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Costs of consanguinity

Analysis of the literature of the effects of consanguinity on mortality puts a figure on the price of inbreeding.

ATTITUDES to the practice of consanguinity, or marriage within the extended family, vary widely around the world. For instance, in some countries the marriage of first cousins is frowned upon, but in many cultures it is actively encouraged. In Britain, for example, only about 1 in 200 marriages are between first cousins, whereas in some parts of Africa and Asia the rate is more like 1 in 20.

In the long term, consanguineous marriages have the desirable effect of removing rare deleterious alleles from the gene pool. But the immediate consequences are that the chances of recessively inherited diseases occurring in the next generation are greatly increased. Such disorders can be debilitating if not actually fatal in themselves, for example hereditary deafness, or life-threatening conditions such as the autosomal recessive muscular dystrophies. In recent years, scientists have made many fruitful visits to places like Tunisia and Japan in search of large, inbred families affected with various rare disorders, and then applied statistical techniques such as homozygosity mapping to localize the genes in question[1].

But to what extent are our negative perceptions of consanguinity coloured by these well-publicized occurrences? This question has preoccupied James Neel of the University of Michigan for almost 40 years, since, with W. J. Schull, he compiled one of the first and most comprehensive surveys of the effects of consanguinity in Japan[2]. In this month's *Nature Genetics*[3], Neel and Alan Bittles, from the Edith Cowan University in Perth, Australia, tackle this issue by presenting a detailed analysis of 38 published studies on the effects of consanguinity on mortality.

Children of first cousins have a 1/16 chance of being homozygous at a particular locus, as a result of inheriting two identical copies of one of their grandparents' genes. By comparing the death rate of children from consanguineous marriages with that from the same population whose parents are unrelated, it is possible to gauge just how deleterious consanguinity actually is.

For the purposes of comparison, Bittles and Neel examined death rates for children from birth (including late miscarriages and premature births after six months or more gestation) to a median age of ten years. Most of the studies they examined dealt with communities in India, Pakistan, Japan and Brazil. With just two exceptions in the 38 reports, the mortality rates among offspring of first cousins exceeded those of children of non-consanguineous unions. The combined data, say the authors, translate into a figure for the excess death rate among children of first cousins of around 4.4 per cent. For higher levels of inbreeding, this figure would in turn increase, although the degree to which such calculations are influenced by socioeconomic status (which tends to be lower among consanguineous families) is uncertain.

Neel and Bittles also suggest that this excess mortality is almost entirely due to the action of 'absolute lethals' — severe genetic disorders that prove fatal regardless of environmental factors — as opposed to 'conditional lethals', where the influence of external stresses may determine the individual's ability to survive. In a further calculation, albeit an approximate one, they derive the number of 'lethal equivalents' — the number of alleles (or combinations thereof) which produce an absolute lethal — from the mortality data. The answer is a surprisingly low 1.4.

The authors conclude by describing a curious paradox. At a rough guess, there are some 3 million (1 in 1,000) polymorphic sites in the human genome, of which 10 per cent (300,000) might lie within or close to genes and whose variation might therefore be considered potentially significant. Yet given that the estimated number of 'lethal equivalents' is orders of magnitude lower, Bittles and Neel are "forced to the conclusion that the vast majority of variation encountered in DNA is of no significance to the organism with respect to survival during a critical portion of the life span". The biggest uncertainty in all this is the degree to which inbreeding causes early fetal losses, for which there is no good measurement.

Also in this month's issue[4] comes characterization of the molecular basis of a new class of recessive neurological disease by Michael Litt and colleagues at the Oregon Health Sciences University. For the first time, scientists have implicated a human potassium channel[5] in a hereditary disorder — episodic myokymia ataxia. Several hereditary disorders have been associated with defects in skeletal muscle, voltage-gated ion channels for sodium, calcium and chloride, including hypokalaemic periodic paralysis and paramyotonia congenita. Patients with episodic ataxia experience periodic bouts of stress-related generalized ataxia with myokymia, or rippling of the muscles.

The recent localization of the disease gene to chromosome 12p implicated a cluster of potassium channel genes. Litt and co-workers have disovered four separate missense mutations in the *KCNA1* gene in four different families, all of the mutations lying within or close to one of the six putative transmembrane regions of the channel, which is a homologue of the *Drosophila Shaker* locus. By analogy with the corresponding rat channel, the KCNA1 protein is probably expressed in both cerebellum and peripheral nerve, in agreement with the observed phenotype.

Ion channels could well be the molecular basis of some cardiac arrhythmias, the leading cause of sudden death which claims many lives each year. Arguably the best known of this class of disorder is long QT syndrome (LQT), so called because of the lengthened interval between Q and T waves on an electrocardiogram.

It was three years ago that Mark Keating's group at the University of Utah mapped a locus for LQT to chromosome 11 (ref. 6). Now, the same group has mapped two additional LQT loci to chromosomes 7q35-36 and 3p21-24 in ten and three families, respectively[7], with evidence for a fourth unmapped locus. Chloride and calcium channels are among the best contenders to be screened for these newly mapped disease genes. With the hitherto most attractive candidate for the original LQT locus, H-*ras*, now excluded by genetic linkage data[8], these new localizations may be a badly needed shot in the arm for understanding LQT syndrome.

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Also in this month's *Nature Genetics*: Adeno-associated viral gene delivery to the brain; microdissecting marker chromosomes in breast cancer; localization of *IDDM3* to chromosome 15; the genetics of biotin deficiency; and the role of stop codons in alternative splicing.

1. Farrall, M. *Nature Genet.* **5**, 107–108 (1993).
2. Neel, J.V. *Physician to the Gene Pool* (Wiley, New York, 1994).
3. Bittles, A.H. & Neel, J.V. *Nature Genet.* **8**, 117–121 (1994).
4. Browne, D.L. *et al. Nature Genet.* **8**, 136–140 (1994).
5. Jan, L.Y. & Jan, Y.N. *Nature* **371**, 119–122 (1994).
6. Keating, M. *et al. Science* **252**, 704–706 (1991).
7. Jiang, C. *et al. Nature Genet.* **8**, 141–147 (1994).
8. Roy, N. *et al. Nature Genet.* **8**, 113–114 (1994).