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News, views and comments

Heritability of intestinal complaints confirmed

Everyday medical experience suggests that general intestinal complaints (abdominal pain, diarrhoea, constipation, excessive gas or bloating, nausea), also described as functional bowel disorder (FBD), run in families and may therefore have a genetic basis, although such an observation may equally well be an indication of exposure to a common family environment. Australian investigators[1] have now quantified the relative contributions to FBD of genetic and environmental factors. They took stock of FBD complaints in 186 monozygotic (MZ) and 157 dizygotic (DZ) same sex twins and found that nearly 57% of the variability in FBD could be ascribed to additive genetic factors and 43% to environmental conditions that are specific to each individual. Thus, when a doctor diagnoses FBD in several members of the same family, this is most likely because of shared genes and not of shared environments.

X inactivation associated with MZ timing

From molecular genetics we know that in mammalian females one X chromosome in every cell of the body is inactive: about half the paternal X chromosomes and half the maternal. This occurs early in embryonic development. After inactivation has occurred, all the descendents of that cell will have the same X chromosome inactivated. Since both X chromosome inactivation and MZ twinning have about the same timing during embryonic development, American and Belgian investigators[2] predicted that chorionicity in MZ twins is associated with X inactivation. It is well known that monochorionicity, ie both twins in one chorion, is more likely in cases of late division of the embryo. The researchers have therefore compared X inactivation patterns (in DNA in peripheral blood and in mucous membrane from the inner cheek) between monochorionic and dichorionic MZ twins, one of these conditions being possibly closer in time to the timing of X inactivation than the other. The monochorionic twins appeared to be more similar with regard to their pattern of X inactivation compared with dichorionic MZ twin pairs. The monochorionic MZ twinning event seems to occur three to four embryonic divisions after X inactivation. Dichorionic MZ twinning, on the other hand, takes place earlier, before or around the time of X inactivation. The timing of twinning must therefore be considered as an additional important variable in twin studies.

Same genetic determinants for conduct disorders and alcoholism

Behaviour geneticists from the US and Australia[3] have tried to find evidence for the latent conjecture that alcoholism in adults is somehow associated with (or preceded by) behavioural problems (conduct disorders) during childhood, suggesting the possibility of a common genetic basis for both problems. They have tried to answer that question by collecting information about alcohol dependency (AD) as well as (retrospectively!) childhood conduct disorders (CD) in a sample of nearly 2700 adult MZ and DZ twin pairs. In the total sample, the two phenotypes appeared to be significantly associated, for both men and women. This association was predominantly due to the correlation between the genotypes of either phenotype. Childhood conduct disorders may therefore be considered as an early predictor of alcohol dependence in later life, although the rather low magnitude of the association between the two phenotypes (tetrachoric correlations $r = 0.34$ and $r = 0.53$ for men and women respectively) suggest that other sources of variance may be equally or more important and consequently reduce the importance of CD as predictor of AD.

No monotonous linear relationship between number of embryos transferred and probability of multiple pregnancy

Readers of this journal share a common interest in twins and higher multiples, both to obtain insight into the mechanisms that underlie multiple birth pregnancy, and as a genetic epidemiological tool to study the contributions of genetic and environmental influences on any phenotype. One should not forget, however, that multiple births are always associated with increased health risk. This risk has been increased by medical technological progress in recent decades (in vitro fertilisation and related techniques), resulting in higher (than before) numbers of multiples. The IVF technique results in more multiples because of the higher number of embryos transferred. British obstetricians[4] have tried to find out whether there are (other) mediating conditions that potentiate or reduce the probability of a multiple birth pregnancy. They studied this in an impressive sample of 25240 women during a total of 44236 cycles, taking women's age, cause and duration of infertility, previous attempts at in vitro fertilisation, previous live births, number of eggs fertilised, and number of embryos transferred, as potential risk-mediating conditions.

The probability of becoming pregnant–either of a singleton or a multiple–is reduced by older age, tubal infertility, and higher number of previous attempts at IVF. Previous successful pregnancies as well as the number of eggs fertilised increase the likelihood of pregnancy of a singleton but not of a multiple. The multiple birth rate increases considerably when three, instead of two, embryos are transferred. Therefore, the increase in multiple birth rate due to IVF can be

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considerably reduced by transferring no more than two embryos after IVF.

Inheritance of language skills in children

Language development in children is, not surprisingly, affected by both genetic and environmental conditions. Even the (genetically) most talented child remains verbally retarded if there is no 'verbal' (speaking parents and friends) environment. And, conversely, the verbally undertalented child will manifest as an individual with normal verbal skills when growing up in 'linguophile' surroundings. This prescientific knowledge has recently been confirmed, quantified and extended in an interesting way by Philip Dale and colleagues in the US and UK.[5] They assessed the vocabulary (number of words a child uses actively) in more than 1000 MZ and nearly 2000 DZ twin pairs, aged about two years. The investigators applied model-fitting procedures for the lowest 5% of the vocabulary distribution and for the total sample and found that heritability among the delayed group was about 73% of the variance, whereas this figure was only 25% in the total sample. This suggests that early language delay has to be considered as a distinct disorder with different causes than those that hold for the normal variation in childhood verbal skills. The findings of Dale et al are in accordance with the known fact that shared environmental influences (about 18%) are less significant for retardation in language delay than for normal language abilities (about 69%). Therefore, the search for genes (quantitative trait loci or QTLs) that contribute to language delay, seems to be easier than that for language ability in children in general.

Hay fever

Hay fever runs in families. Is this because of shared genes or shared environment? Finnish twins have contributed to the answer to this question. Investigators from the university of Helsinki[6] have interrogated nearly 2500 16-year-old twin pairs via a mailed questionnaire, asking both the twins and their parents about 'physician-diagnosed' hay fever. Of these twins, 1765 pairs returned the questionnaire. The researchers found that about 75% of variability in liability to hay fever could be ascribed to genetic factors, no more than about 7% to shared environmental factors and 18% to unique environmental influences. Family influences seem thus to be of negligible value, the research team concludes.

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Twins Days in Twinsburg

Twinsburg, Ohio (http://www.twinsburg.com/) is a small town just south of Cleveland. Every year in the first weekend in August, starting in 1976, the town has hosted the Twins Days Festival where twins and parents of twins from around the world meet to socialize and have fun together. The festival organizers maintain a very informative web page at http://www.twinsdays.org/ The most recent festival was held 31 July to 2 August 1998 and the next festival will be held on 6–8 August 1999. The official attendance count for the 1998 meeting was 2,642 sets of twins and other multiples. This count was based on the number that paid the $8.00 USD registration fee, but unofficial counts exceeded 3,000 sets. In past years, the twins have come from all 50 of the United States and from 10–15 other countries including Austria, Romania, Russia, Hungary, Poland, the United Kingdom, Canada, and Korea.

Excepting the obvious methodological limitation that ascertainment of twins is not systematic, the Twins Days Festival provides an excellent resource for researchers. There are few places where researchers can have face-to-face contact with a large number of twins in a short period of time. Unfortunately, I could find no information about research on the Twins Days web page, so I spoke with Sandy Miller (no relation), one of the festival organizers, about opportunities for researchers.

According to Ms. Miller, researchers may apply to the Twins Days organizing committee for a $1,000 USD grant. The application is reviewed by a panel of researchers whose decision to fund the research is based on the merit of the proposal and on their perception of the level of interest the research will generate among the twins at the festival. The research is usually medical but it could be behavioral. They try to limit the total number of research projects to six, so fewer than six grants would be funded. A research pavilion is erected on the festival grounds to protect researchers against rain and to house booths for the research projects. The costs of conducting research at the festival include a $600 USD fee to cover the cost of the pavilion, the booth and electricity. It should be possible to plug computers into electrical outlets at the research pavilion. In past years, some researchers have parked vans outside the pavilion to provide additional research space. Ms. Miller has worked with Twins Days for 17 years and she has known many researchers, but she only knows of two

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researchers who paid twins to participate in research. Sandy Miller and others are currently in the process of setting up a twins museum in Twinsburg that may hold all of the published papers that used data collected at the festival. The Twins Days Festival organizers (including Sandy Miller) can be reached at (303) 425–3652 or by e-mail to info@twinsdays.org.

Risks of anticoagulant use in IVF pregnancies

A 38-year-old woman, nine weeks pregnant with triplets as a result of in vitro fertilization (IVF), died from massive cerebral swelling following a surgical attempt to stop a brain hemorrhage. The woman had been undergoing anticoagulant therapy with heparin and aspirin — a tactic that is often used to reduce risk of miscarriage in IVF pregnancies. Because of concern that her death may have been related to her use of anticoagulant drugs, the United States' Centers for Disease Control (CDC) assisted state and local health departments in a two-year investigation of the case. A summary report of the investigation was published as part of the 15 May 1998 Morbidity and Mortality Weekly Report (MMWR; pp. 368–371) which can be found at the following URL: http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/00052611.htm.

Treatment with heparin and aspirin (both anticoagulant drugs) has proven effective for women with elevated antiphospholipid antibodies (APA) and a history of early pregnancy loss. The drugs modify the effect of APA on platelet activity and thereby reduce risk of placental thrombosis. Heparin and aspirin are also effective in reducing risk of thromboembolism in surgical patients, but the same studies that demonstrate a salutary effect on thromboembolism risk also establish an adverse effect on risk of hematoma formation and serious bleeding (see the MMWR report for references).

The CDC report concluded that it was not possible to demonstrate a causal relation of anticoagulant therapy and hemorrhage from this single case. (According to the report, "This case is the first reported pregnancy-related death associated with use of heparin and aspirin for infertility." p. 370). However, the report noted that "Because the potential for bleeding exists with heparin and aspirin, the risks for and benefits of anticoagulation therapy to improve success rates in IVF patients require vigorous scientific investigation before being accepted as routine practice." (p. 370). They also note that although the U.S. Food and Drug Administration (FDA) has not approved either heparin or aspirin (alone or in combination) for use by IVF patients, this use is apparently quite common in the United States (74% of respondents in a July 1997 survey of medical practices that provide assisted reproductive technology admitted at least one use of heparin/aspirin combination therapy). Sadly, the pregnant IVF patient whose death triggered the investigation did not have an elevated APA, the major putative indicator for anticoagulant therapy.

Exercise and the twin pregnancy

A paper in the October 1998 issue of the American Journal of Public Health (vol. 88, pp. 1528–1533), by researchers at Columbia School of Public Health, reported on correlates of exercise in a sample of 557 U.S. middle class mothers-to-be. The researchers noted that, in the United States, about 40% of pregnant women engage in regular exercise. They found that low-moderate levels of exercise had no association with gestational length and that heavier levels of exercise were associated with lower risk of preterm birth and with quick deliveries.

This should be encouraging news for pregnant women who enjoy exercise, but what about exercise in twin pregnancies? I know of no systematic epidemiological research on exercise in twin pregnancies, but an interesting case study of a female distance runner was published in the 18 April 1998 issue of The Lancet (vol. 351, p. 1182). The 33-year-old woman was a champion runner whose best marathon (26.2 miles or 42.2 km) time was 2 hours, 36 minutes. She was pregnant with twins, yet she ran 107 km (66 miles) per week until three days before giving birth by elective cesarean section in her 36th week of pregnancy. She started training again eight days later. This athlete's exercise regimen was surely so demanding that it would not appeal to most pregnant women. In fact, the authors of the paper warned that such high levels of exercise should not be undertaken by female athletes who were not well-conditioned before pregnancy. Also, this woman's health was monitored closely by a team of physicians throughout her pregnancy. Still, the favorable outcome shows that vigorous exercise (but with heart rate less than 150 beats per minute) needn't be prohibited in twin pregnancies.

Clone Watch

Martha Stewart: The first human Dolly?

As far as science has been able to determine, all genetically-identical pairs of humans are monozygotic (MZ) twins. Most people seem fascinated by MZ twins and are amazed by their similarities and differences. From my observations, genetic identity seemed to be regarded as a greater good than the mere genetic half-similarity enjoyed by siblings and dizygotic twins. When Ian Wilmut announced in February 1997 that he had succeeded in cloning a lamb named Dolly from a mammary gland cell of an adult ewe, shouldn't we have been surprised when he also announced that he "would find it offensive" to clone a human being and that he fervently hoped no one would try it? (To be precise, Wilmut's method of nuclear somatic transfer clones only the nuclear DNA and not the extranuclear DNA of the adult animal). The President of the United States had a similar negative reaction. When Dr. Richard Seed, a physicist, promised in January 1998 to clone a human, Bill Clinton responded that this was "profoundly troubling news."

I wondered why the notion of human cloning had so offended Wilmut and troubled the President. My curiosity was partially sated by a New York Times article of 14 February 1998 reporting that Wilmut was uncomfortable with the unusual family relationships that cloning would create. He was quoted as saying that if he were cloned, "my wife would grow up not just with me but with a copy of me...How would my wife respond to a teen-age copy of me?...How would I

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respond to a teen-age copy of me?" Perhaps Dr. Wilmut was a difficult teenager.

Despite Dr. Wilmut's concerns, several people have announced plans to clone themselves. A man calling himself Rael (http://www.rael.net/) and claiming to be "the last embassador [sic]" to Earth of an extra-terrestrial species, announced his plan soon after the Dolly result was made public. Rael leads the Raelian Religion and claims 35,000 members in 84 countries. Richard Seed announced in September 1998 he would attempt to clone himself, and that his post-menopausal wife would carry the embryo. Rael has created a company called Clonaid (http://www.clonaid.com/) that intends to fund human cloning projects, including Richard Seed's project (http://www.rael.net/web/aclone2.html). I do not know if Seed plans to work with Rael, nor do I know if either of them seriously intends to attempt human cloning.

In a strange twist, Martha Stewart (http://www.marthastewart.com/), the well-known expert on all things domestic, was quoted in the September 1998 issue of Nature Genetics (vol. 20, no. 1) saying, "Cloning hasn't worked yet, but I'll be the first. The first human Dolly will be me." (p. 11). The journal gave no further information on Stewart's plans. She is often the brunt of jokes about her excessive domesticity, and this may be a joke of her own, or maybe she truly wishes to have a second Martha to hang hand-made Christmas tree ornaments while she serves the cranberry steamed pudding.

"Twins born apart" are doing well

We hear often of "twins reared together" and "twins reared apart," but what of twins born apart? In fact, unless they are conjoined, twins are never born at exactly the same time and the separation in time of birth is sometimes surprisingly large. The Associated Press carried a story on 11 October 1998 announcing the fourth birthday of the first-born member of a record-holding pair of twins. Timothy was born prematurely on 15 October 1994, but his twin sister, Celeste, was born full-term on 18 January 1995. According to the Associated Press report, this 95 day separation in birth date is a record for twins.

At birth, Timothy weighed only 1lb., 14 oz. (850 g.) and required a three month hospital stay. He lagged behind Celeste in developmental milestones for the first six months of his life, but he has since caught up in every domain. Now Celeste is jealous of Timothy because he gets his birthday presents three months before she gets hers!

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