Selected Summaries

Is homosexuality genetically determined?

A linkage between DNA markers on the X-chromosome and male sexual orientation. Hamer DH, Hu S, Magnuson VL, Hu N, Pattatucci AML. (Laboratory of Biochemistry, National Cancer Institute, National Institutes of Health, Bethesda, USA.) *Science* 1993;**261**:321–7.

SUMMARY

The authors studied one hundred and fourteen families to determine whether or not male sexual orientation is genetically influenced. Increased same-sex orientation was observed in the maternal uncles and male cousins (from the mother's side) of these subjects. This suggested the possibility of sex-linked (X-chromosome) transmission of a predisposition to male homosexuality in a group of male homosexuals. Forty families with two gay brothers and no evidence of non-maternal transmission of homosexuality were selected for rigorous genetic analysis of the inheritance of polymorphic markers on the X-chromosome, as it was thought that these families were likely to have a greater possibility of demonstrating a sex-linked inheritance.

In this subgroup, a significant correlation was observed between the inheritance of certain markers to Xq28, the subtelomeric region of the long arm of the X-chromosome and male homosexuality.

COMMENT

The technique of reverse genetics has been useful in identifying the genes involved in monogeneic diseases with a high degree of penetrance, e.g. cystic fibrosis, Duchenne's muscular dystrophy and Huntington's chorea. However, its use in identifying the biological basis for more complex phenomena, especially certain forms of behaviour is less clear. Reverse genetics uses the phenomenon of linkage disequilibrium, i.e. two traits whose genes reside close to one another on a given chromosome are likely to be co-inherited. The closer the genes, the higher the probability that both will be passed on to the offspring from the same allele. If the location of one gene is known, it is a useful guide to the location of the other.

The association of inherited traits such as blood groups and polymorphic proteins especially isozymes with diseases was studied. These markers were few and far apart and yielded little information. With the advent of recombinant DNA techniques and an increase in our understanding of the human genome, the power of such techniques has increased manifold. The reason is simple—most of the eukaryotic DNA does not code for any protein and has a far higher rate of variation than any of the coding regions where the rate of variation has evolutionary constraints. DNA markers are now available which dot the entire genome. If their co-inheritance with a given trait is observed, then the location for the gene predisposing to the trait can be matched with a greater or lesser degree of certainty. For monogeneic diseases such as cystic fibrosis and Duchenne's muscular dystrophy which have precise phenotypic end points, it has been possible to identify not only the chromosomal region but the causative gene as well. It is due to the possibility of identifying the gene even when little or nothing is known about the protein or biochemical changes, that the process is known as reverse genetics (in hoary pre-recombinant DNA days scientists proceeded from the protein to the gene).

Applying the same techniques to the study of behaviour has its pitfalls, but this is a brave attempt, and advances our understanding of the biological basis of sexual preference.

Sexuality and sexual preference is the result of an interplay of social, cultural, religious and biological factors. It is a difficult task to isolate one variable and put it under reductionist scrutiny. Such studies on manic depression, schizophrenia and alcoholism have come to naught. In this investigation, by selecting their subjects carefully, the authors have tried to avoid the pitfalls seen in previous work.

That a predisposition to homosexuality may be inherited, is indicated from studies based on twins, foster children and nuclear families. Hamer *et al.* traced the pedigrees of 76 homosexual men, and found a much higher rate of homosexuality in gay men's brothers (13.5%) compared to the general population (2%). What was remarkable was the higher prevalence among maternal uncles and cousins who were sons of maternal aunts. This indicated an X-linked inheritance. To obtain a clearer picture, Hamer analysed the DNA of 40 pairs of homosexual brothers assuming that two brothers showing homosexual behaviour are more likely to inherit the same allele of the predisposing gene than ones who do not. Since DNA markers spanning the X-chromosome are known, it should be possible to demonstrate the co-inheritance of one or more such markers in homosexual brothers with a greater frequency compared to the average norm. The authors demonstrated the sharing of five markers located in the subtelomeric region of the X-chromosome in homosexual brothers. This indicates, with a 99.5% probability, that the predisposing gene resides in that stretch. It will be some time before the actual gene is identified; the stretch of DNA is about 4 million base pairs long and could contain several hundred genes.

However, this is only one of the many ways of predisposition to homosexuality. There is evidence of non-maternal inheritance in another group of homosexuals.

Reservations about this study have been voiced by many[1–3] including representatives of the gay community.[2] Many have contested the importance of biological predisposition in determining sexual behaviour. Similar issues were raised when differences in the hypothalamus of heterosexual and homosexual men were demonstrated.[4] The method for identifying homosexuality is also worrisome because in this study a lower rate of prevalence (2%) was observed compared to some previous studies (which reported a rate of 4%).[1–3]

There has also been some criticism of subject selection. However, this represents, as the authors themselves state,

'an early application of molecular linkage methods to a normal variation in human behaviour'.

This study has obvious social and ethical ramifications. A demonstration of genetic link with homosexuality might help in obtaining civil rights for homosexuals. However, the danger is that of genetic screening, especially of foetuses, leading to termination of pregnancy. I feel that in India, where a foetus is terminated for being a female—the future is frightening. Each society will have to find means of absorbing and assimilating knowledge generated by the process of science. It is sad that our past record has been so poor.

REFERENCES

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Long term complications of IDDM and intensified insulin treatment

The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin dependent diabetes mellitus. *N Engl J Med* 1993; **329**:977–86.

SUMMARY

In one of the largest studies of this nature, a total of 1441 patients with insulin dependent diabetes mellitus (IDDM) were recruited at 29 centres from 1983 to 1989. The trial was terminated in June 1993, after an average follow up of 6.5 years (range 3–9 years). Eligibility criteria included insulin dependence, age of patients (13–39 years), and absence of hypertension, hypercholesterolaemia, severe complications of diabetes, and other medical conditions. Candidates for primary prevention were required to have had IDDM for 1 to 5 years, no retinopathy and a urinary albumin excretion of less than 40 mg over 24 hours. Eligibility criteria for the secondary prevention cohort included, IDDM for 1 to 15 years, very mild to moderate non-proliferative retinopathy and a urinary albumin excretion of less than 200 mg per 24 hours. Patients were then randomized to conventional therapy and intensive therapy arms. Conventional therapy consisted of one or two daily injections of mixed, intermediate and rapid acting insulins, daily self-monitoring of urine or blood glucose and diabetic education. Intensive therapy included administration of insulin 3 or more times daily by injection or by an external pump, and adjustment of the dose of insulin according to the results of self-monitoring of blood glucose. The goals of intensive therapy included a preprandial blood glucose value between 70 and 120 mg/dl, postprandial blood glucose concentration of less than 180 mg/dl, a weekly 3 a.m. blood glucose measurement greater than 65 mg/dl, and a monthly glycosylated haemoglobin value of less than 6.5%. Strict objective measurements were used to evaluate retinopathy. Patients were then followed up and assessed for nephropathy, neuropathy, macrovascular, neuropsychological and quality of life outcomes.

Ninety-three per cent of patients completed the study. Glycosylated haemoglobin (HbA_1C) reached a nadir at 6 months in the patients receiving intensive therapy, and a significant difference was then maintained in the average HbA_1C value between this group and the conventional treatment arm.

The cumulative incidence of retinopathy, defined as a change of 3 steps or more on fundus photography (sustained over a 6-month period), was similar in the two primary groups until 36 months, when the incidence curves began to separate. At a mean of six years of follow up, intensive therapy reduced the adjusted mean risk of retinopathy by 76% (95% confidence intervals, 62% to 85%). In the secondary prevention cohort, intensive therapy reduced the average risk of such progression by 54% (95% confidence intervals, 39% to 66%). In both cohorts, microalbuminuria developed in fewer patients (mean adjusted risk reduced by 34% in the primary prevention cohort, and by 43% in the secondary intervention cohort) in the intensive treatment group. Similarly, the risk of macroalbuminuria was also reduced. In the primary prevention cohort, those who did not have neuropathy during baseline studies, intensive therapy reduced its appearance at 5 years by 69% and in the secondary prevention cohort by 57%. Intensive therapy also reduced the development of hypercholesterolaemia. When all major cardiovascular and peripheral vascular events were combined, the risk of macrovascular disease was reduced by 41% in the intensive treatment group.

The incidence of severe hypoglycaemia, including multiple episodes in some of the patients, was approximately 3 times higher in the intensively treated patients ($p<0.001$). However, despite this there was no difference in the neuropsychological functions between the patients in the two groups. Weight gain was also observed to be an additional problem.

COMMENT

The Diabetes Control and Complications Trial Research Group (DCCT) study is one of the most important trials in this field and its results have been eagerly awaited by diabetologists all over the world. Studies on the relationship between glycaemic control and long term complications of diabetes were started many years ago and have given rise to many controversies.

It has been clarified that the duration of diabetes is probably the most important risk factor (especially duration after puberty in patients with IDDM), for the development of retinopathy, nephropathy and neuropathy. Perhaps hyperglycaemia over long periods leads to some or all of these complications. Most of the studies concern patients with IDDM and use retinopathy as the marker for diagnosis and monitoring of complications. In a population based study[1] elevated HbA_1C measured at baseline was identified to be a predictor of progression of retinopathy over a period of 4 years in patients with IDDM. Similar observational