

## In the Literature

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This section of News and Views will present updates of recent advances in the medical and scientific literature.

### **A Polymorphic Genomic Duplication on Human Chromosome 15 is a Susceptibility Factor for Panic and Phobic Disorders**

Panic disorder, which manifests itself as unexpected and recurrent attacks of anxiety, affects several million people worldwide. One of a heterogeneous group of psychiatric conditions, it is frequently associated with other anxiety disorders including phobic disorders and depression. Panic disorder, as well as anxiety disorder in general, is considered a complex disease which suggests interplay between genes and the environment. Previous work has shown that the disorder runs in families and that the risk of disease is higher in first-degree relatives. Recent research has also illustrated a clear association between joint laxity (hypermobility) and anxiety disorders. Gratacos and colleagues have identified several Spanish families affected by panic/phobia disorders and/or joint laxity. Using cytogenetic and molecular techniques, the group revealed a duplication of chromosome 15q24-26 (designated DUP25) associated with the clinical phenotypes in these families. Within the families, 90% of the members with anxiety had DUP25 and 87% of the members with joint laxity had DUP25 (compared to 7% of controls). This duplication, however, does not appear to be sufficient for panic disorder/joint laxity because of variable penetrance; not all patients with DUP25 have both manifestations. Another confounding aspect is that DUP25 exists as a somatic mosaicism since patients' cells are variable in relation to the duplication. DNA sequence repeats that flank the duplication region, possibly in concert with additional genetic factors, are considered to be the mechanism by which unequal chromosomal crossover occurs during mitosis, leading to somatic mosaicism. The existence of DUP25, as well as its association with panic disorder and joint laxity, suggests that gene dosage (i.e., overexpression of one or more genes in the duplication) and possibly environmental influences are responsible for the clinical phenotypes. The relevance of the study lies not only in the concept that the duplication of 15q25 is a genetic susceptibil-

ity for a complex psychiatric condition like panic disorder, but that the non-Mendelian somatic mosaicism of chromosomal rearrangements observed herein is a previously unidentified mechanism by which disease may be conferred.

*Gratacos M, Nadal M, Martin-Santos R, et al. (2001). Cell. 106:367-379.*

### **Mortality among Patients Admitted to Ontario Hospitals on Weekends as Compared to Weekdays**

Despite a consistent day-to-day incidence of medical emergencies, the level of staffing in acute care hospitals tends to be lower on weekends than on weekdays. This may lead to shortfalls in patient care and management associated with weekend hospital admissions. Previous work investigating neonatal mortality, as well as the care of frequent medical emergencies such as stroke, myocardial infarction (MI) and drug overdoses, suggests that hospitals may be less effective on weekends as compared to weekdays. A recent study by Bell and Redelmeier examined the relationship between in-hospital mortality of patients with serious medical conditions and weekend versus weekday admission. All acute care admissions from emergency departments in Ontario, Canada between 1988 and 1997 (a total of 3,789,917 admissions) were classified by the ICD-9 code that corresponded to their primary reason for hospital stay. Patients were then grouped according to weekend or weekday admission and in-hospital mortality rates for each group were determined. The authors hypothesized that the care of patients with 'positive' medical conditions (ruptured abdominal aortic aneurysm, acute epiglottitis and pulmonary embolism) would be aggravated by the consequences of lower staffing levels on weekends. Indeed, results of the study indicated that these patients had significantly higher mortality rates when admitted on a weekend as compared to a weekday. This finding persisted after adjustment for age, sex, and coexisting disorders. By comparison, patients with control conditions, hypothesized to have

equivalent day-to-day mortality rates (MI, intracerebral hemorrhage, and acute hip fracture), did not differ in their risk of death according to weekend or weekday admission. The authors also investigated the 100 most frequent causes of death among the study population and 23 of these were found to be associated with a relative increase in mortality if admitted on the weekend. Conversely, weekend admission was not associated with reduced mortality rates for any of the 100 conditions. Based on these findings, Bell and Redelmeier suggest that health care providers should be concerned about an increased risk of death among patients admitted to hospitals on weekends and that greater emphasis should be placed on weekend provision of care.

*Bell CM and Redelmeier DA. (2001). NEJM. 345(9): 663-667.*

### **Short-Term Exposure to Pregnancy Levels of Estrogen Prevents Mammary Carcinogenesis**

Breast cancer is the most common cancer among women worldwide. Epidemiological evidence points to a host of risk factors, including the environment, genetics, and hormones. Within the latter, a role has been suggested for reproductive hormones, such as endogenous ovarian steroids, in the development of breast cancer. It is well established that pregnancy early in life reduces the risk of breast cancer in women. This is a phenomenon known as 'parity protection'. Earlier studies have demonstrated in a rat model that the short-term administration of estradiol in combination with progesterone mimics this protective effect and reduces the incidence of mammary cancer. Research by Rajkumar and colleagues sought to further this work by determining the minimum estradiol dosage required for prevention of mammary cancer in the rat model. An i.p. injection of the carcinogen N-methyl-N-nitrosourea was given to the rats at 7 weeks of age. Subsequently, they underwent a 3-week course of sustained treatment with 20 µg, 100 µg, 200 µg or 30 mg of estradiol via subcutaneous capsules. The rats were then palpated for mammary cancer development, which was confirmed by histopathological examination. Treatment with 100 µg, 200 µg or 30 mg of estradiol resulted in serum levels equivalent to those found during pregnancy and resulted not only in a significant decrease in the incidence of mammary tumors but in the absolute number of tumors as well. An increased latency towards carcinogenesis was also observed in these rats. Conversely, rats treated with 20µg of estradiol did not show levels in their serum corresponding to pregnancy and subsequently did not demonstrate parity protection from tumor development. The authors also investigated the effect of different durations of hormone treatment and the benefit of concomitant progesterone administration on mammary cancer incidence. By varying the length of exposure to treatment, it was determined that a period as short as 1 week (one-third of a rat's gestational term) is sufficient to induce protection

against carcinogenesis. Comparison of estradiol regimens with and without progesterone indicated that a combination of the two hormones yields superior protection. Thus, the authors speculate that in contrast to long-term estrogen exposure, which is thought to increase the risk of breast cancer, short-term exposure mimicking parity may constitute protection against mammary tumorigenesis.

*Rajkumar L, Guzman RC, Yang J, et al. (2001). PNAS. 98(20): 11755-11759.*

### **Hearing Babies Born to Deaf Parents Babble Silently with their Hands**

The function of babbling by babies has long been the subject of debate. Two theories have been advanced in this regard: the motor hypothesis, which regards babbling as simply the result of the opening and closing of the baby's mouth and jaw, and the linguistic hypothesis, in which babbling reflects the baby's learning and application of rhythmic patterns in human language. In order to test these hypotheses, Petitto and colleagues studied two groups of hearing babies: those solely exposed to sign language from deaf parents and those exposed only to spoken language from hearing parents (n=3 for each group). They hypothesized that if babbling were simply a motor phenomenon, then the observed hand activity of both groups should be similar. In contrast, hand activity should differ if the linguistic hypothesis were correct, as hearing babies born to deaf parents would acquire language patterns, or 'babble', with their hands. To this end, hand activity for each baby was recorded in three dimensions using Optotrak, an optoelectronic position-tracking system, in one hour sessions at six, ten and twelve months of age. Blind to Optotrak measurements, videotape recordings were also made for subjective observation of the hand movements. Analysis revealed that sign-exposed babies demonstrate a high-frequency rhythmic hand activity that speech-exposed babies use almost exclusively. Intriguingly, a low-frequency, or slower, set of rhythmic hand movements unique to the sign-exposed babies was also observed. This low-frequency hand activity occurred in a space restricted to the front of the body (82% of these movements), whereas the high-frequency movements observed in both groups occurred outside this space (73%). The spatial and frequency characteristics of these unique hand movements corresponded via Optotrak assessment to the rhythmic patterning of adult sign language syllables. Videotape recordings qualitatively confirmed the similarity in appearance of the low-frequency movements with adult signing. These results support the theory that babbling is used by babies as a method for learning language through rhythmic patterns and that, for hearing babies of deaf parents, babbling is manifested as a novel class of hand activity.

*Petitto LA, Holowka S, Sergio LE, et al. (2001). Nature. 413: 35-36.*

### **Risk of Cardiovascular Events Associated with Selective COX-2 Inhibitors**

The analgesic, anti-inflammatory, and anti-thrombotic properties of aspirin and non-steroidal anti-inflammatory agents (NSAIDs) are well-established. However, they also have a tendency towards gastric toxicity due to a function of the inhibition of the COX-1 enzyme. The development of the COX-2 inhibitors, a new class of NSAIDs, came in response to this adverse effect. While the COX-1 enzyme is ubiquitously expressed and produces gastroprotective prostaglandins, the COX-2 isoform is induced primarily in inflammatory conditions and leads to pain, swelling and discomfort. COX-2 inhibitors, such as rofecoxib and celecoxib, have increased in popularity since their introduction in 1999. Several randomized clinical trials have been conducted on the effects of these new drugs. However, little is known about their association with adverse cardiovascular events. Mukherjee and colleagues indicate that selective COX-2 inhibitors tend to decrease prostacyclin (PGI<sub>2</sub>) production, a vasodilator and inhibitor of platelet aggregation. This may shift the balance towards a prothrombotic environment and, therefore, pose an increased risk of cardiovascular thrombotic events. In order to examine this relationship, the authors undertook a meta-analysis of randomized clinical trials of COX-2 inhibitors used for arthritis and musculoskeletal pain in patients without previous coronary artery disease. The double-blind Vioxx Gastrointestinal Outcomes Research Study (VIGOR; 8076 patients) demonstrated a relative risk of 2.38 of developing a cardiovascular event (including myocardial infarction, unstable angina, cardiac thrombus, ischemic stroke, and transient ischemic attacks) in the rofecoxib treatment group as compared to the naproxen (anti-COX-1 NSAID) group. Conversely, when the COX-2 inhibitor group was compared to other NSAIDs (ibuprofen, diclofenac) in the double-blind Celecoxib Long-Term Arthritis Safety Study (CLASS; 8059 patients), no significant increase in cardiovascular events were found. This result may have been due to the allowance of low-dose aspirin use, which may have provided anti-platelet aggregation effects, counteracting the actions of the COX-2 inhibitor. Annualized myocardial infarction rates from the VIGOR and CLASS trials were compared with the rate in a placebo group from a separate meta-analysis and found to be significantly higher: 0.74% for rofecoxib and 0.80% with celecoxib compared with 0.52% for the placebo. Several important clinical questions are raised with regard to the future use of selective COX-2 inhibitors including their prothrombotic potential and the need for concomitant aspirin use to negate these effects. Mukherjee, Nissen, and Topol urge caution in the prescription of these agents until further work is done to assess their effects on the cardiovascular system.

*Mukherjee D, Nissen, SE and Topol EJ. (2001). JAMA. 286(8): 954-959.*

### **Association between Bone Mass and Breast Cancer Risk in Older Women**

Prolonged estrogen exposure may have a significant role in the development of breast cancer in older women. Bone contains estrogen receptors and is sensitive to manipulation of its density by serum levels of estrogen. Previous research has therefore suggested that bone mineral density (BMD) may serve as a powerful marker of breast cancer risk in elderly women, as it reflects the amount of long-term exposure to endogenous estrogen. Zmuda and colleagues hypothesized that this association may be true not only for early-stage breast cancer tumours, but advanced-stage as well. 8905 participants were assessed initially for BMD by single-photon absorptiometry at three locations: the proximal radius, distal radius, and calcaneus. The patients were then divided into quartiles based on their BMD values. The women were followed for a period of up to 12 years (1986-1998) to determine subsequent development of breast cancer. Breast tumour incidence was found to increase with escalating BMD for each anatomical location. This was also true when BMD at the three locations was grouped together; women who were in the highest quartile for BMD at all three sites had a 2.8 times greater risk of breast cancer than women in the lowest quartile at all three sites. These findings persisted after adjustment for known and suspected breast cancer risk factors, such as age, body mass index, age at menarche and menopause, nulliparity and estrogen use. The strength of the association between BMD and breast cancer risk was also greater among women diagnosed with advanced breast cancer as compared to early-stage cancer. This suggests that biological factors associated with a high BMD may accelerate the growth rate and progression of tumours. On the basis of these results, the authors speculate that BMD, along with other risk factors, may serve as a useful marker in identifying women at high risk for breast cancer. This study also proposes an inverse relationship between osteoporosis and breast cancer, two of the most common conditions affecting the health of older women.

*Zmuda JM, Cauley, JA, Ljung B-M et al. (2001). J Natl Cancer Inst. 93(12): 930-936.*