LETTERS TO THE EDITOR

Detection of a familial cryptic translocation by fluorescent in situ hybridisation

We read with great interest the report by Kohler et al on a family with a half cryptic translocation involving chromosomes 9 and 17. In that report, three females in two generations had seemingly balanced translocations, and one male infant who died had exhibited features typical of Miller-Dieker syndrome. Additionally, two living male sibs, aged 20 and 17, had multiple congenital malformations as well as mental retardation. Chromosome analysis had shown the subtle translocation, which was further defined by FISH analysis using chromosome 17 specific probes.

Recently, we evaluated a family in which we eventually discovered a similar translocation involving chromosomes 17 and 22. The translocation was not detectable cytogenetically, even at a 850 band level. Because of a subtle clinical clue, however, it was discovered fortuitously by FISH analysis using chromosome 17 specific probes.

The proband was a 6 month old white male infant, born to healthy, non-consanguineous parents. The father was 35 years of age, and the mother was 33. The couple had two other healthy children, aged 4 and 3. The mother reported three early spontaneous miscarriages and one ectopic pregnancy. The only other significant family history was mild mental retardation in the mother's paternal uncle, aged 49. The pregnancy was uneventful, until about 39 weeks of gestation, when the mother developed severe pre-eclampsia. Labour was induced one week later, with clinical signs suggesting that partial abruption of the placenta occurred immediately before delivery. The infant weighed 3355 g and the Apgar scores were 3 and 5 at one minute and five minutes, respectively. The infant was hypotonic, with a weak respiratory effort, and had to be intubated and transferred to a neonatal intensive care unit.

Our initial examination findings a few hours after birth included midfacial hypoplasia with a prominent nose, micrognathia, low set, incompletely rotated ears, and a small mouth with a high arched palate and wide alveolar ridges. Also, excess soft tissue was noted around the neck, which showed creasing bilaterally. Other findings included premature closure of the metopic suture, syndactyly between the third and fourth fingers on the left, bilateral simian creases, adducted thumbs, laterally displaced nipples, penile attachment high on the scrotum, rocker bottom feet, second toe overriding the third, and hypoplastic toenails. He had generalised muscular hypotonia and hyperactive deep tendon reflexes. Cardiac evaluation revealed tri-cuspid insufficiency, and an unusual aortic arch in which the transverse aortic section connected with the ascending and descending aortic sections at acute right angles. He had severe anaemia, for which idiopathic haemolytic anaemia was considered as a diagnostic possibility but could not be proven. Our clinical impression was that this patient probably had a triploidy/diploidy mosaicism; however, routine chromosome analysis showed a 46,XY karyotype.

An MRI study of the brain at 3 months of age showed agenesis of the corpus callosum, unusual Sylvian fissures, and probable polymicrogyria. As a result of these findings, the possibility of Miller-Dieker syndrome was considered. High resolution chromosome analysis at the 850 band level was again normal. Then, FISH analysis was carried out using the probe D17S379 for Miller-Dieker syndrome at 17p13.3 (ONCOR). Clear signals were seen on both chromosomes 17p as well as at the control locus, RARA, and an additional signal for D17S379 was seen on the q terminus of a G group chromosome (figure). This chromosome was identified as a 22 by GTL banding, and a 22q deletion was confirmed by FISH using a D22S39 probe at 22q13.3 (ONCOR). FISH analysis was also carried out on both parents using the same probes, and a balanced translocation between 17p13.3 and 22q13.3 was found in the mother. This rearrangement was not detectable by high resolution chromosome analysis. The karyotype of the proband, therefore, is 46,XY,-22,+der(22)(t(17;22)(p13.3;q13.3) mat. No cell line is available.

Unfortunately, the infant continued to have problems with anaemia and pneumonia, and died at 6 months of age. However, we are now able to provide genetic counselling to this family, and offer prenatal diagnosis using FISH analysis in the mother’s future pregnancies, and test her two apparently normal children and other family members for carrier status.

We thank the parents for their cooperation and Drs A J Yazdi and W L Jackson for referring the family.

DONNA P SMITH
MARY FLOYD BURHAN SAY
A Chapman Institute of Medical Genetics,
5300 East Shelly Drive,
Tulsa, Oklahoma 74135, USA.


Chromosome fragments with alphoid sequences derived from a pseudoisodicentric Y chromosome

Isodicentric Y chromosomes constitute a relatively common form of normal length, non-fluorescent Y chromosomes. They probably originate from an isochromatid breakage in the Yq euchromatin following by rejoining of the broken chromatids in the male germline. Their symmetrical appearance would result from centromere division in meiosis.1 Habitually, but not always, one of the resulting centromeres is inactivated, thereby allowing normal segregation. They commonly occur in mosaicism with a 45,X cell line, and the associated phenotypic anomalies can be heterogeneous depending on the frequency of the 45,X cell line and the localisation of breakpoints. Thus, they can be diagnosed in patients with Turner’s syndrome, ambiguous genitalia, apparently normal males, azoospermic males, or autistic children.1,2 Accurate identification was not easy in the past, and G11 banding offered the best results. Nowadays, fluorescent in situ hybridisation (FISH), usually with specific centromeric Y alphoid sequences, allows these chromosome aberrations to be identified precisely.3-5 Demonstration of Y specific sequences may be relevant to therapeutics since gonadal dysgenesis patients with Y chromosome material have a 15–20% risk of developing gonadal neoplasia, gonadectomy usually being recommended.1

FISH analysis using ONCOR probe for Miller-Dieker syndrome (D17S379) showing additional signal on the derivative chromosome 22 (right centre arrow).

Downloaded from http://jmg.bmj.com/ on September 8, 2017 - Published by group.bmj.com
In a previous report, a pseudoisodentric Y chromosome was analysed in a 14 year old girl with signs of Turner’s syndrome and virilisation. In this letter we present a new case of pseudoisodentric Y chromosome, showing particular features. A 64 year old woman was referred because of somatic features of Turner’s syndrome including primary amenorrhoea, small stature, and raised gonadotrophins accompanied by aortic aneurysm and clitoromegaly. Her karyotype was a mosaic 45,X/46,X + mar. FISH with a Y specific classical satellite DNA probe, DYZ1, failed to give a hybridisation signal, while a centromeric alphoid probe, DYIZ3, confirmed 26% of nuclei to have Y sequences, and the marker chromosome was identified as an isodicentric Y, showing two areas of hybridisation in a symmetrical position (figure a,c,e). One centromere was inactivated in all markers examined, since only one primary constriction was evident (figure b,d,e). The alphoid signals were very close to each other so the breakpoint should be localised in the Yq arm, closer to the centromere than in our previously described case. The striking finding was that 6% of mitoses with isodicentric Y chromosomes had very small chromosome fragments with Y specific alphoid sequences (figure f,g,h). Given their low frequency, their presence is difficult to detect and identify with accuracy by current karyotypic analysis without FISH. Though other sequences could be integrated, most of their material seems to be composed of alphoid Y sequences.

The possible function of these fragments, as active centromeres, is difficult to assess. They probably originate in the inactive centromeric area of the pseudoisodentric, since active centromeres from normal Y chromosomes obviously do not develop such structures. The fact that their number changes among different mitoses (one or two fragments) (figure g,h) also suggests that they behave as inactive centromeres. The mechanism of generation of these structures is intriguing. Their morphology resembles double minute-like microchromosomes. Experimentally, the same kind of microchromosomes have been obtained after introduction of human alphoid DNA sequences into simian cells. In these studies, transfected alphoid sequences experienced amplification and gave rise to extrachromosomal elements. Our inactive centromeric area possibly exhibits some instability, showing disturbances in replication, or recombination events, that lead to amplification and fragility of alphoid sequences. This could explain the coexistence of the fragments with the isodicentric Y within the same mitoses.

It is now accepted that a functional human centromere is a complex structure where alphoid DNA sequence arrays and possibly other sequences are organised with specific centromeric proteins, like CENP-B, constituting specific higher order chromatin folding structures. In fact, partial or complete absence of centromere specific proteins, chromatin deletion, or changes in chromatin conformation have been reported in inactive centromeres. Nevertheless, since a large block of transfected and chromosome integrated alphoid DNA does not always form an active centromere, it is possible that additional genetic or epigenetic factors are required for activity. In some cases disruption of these factors might account for instability in certain inactivated centromeric regions.

From the clinical point of view, the presence of this very low frequency of mitoses with fragments does not appear to be of great practical consequence. Our patient was a relatively old woman when diagnosed, and gonadoblastoma has not developed, taking into account that most of these tumours arise between 15 and 30 years. The presumed Y linked gonadoblastoma locus may have been deleted in the rearrangement. It would be of interest to see if this phenomenon were evident in similar cases or with other isodicentric chromosomes, or if it is merely an isolated observation. Interestingly, coexistence of a supernumerary microchromosome of unknown origin with a Yq isodicentric within the same mitosis was described in a case report by Haaf and Schmid. They also observed this phenomenon in a very low proportion of mitoses. Insights into the organisation and mechanism of generation of such structures could produce interesting data about centromeric structure and physiology.

J L FERNANDEZ D VALVERDE Laboratorio de Genética, Centro Oncológico de Galicia, Avda de Montserrat s/n, 15006 La Coruña, Spain.

J GOSALVEZ Unidad de Genética, Universidad Autónoma de Madrid, Spain.

G PINHEIRO S PEREIRA Y GOYANES Sección de Genética y Servicio de Ginecología, Instituto Universitario de Ciencias Médicas, Hospital Juan Canalejo, La Coruña, Spain.


Familial predisposition to both male and female germ cell tumours?

A minority of testicular teratomas are recognised to be familial.1 Some occur as part of the spectrum of cancers in the Li-Fraumeni syndrome; however, the genetic basis of the majority of familial cases is unknown. This has prompted the formation of a Li-Fraumeni Syndrome Family Cancer Registry to identify genes causing testicular teratomas. As one of the participating centres we have been ascertaining familial cases from a registry of testicular teratoma patients at the Royal Marsden Hospital. Among these cases we have identified three families which suggest that a common genetic basis exists between some male and female germ cell tumours.

The first family was identified through an index case who presented with a seminoma at the age of 51, his brother had had a testicular teratoma at the age of 28, and their cousin an endodermal sinus tumour of the ovary diagnosed at 32 years. In the second family the index case presented with a differentiated malignant teratoma at 28 years of age and his sister was diagnosed with bilateral ovarian teratomas at the age of 39. In the third family the index case presented with a retroperitoneal teratoma at 26 years and his sister was diagnosed with an ovarian teratoma at 45 years. None of these families had any features indicative of the Li-Fraumeni syndrome or any other cancer family syndrome, suggesting the identification of a previously unrecognised association. This is supported by reports of single families with ovarian and testicular germ cell tumours2 and a family with multiple cases of dysgerminoma.3 The three families we report were identified from a database of 2000 teratoma patients, suggesting that in 0-2% of pedigrees a female member will develop a germ cell tumour. This may be an underestimate since pedigree information on all 2000 index cases has not been verified and many mature teratomatous cysts are asymptomatic and go undiagnosed.

Whether an association between male and female germ cell tumours is the result of the inheritance of a single gene with effects on both ovary and testis or a consequence of the action of modifying genes will only be established when the gene or genes causing testicular teratomas are identified.

This work is supported by the Cancer Research Campaign and the Royal Marsden Cancer Trust. RAH is supported by a CRC clinical research fellowship.

R A HUDDART
C THOMPSON
R Houlston
Institute of Cancer Research,
15 Clements Road,
Balham, Surrey
SM2 5NG, UK

R A HUDDART
A NICHOLLS
A HOWRICH
The Royal Marsden Hospital,
Dana Road,
Sutton, Surrey
SM2 5PT, UK


13 Haaf T, Schmid M. Y isochromosome association with a mosaic karyotype is a result of inactivation of the centromere. Hum Genet 1990;85:494-5.

Chromosome fragments with alphoid sequences derived from a pseudoisodicentric Y chromosome.

J L Fernández, D Valverde, J Gosálvez, C Pineiro, S Pereira and V Goyanes

*J Med Genet* 1996 33: 84-86
doi: 10.1136/jmg.33.1.84-a

Updated information and services can be found at:
http://jmg.bmj.com/content/33/1/84.2.citation

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/