

## THE LANCET

global improvement rating] and assessment on PSMS (physical self-maintenance scale) were made at baseline, 4 week intervals, and at the end of the 24 weeks. CATS were completed by caregivers both at baseline and at week 24. Velnacrine (225 mg daily) significantly reduced caregiver time requirements, as measured by CATS, in comparison with placebo. At week 24, the time spent on care was reduced by 45% (about 3.2 h per day) versus baseline ( $p < 0.01$ ), compared with a 25 min per day reduction for the placebo group. The main component contributing to this difference was time spent supervising the patient. The validity of the CATS data was verified by a comparison with a patient-based assessment scale. Allocation of daily caregiver time increased in proportion to disease severity, as measured by both the ADAS memory ( $p < 0.0037$ ) and non-cognitive ( $p < 0.0066$ ) components at baseline.

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### Y chromosome sequences in Turner's syndrome and risk of gonadoblastoma or virilisation

SIR—Kocova and colleagues (July 17, p 140) report mosaicism for cell lines containing partial Y chromosomes in 6 of 18 individuals with Turner's syndrome. Mosaicism was detected by Southern blotting of Y-DNA sequences amplified by polymerase chain reaction (PCR). The results are interpreted as evidence that (1) roughly 40% of 45,X individuals are actually mosaics for a Y-DNA-containing cell line, and (2) perhaps 33% of Turner individuals are at risk of Y-induced gonadoblastoma—and at risk of Y-induced "virilisation" of unspecified nature. Girls and women at risk of gonadoblastoma are usually advised to undergo prophylactic gonadectomy, or at least gonadal examination via laparoscopy. By inference, perhaps 1 of 3 individuals with Turner's syndrome should undergo gonadectomy or laparoscopy. I have several concerns.

First, the results are biologically unlikely. In all 6 cases in which SRY (a gene on the short arm of the Y chromosome) was present, the Y centromere was absent. As Held in his accompanying commentary points out, mosaicism for such Y fragments could result only from chromosomal mechanisms of striking complexity, especially in the SRY-positive individuals who are 45,X/46,XX or 45,X/47,XXX mosaics. Several groups, including my own, have investigated hundreds of individuals who carry part but not all of the Y chromosome.<sup>1</sup> I am aware of only one or two cases in which there is solid evidence of mosaicism for a Y chromosomal segment that lacks the centromere. It is improbable that all 6 individuals in whom Kocova and colleagues recorded Y DNA would be mosaics for segments lacking the centromere.

Second, the possibility of artifact is great. Kocova and colleagues were careful to avoid contamination of patient samples with trace amounts of male DNA. (Such contamination, which should result in false-positive results for both SRY and the Y centromere, is an unlikely reason for the findings.) However, Kocova's experimental design introduces the possibility of contamination from another source—ie, the hybridisation probe. The PCR primers used to produce the hybridisation probe were identical to those used to amplify patient DNA. Thus, the hybridisation probe, presumably produced and handled in the same laboratory as the patient DNAs, is a potential contaminant that could artifactually produce the recorded results—ie, SRY positive, Y centromere negative. (This difficulty might be circumvented by use as a hybridisation probe of a smaller SRY segment than that amplified from experimental and control subjects.)

Third, with respect to the clinical significance of virilisation, it is generally held that the gonad is the only organ through which the masculinising effects of the Y chromosome are mediated and that those effects are much more pronounced during embryonic and fetal development than during postnatal life. In girls with no external evidence of virilisation (eg, clitoromegaly), it is not obvious that slight mosaicism in blood or skin (the tissues tested by Kocova and co-workers) constitutes an important risk factor for virilisation later in life.

Further, as Kocova recognises, one or more particular Y-chromosomal genes predispose girls and women with dysgenetic gonads to development of gonadoblastomas. The identity of the Y-chromosomal so-called gonadoblastoma gene(s) has not yet been established, but some information is available about the location of that gene (or genes) on the Y chromosome. The evidence implicates a middle portion of the chromosome (intervals 4B and 5), a region that includes the centromere.<sup>2,3</sup> SRY and its neighbouring DNA sequences are located outside this region and seem to play no part in the aetiology of gonadoblastoma. In the absence of the Y centromere, the presence or absence of SRY probably has little bearing on the risk of gonadoblastoma.

I disagree with Held's assertion that Y-DNA PCR is not a sufficiently proven method to be applied clinically in testing for mosaicism when none is detected by conventional cytogenetic methods. PCR has been applied successfully in detecting and characterising complete or partial Y chromosomes in hundreds of individuals, including many known or suspected to have mosaic karyotypes.<sup>1</sup> Of course, the fluorescence-in-situ-hybridisation (FISH) method favoured by Held is a suitable alternative. Which individuals with Turner syndrome should be tested (by PCR or FISH) for DNA sequences located at or near the centromere of the Y chromosome? The answer is, those in whom some or all cells contain a marker chromosome of unknown origin, and those in whom there is clitoromegaly or other evident virilisation.

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- 1 Vollrath D, Foote S, Hilton A, et al. The human Y chromosome: a 43-interval map based on naturally occurring deletions. *Science* 1992; **258**: 52-59.
- 2 Page DC. Hypothesis: a Y-chromosomal gene causes gonadoblastoma in dysgenetic gonads. *Development* 1987; **101** (suppl): 151-55.
- 3 Petrovic V, Nasioulas S, Chow CW, Voullaire L, Schmidt M, Dahl H. Minute Y chromosome-derived marker in a child with gonadoblastoma: cytogenetic and DNA studies. *J Med Genet* 1992; **29**: 542-46.

### SRY-negative XX fetus with complete male phenotype

SIR—The majority of XX males without genital ambiguities are Y-DNA positive.<sup>1</sup> In contrast, Y-DNA-negative XX males usually present with genital ambiguities. However, in many cases it is difficult to exclude a mosaicism of Y-specific DNA limited to the gonad. We describe an XX male without genital ambiguities, diagnosed during fetal life where Y-specific DNA was not detected in gonad tissue.

During her second pregnancy, a 37-year-old woman with a normal family history requested an amniocentesis for fetal karyotype at 16 weeks of amenorrhoea. The karyotype was found to be 46,XX. At 21 weeks of amenorrhoea ultrasonography showed an apparently normal male phenotype, with a normal sized penis and scrotum. Müllerian inhibitory factor measured in fetal blood was 48 ng/mL, within normal limits for a normal male at this stage of development. 17-hydroxyprogesterone (2.9 ng/mL), testosterone (0.48