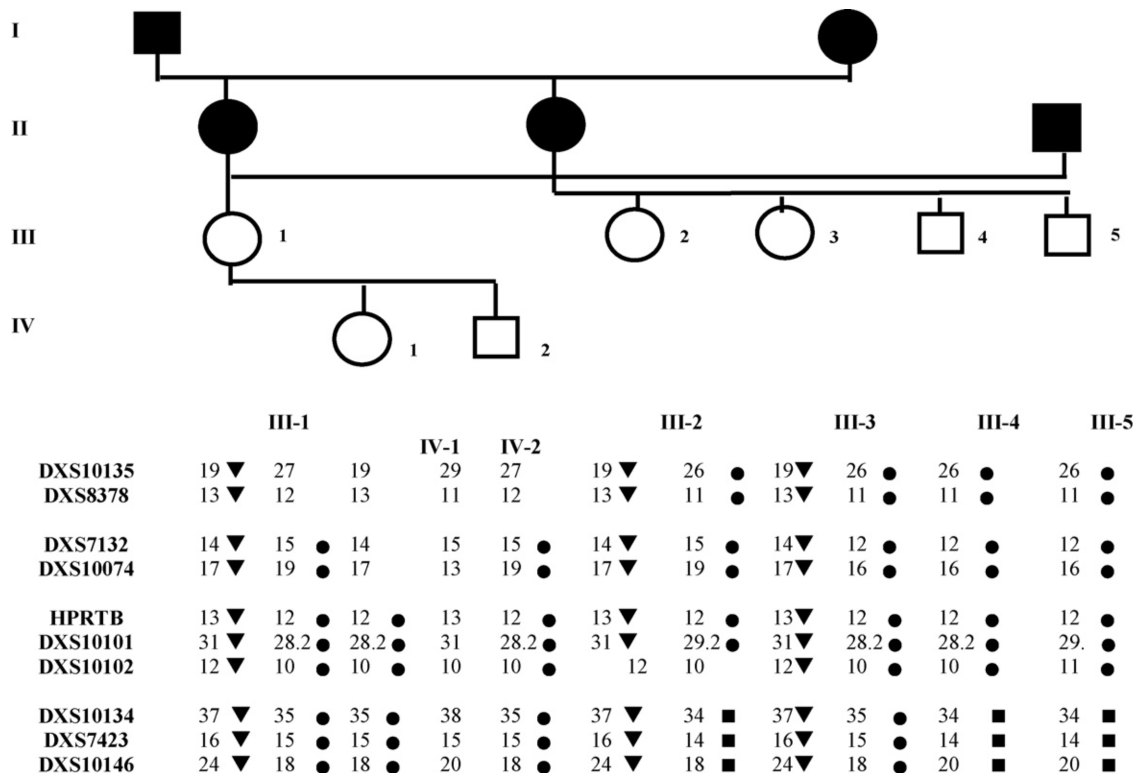

Fig. 2. The pedigree depicts kinship according to hypothesis 2. Black triangles indicate the ChrX haplotype which was donated by the common father to all daughters. Black circles indicate corresponding haplotypes on the second ChrX which are of maternal origin. Black squares are inserted to facilitate recognition of allele orientation as haplotypes. The congruence of haplotypes on both chromosomes demonstrates paternal and maternal kinship for the females in generation III ($p = 99.9999$).

applies to STR clusters, which can be typed using the Argus X-8® Kit.

8. Incest cases and paternity cases involving blood-relatives

In paternity cases involving close blood-relatives as putative fathers, the exclusion power of STRs is considerably reduced and ChrX STRs may be superior to AS markers. For example, if two alleged fathers are father and son, they would not share any X-chromosomal alleles identical by descent (ibd), and hence ChrX markers would be more efficient than AS markers. Brothers, in contrast, share a given maternal ChrX allele with a probability of 0.5, which corresponds to the probability of exactly one allele shared ibd at an AS locus.

The following short casuistic is aimed at demonstrating the power of ChrX markers in solving cases of an alleged incest. In this case, we carried out a prenatal diagnosis [22]. A young lady was pregnant and paternity was uncertain. Hypothesis 1 was that the foetus was fathered by the girl's boyfriend. The alternative hypothesis was an incest carried out with her own father. For some reasons, we could not get samples from the fathers in question. Hence, we solved the question as a deficiency case. Naturally, the pregnant women carries the complete ChrX haplotype of her father. If the same male had fathered the embryo, no additional alleles would occur in the foetus. The result was, that 12 of the 16 ChrX STR investigated revealed an allele, which could not be detected in the women's genotype. Therefore, the results at 12 loci gave reason to reject hypothesis 2. Thus, the child was carried to term.

9. ChrX haplotyping

If markers are linked, they do not segregate independently. For practical reasons we divided the ChrX into the linkage groups 1–4 located at Xp22.2, Xq12, Xq26 and Xq28, which yield independent genotype information. Under practical aspects four unlinked STRs, i.e. DXS8378, DXS7132, HPRTB and DXS7423, were chosen and considered the cores of these four linkage groups. This set of unlinked STRs (plus amelogenin) could be typed using the commercial available forensic ChrX typing kit Mentype® Argus X-UL. In a second stage, the kit was extended by further STRs. Mentype® Argus 8-X is a valuable tool for ChrX haplotyping. It presents the four clusters DXS10135–DXS8378; DXS7132–DXS10074 [23]; HPRTB-DXS10101 [24]; DXS7423–DXS10134 and provides haplotypes for forensic practise. Each of the four STR clusters spans less than 0.5 cM, and therefore represents a stable haplotype. Consequently, the probability of meiotic recombination within each of the four clusters is less than 0.5%. However, confirmation of this assumption as established on the base of their physical localisation, requires observation of the allele segregation in several hundreds of siblinghoods. Our suggestion is to extend the STR clusters to four STR triplets and create an extremely powerful 12 ChrX marker kit. Alternatively, other STR cluster haplotypes, such as DXS101–DXS7424 [25], DXS6801–DXS6809–DXS6789 [26], DXS10076–DXS10077–DXS10078 [27], may be chosen from Table 1 and Fig. 1. Amplification can be carried out by using home-made multiplex mixtures.

10. Linkage and linkage disequilibrium

Generally, alleles of linked loci form haplotypes that recombine during meioses at a frequency corresponding to the inter-marker genetic distance. For ChrX markers, this phenomenon is limited to female meiosis. In kinship testing, haplotypes of closely linked STRs must therefore be analysed as a whole, rather than through their constituent alleles. Linkage disequilibrium (LD), which refers to this ''non-random'' association of alleles at different loci, measures the deviation of population-specific haplotype frequencies from the product of the corresponding allele frequencies. For markers with strong LD, haplotype frequencies cannot be inferred from allele frequencies alone, but have to be estimated directly from population data instead. Due to their higher mutation rate, STRs tend to show less LD than SNPs. However, the LD can still occur between closely linked STRs, and therefore has to be assessed prior to their practical application. In some ChrX regions, we analysed inter-marker LD of STRs by genotyping male DNA samples. A significant LD was observed for some very tightly linked marker cluster, namely DXS101 and DXS7424 [25], DXS6801, DXS6809 and DXS6789 [26] DXS10076, DXS10077 and DXS10078 [27] and DXS10079, DXS10074 and DXS10075 [23]. For example, testing the latter cluster in an east German population has the potential to provide 2548 different haplotypes. However, a sample of 781 unrelated men revealed 172 haplotypes. Due to a considerable LD the number of observed haplotypes is smaller than expected. Nevertheless, 72% of all observed haplotypes showed frequencies <0.02. Hence, these STRs and the other STR clusters mentioned are of a high evidentiary value for kinship testing despite the existence of an LD.

Considering ChrX markers, differences of allele distribution are marginal if closely related populations are compared [28]. However, if investigated in a worldwide context, they may show noteworthy differences in their allele frequency [29,30].

Linkage disequilibrium (LD), or the non-random association of alleles, is not completely understood in the human genome. However, studies of the LD between microsatellites and, more recently, between SNPs [31] have provided new insights into the origin and history of human populations. For example, LD levels, which are much higher in non-African than in African populations [31], may reflect a population bottleneck that is associated with the origin of non-African populations [32]. Especially, the LD between ChrX markers can be highly efficient in revealing ethnic differences [33].

11. Case report

The complex kinship case depicted in Fig. 2 may illustrate the power of ChrX haplotyping in kinship testing: we were

asked to clarify whether, or not, Linda, Nora and Eva have the same father. Hypothesis 1 is that Linda and Nora and Eva are cousins, and they have different fathers. The alternative hypothesis is that they all have the same father. Usually, the question of the father can be easily answered: if all sisters in question share a common X chromosome, they have the same father. However, in this case, a common X chromosome could be caused by maternal transfer and be misinterpreted as a common paternal X chromosome. Therefore, a common father can only be established if the cousins share highly indicative markers at both X chromosomes. In this specific case, sharing a common complete ChrX and spots of very rare haplotypes on the second chromosome produced evidence for paternal and maternal kinship ($p > 0.99999$). This case was solved by using the Argus X-8® Kit, which was extended by the addition of two further STRs DXS10102 and DXS10146. We hope that in future biotechnology companies will offer DNA ChrX identification kits, with four triplex STR clusters located at Xp22.2, Xq12, Xq26 and Xq28.

References

[1] P. Tippett, N.A. Ellis, The Xg blood group system: a review, Transfus. Med. Rev. 12 (4) (1998) 233–257.

[3] C.M. Hearne, J.A. Todd, Tetranucleotide repeat polymorphism at the HPRT locus, Nucleic Acids Res. 19 (19) (1991) 5450.

[4] A. Edwards, H.A. Hammond, L. Jin, C.T. Caskey, R. Chakraborty, Genetic variation at five trimeric and tetrameric tandem repeat loci in four human population groups, Genomics 12 (2) (1992) 241–253.

[5] D. Desmarais, Y. Zhong, R. Chakraborty, C. Perreault, L. Busque, Development of a highly polymorphic STR marker for identity testing purposes at the human androgen receptor gene (HUMARA), J. Forensic Sci. 43 (5) (1998) 1046–1049.

[6] T. Kishida, W. Wang, M. Fukuda, Y. Tamaki, Duplex PCR of the Y-27H39 and HPRT loci with reference to Japanese population data on the HPRT locus, Nippon Hoigaku Zasshi 51 (2) (1997) 67–69.

[7] J. Krüger, W. Fuhrmann, K.H. Lichte, C. Steffens, On the utilization of erythrocyte acid phosphatase polymorphism in paternity evaluation, Dtsch. Z. Gesamte Gerichtl. Med. 64 (2) (1968) 127–146.

[8] R. Szibor, M. Krawczak, S. Hering, J. Edelmann, E. Kuhlisch, D. Krause, Use of X-linked markers for forensic purposes, Int. J. Legal Med. 117 (2) (2003) 67–74.

[9] M.F. Lyon, Gene action in the X-chromosome of the mouse (*Mus musculus* L.), Nature 190 (1961) 372–373.

[10] M. Clement-Jones, S. Schiller, E. Rao, R.J. Blaschke, A. Zuniga, R. Zeller, S.C. Robson, G. Binder, I. Glass, T. Strachan, S. Lindsay, G.A. Rappold, The short stature homeobox gene SHOX is involved in skeletal abnormalities in Turner syndrome, Hum. Mol. Genet. 9 (5) (2000) 695–702.

[11] P.F. Wieacker, I. Knoke, S. Jakubiczka, Clinical and molecular aspects of androgen receptor defects, Exp. Clin. Endocrinol. Diabetes 106 (6) (1998) 446–453.

[12] G. Bein, B. Driller, M. Schurmann, P.M. Schneider, H. Kirchner, Pseudo-exclusion from paternity due to maternal uniparental disomy 16, Int. J. Legal Med. 111 (6) (1998) 328–330.

[13] R. Wegener, V. Weirich, E.M. Dauber, W.R. Mayr, Mother–child exclusion due to paternal uniparental disomy 6, Int. J. Legal Med. 120 (2006) 282–285.

[14] A. Bojesen, S. Juul, C.H. Gravholt, Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study, J. Clin. Endocrinol. Metab. 88 (2) (2003) 622–626.

[15] M. Kayser, A. Caglia, D. Corach, N. Fretwell, C. Gehrig, G. Graziosi, F. Heidorn, S. Herrmann, B. Herzog, M. Hidding, K. Honda, M. Jobling, M. Krawczak, K. Leim, S. Meuser, E. Meyer, W. Oesterreich, A. Pandya, W. Parson, G. Penacino, A. Perez-Lezaun, A. Piccinini, M. Prinz, C. Schmitt, L. Roewer, et al., Evaluation of Y-chromosomal STRs: a multicenter study, Int. J. Legal Med. 110 (3) (1997) 125–133, 141–129.

[16] L. Roewer, J. Arnemann, N.K. Spurr, K.H. Grzeschik, J.T. Epplen, Simple repeat sequences on the human Y chromosome are equally polymorphic as their autosomal counterparts, Hum. Genet. 89 (4) (1992) 389–394.

[17] M.M. Mahtani, H.F. Willard, A polymorphic X-linked tetranucleotide repeat locus displaying a high rate of new mutation: implications for mechanisms of mutation at short tandem repeat loci, Hum. Mol. Genet. 2 (4) (1993) 431–437.

[18] R. Szibor, S. Hering, J. Edelmann, The HumARA genotype is linked to spinal and bulbar muscular dystrophy and some further disease risks and should no longer be used as a DNA marker for forensic purposes, Int. J. Legal Med. 119 (3) (2005) 179–180.

[19] A.R. La Spada, E.M. Wilson, D.B. Lubahn, A.E. Harding, K.H. Fischbeck, Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy, Nature 352 (6330) (1991) 77–79.

[20] S. Hering, N. Brundirs, E. Kuhlisch, J. Edelmann, I. Plate, M. Benecke, P.H. Van, M. Michael, R. Szibor, DXS10011: studies on structure, allele distribution in three populations and genetic linkage to further q-telomeric chromosome X markers, Int. J. Legal Med. 118 (6) (2004) 313–319.

[21] H. Asamura, H. Sakai, K. Kobayashi, M. Ota, H. Fukushima, MiniX-STR multiplex system population study in Japan and application to degraded DNA analysis, Int. J. Legal Med. (2006) 1–8.

[22] J. Schmidtke, W. Kuhnau, D. Wand, J. Edelmann, R. Szibor, M. Krawczak, Prenatal exclusion without involving the putative fathers of an incestuous father–daughter parenthood, Prenat. Diagn. 24 (8) (2004) 662–664.

[23] S. Hering, C. Augustin, J. Edelmann, M. Heidel, J. Dressler, H. Rodig, E. Kuhlisch, R. Szibor, DXS10079, DXS10074 and DXS10075 are STRs located within a 280-kb region of Xq12 and provide stable haplotypes useful for complex kinship cases, Int. J. Legal Med. (2005) 1–9.

[24] H. Rodig, F. Kloep, L. Weißbach, C. Augustin, J. Edelmann, S. Hering, R. Szibor, F. Götz, W. Brabetz, Evaluation of 7 X-chromosomal Short Tandem Repeat loci located within the Xq26 region, in press.

[25] J. Edelmann, S. Hering, E. Kuhlisch, R. Szibor, Validation of the STR DXS7424 and the linkage situation on the X-chromosome, Forensic Sci. Int. 125 (2002) 217–222.

[26] R. Szibor, S. Hering, E. Kuhlisch, I. Plate, S. Demberger, M. Krawczak, J. Edelmann, Haplotyping of STR cluster DXS6801–DXS6809–DXS6789 on Xq21 provides a powerful tool for kinship testing, Int. J. Legal Med. 119 (6) (2005) 363–369.

[27] C. Augustin, R. Cichy, S. Hering, J. Edelmann, E. Kuhlisch, R. Szibor, Forensic evaluation of three closely linked STR markers in a 13kb region at Xp11.23, Int. Congress Ser. 1239 (2006) 311–314.

[28] M.T. Zarrabeitia, A. Alonso, J. Martin, M.A. Gonzalez-Gay, J.C. Martin-Escudero, M.M. de Pancorbo, P. Sanz, F. Ruiz-Cabello, J.A. Riancho, Study of six X-linked tetranucleotide microsatellites: population data from five Spanish regions, Int. J. Legal Med. (2005) 1–4.

[29] S.H. Shin, J.S. Yu, S.W. Park, G.S. Min, K.W. Chung, Genetic analysis of 18 X-linked short tandem repeat markers in Korean population, Forensic Sci. Int. 147 (1) (2005) 35–41.

[30] K.A. Tabbada, M.C. De Ungria, L.P. Faustino, D. Athanasiadou, B. Stradmann-Bellinghausen, P.M. Schneider, Development of a pentaplex X-chromosomal short tandem repeat typing system and population genetic studies, Forensic Sci. Int. 154 (2/3) (2005) 173–180.

[31] D.E. Reich, M. Cargill, S. Bolk, J. Ireland, P.C. Sabeti, D.J. Richter, T. Lavery, R. Kouyoumjian, S.F. Farhadian, R. Ward, E.S. Lander, Linkage disequilibrium in the human genome, Nature 411 (6834) (2001) 199–204.

[32] L.B. Jorde, M. Bamshad, A.R. Rogers, Using mitochondrial and nuclear DNA markers to reconstruct human evolution, Bioessays 20 (2) (1998) 126–136.

[33] H. Kaessmann, S. Zollner, A.C. Gustafsson, V. Wiebe, M. Laan, J. Lundeberg, M. Uhlen, S. Paabo, Extensive linkage disequilibrium in small human populations in Eurasia, Am. J. Hum. Genet. 70 (3) (2002) 673–685.

[34] J. Edelmann, R. Szibor, Validation of the HumDXS6807 short tandem repeat polymorphism for forensic application, Electrophoresis 20 (14) (1999) 2844–2846.

[35] J. Edelmann, S. Hering, M. Michael, R. Lessig, D. Deichsel, G. Meier-Sundhausen, L. Roewer, I. Plate, R. Szibor, 16 X-chromosome STR loci frequency data from a German population, Forensic Sci. Int. 124 (2/3) (2001) 215–218.

[36] S. Hering, R. Szibor, Development of the X-linked tetrameric microsatellite marker DXS9898 for forensic purposes, J. Forensic Sci. 45 (4) (2000) 929–931.

[37] J. Edelmann, R. Szibor, Validation of the X-linked STR DXS6801, Forensic Sci. Int. 148 (2005) 219–220.

[38] J. Edelmann, D. Deichsel, I. Plate, M. Kaser, R. Szibor, Validation of the X-chromosomal STR DXS6809, Int. J. Legal Med. 117 (4) (2003) 241–244.

[39] S. Hering, E. Kuhlisch, R. Szibor, Development of the X-linked tetrameric microsatellite marker HumDXS6789 for forensic purposes, Forensic Sci. Int. 119 (1) (2001) 42–46.

[40] J. Edelmann, R. Szibor, DXS101: a highly polymorphic X-linked STR, Int. J. Legal Med. 114 (4/5) (2001) 301–304.

[41] M. Poetsch, A. Repenning, E. Lignitz, E. Kuhlisch, R. Szibor, DXS6797 contains two STRs which can be easily haplotyped in both sexes, Int. J. Legal Med. 120 (2) (2006) 61–66.

[42] M. Poetsch, H. Petersmann, A. Repenning, E. Lignitz, Development of two pentaplex systems with X-chromosomal STR loci and their allele frequencies in a northeast German population, Forensic Sci. Int. 155 (1) (2005) 71–76.

[43] J. Edelmann, R. Lessig, A. Willenberg, R. Wildgrube, S. Hering, R. Szibor, Forensic validation of the X-chromosomal STR-markers GATA165B12, GATA164A09, DXS9908 and DXS7127 in German population, Int. Congress Ser. 1239 (2006) 298–300.

[44] R. Szibor, J. Edelmann, M.T. Zarrabeitia, J.A. Riancho, Sequence structure and population data of the X-linked markers DXS7423 and DXS8377—clarification of conflicting statements published by two working groups, Forensic Sci. Int. 134 (1) (2003) 72–73.