Medical genetics: advances in brief

Stable dicentric X chromosomes with two functional centromeres

Sullivan BA, Willard FW. *Nat Genet* 1998;**20**:227-8.

It has long been speculated, from cytogenetic observation of primary constrictions, that when the two centromeres of a dicentric chromosome are close then they may both be active. That is, orientation of the respective kinetochores on each chromatid to opposite spindle poles is possible so that the dicentric can evade the "fusion-breakage-bridge" cycle of Barbara McClintock and segregate efficiently. Thus, for example, Robertsonian translocation chromosomes usually have two active centromeres. Conversely, it is suggested that widely spaced centromeres of a dicentric may misalign on the spindle, since the chromatin between them can twist; the dicentric is thus forced to somehow undergo inactivation of one of the centromeres for efficient segregation to be possible. Until now it has not been possible to extrapolate from cytogenetic observations of dicentric chromosomes to centromere distances in terms of megabases of DNA. The recent letter to *Nature Genetics* by Sullivan and Willard now addresses this problem nicely. These authors describe experiments with a variety of dicentric (dic)X chromosomes, in which the extent of the X short arm chromatin between centromeres is defined, varying from 4 to 34 Mb. Sullivan and Willard used antibodies to CENP-C and E, specific to active centromeres. They found that, in the four dic(X)s with the shortest intercentromeric distances (4-12 Mb), these proteins were present at both centromeres in 67-87% of cells. Excitingly, however, dic(X) chromosomes with greater intercentromeric distances, for example, the cited case of 34 Mb, showed only a single CENP positive centromere in 100% of cells; they were thus functionally monocentric. The authors attempted to correlate these findings with stability of chromosome segregation at anaphase. They therefore monitored movement of the respective dicentric and control chromosomes using a technique involving enriching for anaphase and telophase cells. As expected, controls and functionally monocentric X chromosomes showed no evidence of anaphase lag, that is, they segregated efficiently. However, in two of three functionally dicentric X cell lines the dic(X) was shown at the spindle midzone in anaphase, or between two newly formed daughter cells in telophase, in approximately 25% of cells, as illustrated in the elegantly presented figures. It is not clear why the above unstable segregation was not seen in the third functionally dicentric X cell line tested, or why the two cell lines showing high degrees of anaphase lag did not eventually lose the dic(X) completely. Sullivan and Willard suggest that there are other mechanisms involved in ensuring the stability of dicentric chromosomes. Behaviour of the dic(X)s at cell division did not, moreover, correlate with the presence of mosaicism in the karyotype, although it was not made clear whether this mosaicism applied to the original patients' karyotypes or to those of the cell lines derived from these patients (mosaicism in cell lines being subject to distortion by clonal expansion). The authors, therefore, propose that the mosaicism associated with dic(X) cases reflects chromosome loss at the time of dicentric formation and not subsequent instability and ongoing clonal evolution. Their inference may be somewhat of a conceptual leap, but this caveat should not detract from what is otherwise an elegant and concisely described piece of work.

ANDREW FISHER

Chinese geneticists' views of ethical issues in genetic testing and screening: evidence for eugenics in China

Mao X. *Am J Hum Genet* 1998;**63**:688-95.

Invited editorial. "Well-bear and well-rear in China"

Knoppers BM. *Am J Hum Genet* 1998;**63**:686-7.

Mao reports the results of the responses of 63% (255) of 402 Chinese geneticists who participated in a national survey designed to identify their views on the ethical issues involved in genetic testing and screening. The Chinese geneticists differ in almost every area from their North American and west European counterparts, and the degree of polarisation may at first seem astonishing to geneticists working in developed countries who have a fundamental objection to eugenics. The Chinese respondents strongly favoured offering genetic testing at work for α1-antitrypsin deficiency (95%) and for genetic predisposition to heart disease, cancer, and diabetes in executives (94%). A total of 86% wanted genetic testing included in pre-employment physical examinations and 86% also felt that the government should require premarital carrier tests. Newborn screening tests for sickle cell disease (77%) and Duchenne muscular dystrophy (71%) were recommended and, perhaps most surprisingly, 85% felt that children should be tested for late onset disorders such as Huntington's disease. In the western world there is almost universal opposition to testing children for genetic susceptibility to late onset disorders because of a fundamental respect for the autonomy of the child, but most Chinese geneticists favoured such testing on the grounds that parents should be able to decide for their children and should have the power to direct their children's lives. This cultural division reflects the extent of individual autonomy in developed countries including the preservation of the autonomy of minors. In China, the child is seen as part of the family, rather than as a potentially autonomous person. Traditionally, China is a very paternalistic society and parents have absolute power to make family decisions. Most Chinese geneticists believed that partners should know each other's genetic status before marriage (92%) and 91% believe that carriers of the same recessive gene should not have children; 91% felt that a woman at risk of having a child with a genetic condition should have prenatal diagnosis. Finally, more than half of the respondents felt that there were no laws in China to prevent discrimination on the grounds of disability. The frankly eugenic views expressed are hard for western geneticists to begin to comprehend because they are so diametrically opposed to our own. The word "eugenics", when translated into Chinese, apparently means "well-bear and well-rear". Chinese geneticists believe eugenics implies processes designed to ensure that children who are born are, as far as possible, normal, and they strive to achieve this in the context of a strict limitation in the size of population growth and a fundamental lack of resources. They feel that their goal is "improvement in population quality, decrease in population quantity and the furtherance of eugenic principles". In the accompanying editorial, Knoppers tries to understand how such diametrically opposing views could have arisen on opposite sides of the world. Primarily, the argument is between the North American ideal of individualism at all costs versus communitarian values. However, it is important to acknowledge that even though the rights of people with genetic disorders may be more freely acknowledged in the west, such people do not necessarily receive better care, particularly in countries where large numbers of people have no access to free health care.

FRANCES FLINTER

Mutations in the gene encoding gap junction protein beta-3 associated with autosomal dominant hearing impairment

Xia J-H, Liu C-Y, Tang B-S, *et al*. *Nat Genet* 1998;**20.4**:370-3.

Over 40 loci for deafness have been genetically mapped but only in very recent years have causative genes been identified. Two of these are connexins and this promted Xia *et al* to search for new human connexin genes and look for mutations in families with deafness. From a database, two overlapping ESTs were identified with 83% identity to rat Gjb3 and a homologous fragment amplified from human DNA. This identified human GJB3 (connexin 31) which mapped to 1p32-p35. RT-PCR analysis showed it to be expressed in the inner ear. Of six families with sensorineural deafness linked to 1p32-p35, two were found to have mutations in the connexin 31 gene. One resulted in an amino acid change and the other in a premature stop codon causing absence of part of the C terminus of the protein. Both of these mutations were in regions highly conserved in other connexins. In both families, inheritance was autosomal dominant but males were affected with progressive bilateral high frequency hearing impairment with onset from 20 to 40 years of age, whereas females were either unaffected or much less severely affected. A significant proportion of families with AD hearing loss show linkage to 1p32-35, so Xia *et al* may have identified a common cause of deafness. Interestingly, in the same issue of *Nature Genetics*, an independent group describe the identification of the same gene but found mutations in a different region to be responsible for erythrokeratodermia variabilis in which deafness is not a feature. These findings are discussed in the "News and views" section and represent an interesting example of different mutations in the same gene being responsible for two completely different phenotypes.

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