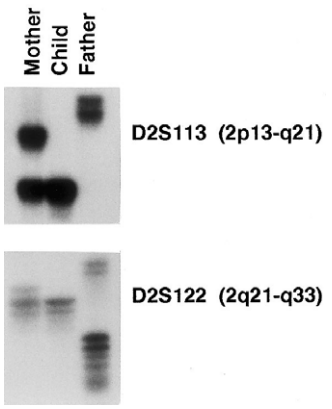


**Figure 2** Molecular results for two markers located on 2p (D2S113) and 2q (D2S122). The child shows the homozygous inheritance of a single maternal allele and failure to inherit a paternal allele.

normalities or unusual childhood illnesses, our patient and three previously reported patients with maternal disomy 2 had both severe IUGR with oligohydramnios or anhydramnios and postnatal growth retardation (Bernard et al. 1995; Harrison et al. 1995; Webb et al. 1996; present study), atypical bronchopulmonary dysplasia (Harrison et al. 1995; present study) or pulmonary hypoplasia (Bernard et al. 1995), hypospadias (current case; Bernard et al. 1995), and good motor and intellectual development (Harrison et al. 1995; Webb et al. 1996; present study). Our case also had preauricular ear pits, pectus carinatum, and fifth-finger clinodactyly. Of interest, perineal hypospadias has recently been reported in association with placental dysfunction and IUGR (Nesbitt et al. 1996). The possible causes for the phenotypic features associated with maternal disomy 2 include maternal imprinting effects of chromosome 2, unmasking of autosomal recessive disease due to homozygosity, undetected low-level fetal mosaicism for trisomy 2, or placental dysfunction secondary to trisomy-2 mosaicism or uniparental disomy (UPD). Two of the previously reported cases had demonstrated confined placental mosaicism for trisomy 2 (Bernard et al. 1995; Webb et al. 1996). The finding of no phenotypic abnormalities in the case reported by Bernasconi et al. (1996) is suggestive that the findings in these other four cases (Bernard et al. 1995; Harrison et al. 1995; Webb et al. 1996; present study) are not contributed by or influenced by the maternal UPD. However, the common features of IUGR, oligohydramnios/anhydramnios, pulmonary dysplasia/hypoplasia, and hypospadias suggest the possibility of an underlying etiology. Cases identified with placental mosaicism for trisomy 2 and/or maternal UPD 2 should be assessed prenatally for oligohydramnios and IUGR and postnatally for hypospadias, bronchopulmonary dysplasia, and growth retardation. Through identification and assessment of additional cases, the clinical impact of maternal disomy 2 and placental mosaicism for trisomy 2 can be delineated.

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## References

Bernard LE, Kalousek DK, Langlois S, Barrett IJ, Hansen WF, Aylsworth AS, Smith DI, et al (1995) Confined placental mosaicism for trisomy 2 with fetal maternal uniparental disomy of chromosome 2. Am J Hum Genet Suppl 57:A51

Bernasconi F, Karagüzel A, Celep F, Keser I, Lüleci G, Dutly F, Schinzel AA (1996) Normal phenotype with maternal isodisomy in a female with two isochromosomes: i(2p) and i(2q). Am J Hum Genet 59:1114–1118

Harrison K, Eisenger K, Anyane-Yeboa K, Brown S (1995) Maternal uniparental disomy of chromosome 2 in a baby with trisomy 2 mosaicism in amniotic fluid culture. Am J Med Genet 58:147–151

Nesbitt TH, Bodine CL, Kahler SG, Decker-Phillips M (1996) Abnormal genital development in XY neonates associated with severe placental insufficiency and chronic intrauterine growth restriction. Am J Hum Genet Suppl 59:A40

Webb AL, Sturgiss S, Warwicker P, Robson SC, Goodship JA, Wolstenholme J (1996) Maternal uniparental disomy for chromosome 2 in association with confined placental mosaicism for trisomy 2 and severe intrauterine growth retardation. Prenat Diagn 16:958–962

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## Evidence for a Possible Asian Origin of YAP$^+$ Y Chromosomes

*To the Editor:*

The nonrecombining portion of the human Y chromosome has become an important tool for evolutionary studies (Hammer and Zegura, 1996). Its exclusive paternal inheritance and lack of recombination with the X chromosome preserve a unique record of mutational events from previous generations. Mutational changes that have occurred a single time in human evolution can be used to construct bifurcating haplotype trees that

reflect the history of human Y-chromosome lineages. These haplotype trees, in turn, can be used to generate and test hypotheses about the origin and migration patterns of human populations.

One of the most useful and widely studied Y-linked polymorphisms is known as the "Y Alu polymorphic" (YAP) element (Hammer 1994). This polymorphism has resulted from the single and stable insertion of a member of the repetitive Alu family at a specific site (locus *DYS287*) on the long arm of the human Y chromosome during the past 29,000–334,000 years (Hammer 1995). The frequency of Y chromosomes carrying the YAP element ($YAP^+$) varies greatly among human populations from different geographic locations (Hammer 1994; Spurdle et al. 1994*a,* 1994*b;* Hammer and Horai 1995; Hammer et al. 1997; Karafet et al. 1997). For example, global surveys have shown that sub-Saharan African populations have the highest overall frequency of $YAP^+$ chromosomes, followed by populations from northern Africa, Asia, Europe, the New World, and Oceania. Therefore, it was proposed that the original YAP insertion occurred on an African Y chromosome and subsequently spread to other continents (Hammer 1994).

Hammer (1995) sequenced a 2.6-kb region encompassing the YAP insertion in 16 humans, found three polymorphic nucleotide sites (PN1, PN2, and PN3) plus a variable-length poly(A) tail associated with the YAP element, and constructed a haplotype tree composed of five YAP haplotypes. Haplotypes 1 and 2 were $YAP^-$ (lacking the YAP element, which is the ancestral state), whereas haplotypes 3-5 were $YAP^+$ (see fig. 1). YAP haplotype 3 represented the most ancestral $YAP^+$ lineage and was initially identified in a single African and two Japanese males. A global survey of these five haplotypes in 1,500 individuals revealed both the presence of all five YAP haplotypes in sub-Saharan African populations and subsets of these five haplotypes in non-African populations (Hammer et al. 1997). For instance, YAP haplotypes 1 and 4 were present in European populations, and haplotypes 1 and 3 were present in Asian populations.

Similar patterns of variation at non–Y chromosome loci have been interpreted to support a recent African origin of contemporary human genetic lineages (Cann et al. 1987; Armour et al. 1996; Tishkoff et al. 1996); however, Hammer et al. (1997) have raised the possibility that YAP haplotype 3 originated in Asia and migrated to Africa. This hypothesis is supported by the finding of high frequencies of haplotype 3 in some Asian populations (i.e., ~50% in Tibet) and by the observation of higher levels of diversity (based on the number and frequency of alleles at the *DYS19* microsatellite locus) associated with Asian versus African haplotype 3 chromosomes. Because YAP haplotypes 4 and 5 evolved from haplotype 3 and account for the majority of Y chromosomes in Africa (table 1), this hypothesis implies a substantial Asian contribution to the African paternal gene pool (Hammer et al. 1997).

We now report additional evidence in support of the hypothesis of an Asian origin of $YAP^+$ chromosomes, based on the distribution of a G→A transition in the SRY region. Whitfield et al. (1995) sequenced 18.3 kb encompassing the SRY gene from five humans and found three polymorphic nucleotide sites. We examined the polymorphism at nucleotide site 4064 (referred to here as "$SRY_{4064}$") in a set of individuals already typed at the polymorphic sites in the YAP region (Hammer et al. 1997). We found complete associations both between the $SRY_{4064}$-G allele (the ancestral state) and YAP haplotypes 1 and 2 and between the $SRY_{4064}$-A allele and haplotypes 4 and 5. Haplotype 3 was found to be associated with both the $SRY_{4064}$-G allele and the $SRY_{4064}$-A allele, thus giving rise to two new haplotypes—3G and 3A, respectively (fig. 1). This pattern of association between $SRY_{4064}$ alleles and YAP haplotypes is consistent with a single occurrence of the G→A transition at $SRY_{4064}$ on a $YAP^+$ chromosome, before the occurrence of the PN2 C→T transition (fig. 1). A clear-cut geographic trend was apparent in the distribution of $YAP^+$/$SRY_{4064}$ chromosomes in the populations studied by Hammer et al. (1997). Remarkably, the ancestral $YAP^+$ lineage represented by haplotype 3G was present only in Asian populations, and the derived 3A haplotype was present only in African populations and in a single European individual (table 1). No population was found to be polymorphic for both the 3G haplotype and the 3A haplotype.

We present three alternative hypotheses to explain this pattern (table 2). In the first Asian-origin hypothesis, the YAP element inserted into an Asian Y chromosome carrying the ancestral $SRY_{4064}$-G allele. Subsequently, the $SRY_{4064}$-A allele arose on a $YAP^+$/$SRY_{4064}$-G (3G) chromosome in a small deme during migration to Africa. A variant of this hypothesis posits that the $SRY_{4064}$-A allele originated on a 3G chromosome in an Asian population, before migrating to Africa. The main difference between these two Asian-origin hypotheses is that in the "Asia/founder" hypothesis the 3G chromosome was lost in the migrating deme, whereas in the "Asia/Asia" hypothesis the 3A chromosome was lost in Asian populations (table 2). According to the African-origin hypothesis, the YAP element inserted into an African Y chromosome (Hammer 1994). The 3G haplotype then migrated to Asia and gave rise to the 3A haplotype in Africa. At some later time, perhaps because of increasing drift, the 3G haplotype was lost from African populations. Both the African-origin hypothesis and the two Asian-origin hypotheses require the same number of evolutionary events—namely, (1) the insertion of the YAP element, (2) a G→A transition at $SRY_{4064}$, (3) a migration event, and (4) a loss event (table 2).

**Table 1**

**Frequency of YAP/$SRY_{4064}$ Haplotypes in African, European, and Asian Populations**

| | Frequency of Haplotype (%) | | | | | |
|---|---|---|---|---|---|---|
| | $YAP^-$ | | $YAP^+$ | | | |
| Region (*N*) | 1G | 2G | 3G | 3A | 4A | 5A |
| Africa (502) | .338 | .045 | .000 | .061 | .127 | .429 |
| Asia (399) | .825 | .000 | .175 | .000 | .000 | .000 |
| Europe (384) | .862 | .000 | .000 | .003 | .135 | .000 |

Note.—For description of populations, see Hammer et al. (1997).

Circumstantial evidence lends some support to the Asian-origin hypotheses. For example, African populations are inferred to have had larger long-term effective sizes than either Asian or European populations (Relethford and Harpending 1994; Harding et al. 1997; Jorde et al. 1997). Also, theoretical results based on restricted-gene-flow models indicate that ancestral haplotypes are more geographically widespread than derived haplotypes created by more recent mutations (Templeton et al. 1995). However, in this case the derived 3A haplotype is found in many widespread populations from western, central, southern, and eastern Africa, where the ancestral 3G haplotype is absent (Hammer et al. 1997). Thus, the loss of 3G by drift in African populations is less likely than either the loss of 3G in a small founding population migrating to Africa or the loss of 3A in Asian populations. To test these hypotheses, we are searching for populations that are polymorphic for haplotypes 3G and 3A, to identify candidate source regions for the origin of the $SRY_{4064}$-A allele.

Additional support for the hypotheses involving an Asian origin of $YAP^+$ chromosomes could come from studies of new polymorphisms associated with either more-ancestral $YAP^+$ lineages (i.e., "b" in fig. 1) or $YAP^-$ lineages closely related to the lineage on which the YAP element was inserted (i.e., "a" in fig. 1). In this regard, the alphoid heteroduplex (αh) system described by Santos et al. (1995) may prove to be

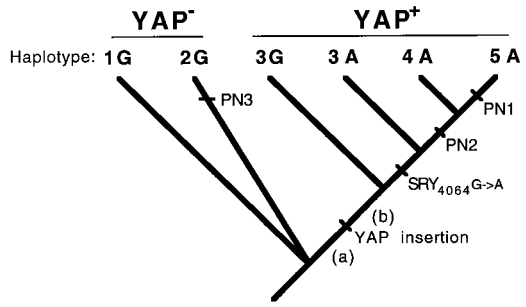


**Figure 1** Evolutionary tree of six human YAP/$SRY_{4064}$ combination haplotypes. The number of each combination haplotype refers to the YAP haplotype (1–5; Hammer et al. 1997), and the letter refers to the nucleotide state (G or A) at $SRY_{4064}$. Mutational changes are denoted by a cross-hatch through the branch of the tree. The ancestral state at each polymorphic site was determined by comparison with the chimpanzee sequence. Haplotype 1G has undergone no change from the ancestral human Y haplotype ($YAP^-$, PN1-C, PN2-C, PN3-G, and $SRY_{4064}$-G), whereas haplotype 2G has undergone a single G→A transition at PN3 (Hammer 1995). The remainder of the mutations have occurred on the lineage leading to $YAP^+$ haplotypes. The first event on this lineage was the insertion of the YAP element on a Y chromosome with a G at the $SRY_{4064}$ site. Subsequently, there were a G→A transition at $SRY_{4064}$, giving rise to haplotype 3A; a C→T transition at PN2, giving rise to haplotype 4A; and a C→T transition at PN1, giving rise to haplotype 5A. The lowercase letters "a" and "b" refer to hypothetical polymorphisms associated with ancestral $YAP^-$ and $YAP^+$ lineages, respectively.

**Table 2**

**Models for Origin of the $YAP^+$/$SRY_{4064}$ Haplotypes**

| Origin of YAP/$SRY_{4064}$-A | Evolutionary Events |
|---|---|
| Asia/founder population | 1. Insertion of YAP element (3G) in Asia<br>2. Origin of $SRY_{4064}$-A allele (3A) in a small deme<br>3. Migration of deme with 3A to Africa<br>4. Loss of 3G in migrating deme |
| Asia/Asia | 1. Insertion of YAP element (3G) in Asia<br>2. Origin of $SRY_{4064}$-A allele (3A) in Asia<br>3. Migration of 3A to Africa<br>4. Loss of 3A in Asia |
| Africa/Africa | 1. Insertion of YAP element (3G) in Africa<br>2. Origin of $SRY_{4064}$-A allele (3A) in Africa<br>3. Migration of 3G to Asia<br>4. Loss of 3G in Africa |

useful. Currently, 22 distinct heteroduplex patterns have been observed in human populations, each of which is referred to as an "αh" type (i.e., I–XXIII, number XXI is not designated: Santos et al. 1996). A global analysis of 240 Y chromosomes sampled from Africa, Europe, Asia, and South America indicated that only a single αh type (αhV) was shared between $YAP^+$ and $YAP^-$ chromosomes. Thus, the YAP insertion was postulated to have occurred on an αhV Y chromosome, and all other αh types associated with $YAP^+$ chromosomes were assumed to be derivatives of αhV (Santos et al. 1996). In the same global survey, several $YAP^+$/αhV chromosomes were identified in males from Africa, Mongolia, and the New World, whereas only two $YAP^-$/αhV chromosomes were found (Santos et al. 1996). One of the $YAP^-$/αhV chromosomes was also from the Mongolian population, the only population found to possess both $YAP^+$/αhV and $YAP^-$/αhV chromosomes (the other $YAP^-$/αhV chromosome was found in a cell line derived from a male of uncertain geographic origin). Interestingly, we have found several $YAP^+$ chromosomes in Mongolia (Karafet et al. 1997), and all of these are associated with the ancestral $SRY_{4064}$-G allele (data not shown).

We infer that Mongolian populations have both the ancestral $YAP^-$/$SRY_{4064}$-G/αhV haplotye and the ancestral $YAP^+$/$SRY_{4064}$-G/αhV haplotype, and we tentatively take this as additional evidence in support of the hypothesis of an Asian origin of $YAP^+$ chromosomes. We have begun to type the αh system in our global sample of chromosomes and now have confirmed the presence of the $YAP^+$/$SRY_{4064}$-G/αhV haplotype in another Asian population—Tibetans (M. Hammer and N. Bianchi, unpublished data). Continued global studies of the αh and $SRY_{4064}$ polymorphisms, in conjunction with study of both $YAP^+$ and $YAP^-$ chromosomes, should provide a sound framework for testing hypotheses about the geographic origin of the original YAP element–insertion event.

In sum, the ancestral states associated with polymorphisms that originated just before and after the YAP insertion into the Y-haplotype tree are currently found in Asian—and not in African—populations. The obvious implication, if this pattern continues as new systems are discovered, is that a major component of African Y-chromosome diversity had its roots in Asia. Similar patterns of variation at other loci are needed to support the hypothesis of an ancient migration of human populations from Asia to Africa. In this regard, it is interesting that recent studies of β-globin sequence variation indicate that modern human populations, including those from Africa, carry ancient globin haplotypes that also appear to have originated in Asia (Harding et al. 1997).

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## References

Armour JA, Anttinen T, May CA, Vega EE, Sajantila A, Kidd JR, Kidd KK, et al (1996) Minisatellite diversity supports a recent African origin for modern humans. Nat Genet 13: 154–160

Cann RL, Stoneking M, Wilson AC (1987) Mitochondrial DNA and human evolution. Nature 325:31–36

Hammer MF (1994) A recent insertion of an Alu element on the Y chromosome is a useful marker for human population studies. Mol Biol Evol 11:749–761

——— (1995) A recent common ancestry for human Y chromosomes. Nature 378:376–378

Hammer MF, Horai S (1995) Y chromosomal DNA variation and the peopling of Japan. Am J Hum Genet 56:951–962

Hammer MF, Spurdle AB, Karafet T, Bonner MR, Wood ET, Novelletto A, Malaspina P, et al (1997) The geographic distribution of human Y chromosome variation. Genetics 145:787–806

Hammer MF, Zegura SL (1996) The role of the Y chromosome in human evolutionary studies. Evol Anthropol 5:116–134

Harding RM, Fullerton SM, Griffiths RC, Bond J, Cox MJ, Schneider JA, Moulin DS, et al (1997) Archaic African *and* Asian lineages in the genetic ancestry of modern humans. Am J Hum Genet 60:772–789

Jorde LB, Rogers AR, Bamshad M, Watkins WS, Krakowiak P, Sung S, Kere J, et al (1997) Microsatellite diversity and the demographic history of modern humans. Proc Natl Acad Sci USA 94:3100–3103

Karafet T, Zegura SL, Vuturo-Brady J, Posukh O, Osipova L, Weibe V, Romero F, et al (1997) Y chromosome markers and trans-Bering Strait dispersals. Am J Phys Anthropol 102: 301–314

Relethford JH, Harpending HC (1994) Craniometric variation, genetic theory, and modern human origins. Am J Phys Anthropol 95:249–270

Santos FR, Bianchi NO, Pena SDJ (1996) Worldwide distribution of human Y-chromosome haplotypes. Genome Res 6: 601–611

Santos FR, Pena SDJ, Tyler-Smith C (1995) PCR haplotypes for the human Y chromosome based on alphoid satellite variants and heteroduplex analysis. Gene 165:191–198

Spurdle AB, Hammer MF, Jenkins T (1994*a*) The Y *Alu* polymorphism in southern African populations and its relation-

ship to other Y-specific polymorphisms. Am J Hum Genet 54:319–330

Spurdle AB, Woodfield DG, Hammer MF, Jenkins T (1994*b*) The genetic affinity of Polynesians: evidence from Y chromosome polymorphisms. Ann Hum Genet 258:251–263

Templeton AR, Routman E, Phillips CA (1995) Separating population structure from population history: a cladistic analysis of the geographical distribution of mitochondrial DNA haplotypes in the tiger salamander, *Ambystoma tigrinum*. Genetics 140:767–782

Tishkoff SA, Dietzsch E, Speed W, Pakstis AJ, Kidd JR, Cheung K, Bonne-Tamir B, et al (1996) Global patterns of linkage disequilibrium at the *CD4* locus and modern human origins. Science 271:1380–1387

Whitfield LS, Sulston JE, Goodfellow PN (1995) Sequence variation of the human Y chromosome. Nature 378:379–380

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0002-9297/97/6102-0030$02.00

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## Genetic Counseling Is Directive? Look Again

*To the Editor:*

Bernhardt (1997) reads the data of Michie et al. (1997) and concludes that nondirectiveness cannot be achieved. I reach the opposite conclusion. The difference in these two views depends on the definition that one accepts for directiveness and how one conceptualizes the relationship between directiveness and nondirectiveness. Communication marked by persuasive coercion is the core aspect of directiveness. The data of Michie et al. take on different meaning in the light of this definition.

First of all, despite the title of their study, the authors clearly state that their work "is an empirical investigation of directiveness" (Michie et al. 1997, p. 40). Thus, whatever inferences can be drawn about nondirectiveness will depend largely on how one conceptualizes the relationship between directiveness and nondirectiveness. If one assumes, as Ms. Bernhardt and many others seem to do, that directiveness and nondirectiveness are opposite sides of the same coin (it's either heads or tails) as opposed to, let us say, extremes of a more or less normal distribution of transactual possibilities in counseling sessions, one might come to very different conclusions about just what the Michie et al. study does or does not demonstrate.

Second, Michie et al. (1997, p. 42) define directiveness as "directions or advice . . . in regard to specific behaviors or making decisions. . . . or advice about the client's views, attitudes or emotions." However, not all geneticists or psychologists see it this way. Rather, they see *coercion,* not advice giving, as the core issue of directiveness.

Directiveness in genetic counseling is a form of persuasive communication in which there is a deliberate attempt—through deception, threat, or coercion—to undermine the individual's autonomy and compromise his or her ability to make an autonomous decision (Kessler, in press-*a,* in press-*b*). Singer (1995) and other psychologists call this communication process *persuasive coercion.* This is what I think most of us have in mind when we address the issue of directiveness in genetic counseling.

Both the "Code of Professional Ethics" adopted by the National Society of Genetic Counselors (1992) and the recent "Code of Ethical Priniciples for Genetics Professionals" (Baumiller et al. 1996) specifically highlight coercion as the defining aspect of directiveness. There is a qualitative difference between saying "It'd be sensible if you spoke to Michael and Carol about this" (Michie et al. 1997, p. 42) and "Your risk is too high to have children and if you decide to do so I will no longer offer you my services." In the latter situation a strategy of threat is used to coerce a decision, whereas in the former case the client's ability to decide for him- or herself is not compromised.

Removing coercion as the defining issue in directiveness leads to an absurd position in which almost any action or utterance in genetic counseling could be interpreted as directiveness, and, in fact, contextualists, such as Clarke (1991) and Brunger and Lippman (1995), seem to do exactly that. The result is an unrealistic lumping together of all forms of advice, directions, suggestions, and recommendations, helpful or not, coercive and noncoercive, into a single, undifferentiated mishmash. This, in turn, has lead to confusion and to an ever-widening chasm between academics, theorists, and researchers, on one hand, and practitioners, who just want to do the best that they can to help their clients, on the other.

Seen through the lens of coercion, the results of the Michie et al. study take on a significance different than the one that Ms. Bernhardt assigns to it. Examine the instances that Michie et al. (1997, p. 42) give of directiveness. Even Bernhardt points out that one category, reinforcement, can hardly be considered directive. I would go further and say that *none* of the examples that Michie et al. list are unequivocal cases of directiveness; not one example can be misconstrued as an attempt to coerce, deceive, or threaten a client or to undermine their autonomy. It might be argued that not only have Michie et al. not studied nondirectiveness, but they haven't studied directiveness either. But, in that case, what has been investigated? What indeed.

There are two possibilities: