doi: 10.3325/cmj.2010.51.177

CROATIAN INTERNATIONAL PUBLICATIONS

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Rudan I, Chan KY, Zhang JSF, Theodoratou E, Feng XL, Salomon JA et al. Causes of deaths in children younger than 5 years in China in 2008. Lancet 2010;375:1083-9

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Background. Previous estimates of the global burden of disease for children have not included much information from China, leading to a large gap in data. We identified the main causes of deaths in neonates (<1 month), postneonatal infants (1–11 months), and children (<5 years) in China using information that was available to the public. Methods. The Child Health Epidemiology Reference Group in collaboration with colleagues from Peking University systematically searched Chinese databases that were available to the public. Information was obtained from the Chinese Ministry of Health and Bureau of Statistics websites, Chinese National Knowledge Infrastructure database, and Chinese Health Statistics yearbooks for 1990–2008. We also obtained information from 206 high-quality community-based longitudinal studies of different causes of deaths in children (<5 years) that were written in the Chinese language. A statistical model was developed to estimate the total number of deaths in children according to provinces, age groups, and main causes. Findings. During 1990–2008, the mortality rates in neonates, postneonatal infants, and children were reduced by 70% (from 34·0 to 10·2 per 1000 livebirths), 72% (from 53·5 to 14·9 per 1000 livebirths), and 71% (from 64·6 to 18·5 per 1000 livebirths), respectively, meeting the targets set in the Millennium Development Goal 4. The leading causes of deaths in 2008 were pneumonia, birth asphyxia, and preterm birth complications, each accounting for 15–17% of all deaths. Congenital abnormalities and accidents increased in importance during this period, contributing to 11% and 10% of child deaths, respectively. Sudden infant death syndrome contributed to 5% of deaths in children. Interpretation. Publically available Chinese databases contain much important information that has been underused in the estimation of global and regional burden of disease. On the basis of trends, preterm birth complications are expected to become the leading cause of child mortality in China, whereas deaths from congenital abnormalities, accidents, and sudden infant death syndrome are predicted to continue increasing in importance in the long term.

Polašek O, Hayward C, Bellenguez C, Vitart V, Kolčić I, McQuillan R et al. Comparative assessment of methods for estimating individual genome-wide homozygosity-by-descent from human genomic data. BMC Genomics. 2010;11:139.

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Background. Genome-wide homozygosity estimation from genomic data is becoming an increasingly interesting research topic. The aim of this study was to compare different methods for estimating individual homozygosity-by-descent based on the information from human genome-wide scans rather than genealogies. We considered the four most commonly used methods and investigated their applicability to single-nucleotide polymorphism (SNP) data in both a simulation study and by using the human genotyped data. A total of 986 inhabitants from the isolated Island of Vis, Croatia (where inbreeding is present, but no pedigree-based inbreeding was observed at the level of $F > 0.0625$) were included in this study. All individuals were genotyped with the Illumina HumanHap300 array with 317,503 SNP markers. Results. Simulation data suggested that multi-point FEstim is the method most strongly correlated to true homozygosity-by-descent. Correlation coefficients between the homozygosity-by-descent estimates were high but only for inbred

individuals, with nearly absolute correlation between single-point measures. Conclusions. Deciding who is really inbred is a methodological challenge where multi-point approaches can be very helpful once the set of SNP markers is filtered to remove linkage disequilibrium. The use of several different methodological approaches and hence different homozygosity measures can help to distinguish between homozygosity-by-state and homozygosity-by-descent in studies investigating the effects of genomic autozygosity on human health.

Brešković T, Ivančev V, Banić I, Jordan J, Dujić Ž. Peripheral chemoreflex sensitivity and sympathetic nerve activity are normal in apnea divers during training season. Auton Neurosci. 2010;154:42-7.

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Apnea divers are exposed to repeated massive arterial oxygen desaturation, which could perturb chemoreflexes. An earlier study suggested that peripheral chemoreflex regulation of sympathetic vasomotor tone and ventilation may have recovered 4 or more weeks into the off season. Therefore, we tested the hypothesis that peripheral chemoreflex regulation of ventilation and sympathetic vasomotor tone is present during the training season. We determined ventilation, heart rate, blood pressure, cardiac stroke volume, and muscle sympathetic nerve activity (MSNA) during isocapnic hypoxia in 10 breath hold divers and 11 matched control subjects. The study was carried out at the end of the season of intense apnea trainings. Baseline MSNA frequency was 30+/-4bursts/min in control subjects and 25+/-4bursts/min in breath hold divers (P=0.053). During hypoxia burst frequency and total sympathetic activity increased similarly in both groups. Sympathetic activity normalized during the 30-minute recovery. Hypoxia-induced stimulation of minute ventilation was similar in both groups, although in divers it was maintained by higher tidal volumes and lower breathing frequency compared with control subjects. In both groups, hypoxia increased heart rate and cardiac output whereas total peripheral resistance decreased. Blood pressure remained unchanged. We conclude that peripheral chemoreflex regulation of ventilation and sympathetic vasomotor tone is paradoxically preserved in apnea divers, both, during the off and during the training season. The observation suggests that repeated arterial oxygen desaturation may not be sufficient explaining sympathetic reflex abnormalities similar to those in obstructive sleep apnea patients.

Zhi L, Mans J, Paskow MJ, Brown PH, Schuck P, Jonjić S* et al. Direct interaction of the mouse cytomegalovirus m152/gp40 immunoevasin with RAE-1 isoforms. Biochemistry. 2010;49:2443-53.

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Cytomegaloviruses (CMVs) are ubiquitous species-specific viruses that establish acute, persistent, and latent infections. Both human and mouse CMVs encode proteins that inhibit the activation of natural killer (NK) cells by downregulating cellular ligands for the NK cell activating receptor, NKG2D. The MCMV glycoprotein m152/gp40 downregulates the surface expression of RAE-1 to prevent NK cell control in vivo. So far, it is unclear if there is a direct interaction between m152 and RAE-1 and, if so, if m152 interacts differentially with the five identified RAE-1 isoforms, which are expressed as two groups in MCMV-susceptible or -resistant mouse strains. To address these questions, we expressed and purified the extracellular domains of RAE-1 and m152 and performed size exclusion chromatography binding assays as well as analytical ultracentrifugation and isothermal titration calorimetry to characterize these interactions quantitatively. We further evaluated the role of full-length and naturally glycosylated m152 and RAE-1 in cotransfected HEK293T cells. Our results confirmed that m152 binds RAE-1 directly, relatively tightly (K(d) < 5 microM), and with 1:1 stoichiometry. The binding is quantitatively different depending on particular RAE-1 isoforms, corresponding to the susceptibility to downregulation by m152. A PLWY motif found in RAE-1beta, although contributing to its affinity for m152, does not influence the affinity of RAE-1gamma or RAE-1delta, suggesting that other differences contribute to the RAE-1-m152 interaction. Molecular modeling of the different RAE-1 isoforms suggests a potential site for the m152 interaction.

Navarro P, Vitart V, Hayward C, Tenesa A, Zgaga L*, Juričić D* et al. Genetic comparison of a Croatian isolate and CEPH European founders. Genet Epidemiol. 2010;34:140-5.

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Human isolates have been postulated as a good resource for the identification of QTL due to reduced genetic diversity and a more homogeneous environment. Isolates may

also have increased linkage disequilibrium (LD) due to small effective population size and, either loss or increase in frequency of alleles that are rare in the general population from which they originate. Here we investigate the difference in allele and genotype frequencies, LD and homozygous tracts between an isolate-several villages from the island of Vis in Croatia-and an outbred population of European origin: the Hapmap CEPH founders. Using the HumanHap300 v1 Genotyping BeadChip, we show that our population does not differ greatly from the reference CEU outbred population despite having a slightly higher proportion of monomorphic loci, a slightly higher long-range LD, and a greater proportion of individuals with long homozygous tracts. We conclude that genotyping arrays should perform equally well in our isolate as in outbred European populations for disease mapping studies and that SNP-trait associations discovered in our well-characterized Croatian isolate should be valid in the general European population from which they descend.

Hadzisejdić I, Mustać E, Jonjić N, Petković M, Grahovac B. Nuclear EGFR in ductal invasive breast cancer: correlation with cyclin-D1 and prognosis. Mod Pathol. 2010;23:392-403.

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The epidermal growth factor receptor (EGFR)-family and cyclin-D1 have been extensively studied in breast cancer; however systematic studies that examine protein expression and gene status in the same cohort of patients are lacking. Also emerging evidences suggest existence of a direct EGFR-signaling pathway, which involves cellular transport of EGFR from cell membrane to the nucleus, and transcriptional regulation of the target genes. Thus, we examined the protein expression of membrane EGFR, nuclear EGFR, cyclin-D1 and the corresponding gene status in 113 breast carcinomas by immunohistochemistry and fluorescence in situ hybridization using tissue microarrays. Membrane EGFR overexpression and EGFR gene amplification were detected in 2% cases, while nuclear EGFR was detected in 40% of cases, with 12% having high nuclear EGFR staining. Nuclear EGFR correlated with tumor size (P=0.0005), lymph node metastasis (P=0.0288), Nottingham prognostic index (P=0.0011) and estrogen receptor (ER) expression (P=0.0258) but the letter correlation was observed only in premenopausal group of patients. Strong cyclin-D1 expression and cyclin-D1 gene (CCND1) amplification were found in 64 and 13% of the cases, respectively. Cyclin-D1 expression showed positive correlation with ER (P=0.0113) and inverse correlation with Nottingham prognostic index (P=0.0309) and membrane EGFR (P=0.0201). CCND1 amplification also showed inverse correlation with membrane EGFR (P=0.0420). A strong correlation between membrane EGFR expression and gene amplification (P=0.0035), as well as cyclin-D1 overexpression and gene amplification (P=0.0362), was demonstrated. On univariate analysis cyclin-D1 expression showed a correlation with longer overall survival in the premenopausal group and nuclear EGFR correlated with shorter overall survival in whole cohort as well in the premenopausal group of patients. Multivariate analysis revealed nuclear EGFR to be an independent prognostic factor and showed 3.4 times greater mortality risk for nuclear EGFR+++ patients as compared with nuclear EGFR negative patients (hazard ratio =3.402; P=0.0026).

Erratum

A mistake was noticed in the spelling of authors' names in an article published in the Croatian Medical Journal in 1994. The correct bibliographical information is: Matanović B, Kovačić K, Kovač I, Kovač V. The influence of functional characteristics of above-knee stump on lumbosacral spine degenerative changes Croat Med J, 1994;111-112.