CROATIAN INTERNATIONAL PUBLICATIONS

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Bojanić I, Dubravčić K, Batinić D, Čepulić BG, Mazić S, Hren D, Nemet D, Labar B. Large volume leukapheresis: Efficacy and safety of processing patient's total blood volume six times. Transfus Apher Sci. 2011;44:139-47.

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Large-volume leukapheresis (LVL) differs from standard leukapheresis by increased blood flow and an altered anticoagulation regimen. An open issue is to what degree a further increase in processed blood volume is reasonable in terms of higher yields and safety. In 30 LVL performed in patients with hematologic malignancies, 6 total blood volumes were processed. LVL resulted in a higher CD34+ cell yield without a change in graft quality. Although a marked platelet decrease can be expected, LVL is safe and can be recommended as the standard procedure for patients who mobilize low numbers of CD34+ cells and when high number of CD34+ cells are required.

Kuzman MR, Medved V, Božina N, Grubišin J, Jovanović N, Sertić J. Association study of MDR1 and 5-HT2C genetic polymorphisms and antipsychotic-induced metabolic disturbances in female patients with schizophrenia. Pharmacogenomics J. 2011;11:35-44.

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The objective of this study was to determine the association of 5-HT2C (serotonin 2C receptor) and MDR1 (multidrug resistant protein) genetic polymorphisms and antipsychotic-induced metabolic abnormalities among female patients with DSM IV schizophrenia spectrum disorders. We have previously reported the associations of -759CT 5-HT2C and G2677T and C3435T MDR1 genetic polymorphisms and olanzapine/risperidone-induced weight gain in a similar sample of patients. Here, we included a total of 101 previously non-medicated female patients treated with olanzapine/risperidone over a 3-month period. The variables analyzed included fasting glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein and triglyceride levels in blood, blood pressure and waist circumferences. We observed significant association of -759T 5-HT2C genetic variant and greater increase in waist circumference (P=0.03), fasting glucose level (P=0.046) and triglyceride level (P=0.045) in blood after a 3-month period. The 2677T and 3435T MDR1 genetic variants were significantly associated with the greater increase in fasting glucose level in blood when patients were using olanzapine (P<0.001 and P=0.028, respectively). Our data indicate a possible influence of -759CT 5-HT2C and MDR1 G2677T and C3435T MDR1 genetic polymorphisms on the development of metabolic abnormalities among female patients treated with olanzapine/risperidone.

Gršković B, Mršić G, Polašek O, Vrdoljak A, Merkaš S, Anđelinović S. Population data for 17 short tandem repeat loci on Y chromosome in northern Croatia. Mol Biol Rep. 2011;38:2203-9.

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Human Y-short tandem repeats (STRs) are tandem repeat arrays of two to seven base pair units on non-recombining region (NRY) of the human Y chromosome. Studies on Y-STR are interesting in both population genetics and forensics. The aim of this study was to investigate the population genetic properties of 17 STR loci on Y chromosome in the northern Croatia region. We carried out a statistical analysis of the data from previously performed genetic analysis collected during routine forensic work by the Forensic Science Centre "Ivan Vučetić". A total of 220 unrelated healthy men from northern Croatia were selected for the purpose of this study. Genomic DNA was extracted using Chelex procedure from FTA(®) cards. Y-chromosomal STRs were determined using the AmpFISTR Yfiler PCR amplification kit. The haplotype frequencies were determined by direct counting and analyzed using Arlequin 3.1

and analysis of molecular variance calculated with the Y chromosome haplotype reference database online analysis tool. A total of 210 haplotypes were identified, 200 of which were unique. Total haplotype diversity was 0.995. Locus diversity varied from 0.331 for DYS392 to 0.783 for DYS385 locus. Allele frequencies diversity was 0.662. Discrimination capacity was 95.7%. The use of European minimal haplotype set indicated the most resemblance of this population to the Croatian capital of Zagreb, with modest resemblance to Bosnia and Herzegovina, Serbia and Hungary. This article provides the first overview of the Y chromosome STR variability in northern Croatia, thus providing the referent point for any future forensic and genetic epidemiology efforts in this region.

Novokmet N, Marjanović D, Škaro V, Projić P, Lauc G, Grahovac B, Ostojić S, Kapović M, Rudan P. Genetic polymorphisms of 15 STR loci in the population of the island of Cres (Croatia). Ann Hum Biol. 2011;38:12-21.

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BACKGROUND: The population of the island of Cres presents one of the few persisting Eastern Adriatic isolates and is thereby suitable for human population differentiation analyses.
AIM: The aim of this study was to analyse the genetic structure of the island of Cres with respect to its eight sub-populations and to compare the genetic variation of the island of Cres with other Eastern Adriatic islands and the Croatian mainland.
SUBJECTS AND METHODS: Fifteen AmpFlSTR identifiler loci were analysed in a sample group of 122 unrelated autochthonous individuals from the island of Cres, Croatia.
RESULTS: Analysis of STR polymorphisms revealed genetic homogeneity among sub-populations of the island of Cres and small but significant levels of genetic heterogeneity among geographically distant Eastern Adriatic islands.
CONCLUSION: Despite a considerable degree of genetic homogeneity among the studied Eastern Adriatic islands, small but significant differentiation between distant islands indicates geographic sub-structuring which follows the isolation by distance model. This study is supportive of the notion that STR markers are useful for genetic differentiation between larger and geographically more distant regions.

Pivac N, Knezević A, Gornik O, Pucić M, Igl W, Peeters H, Crepel A, Steyaert J, Novokmet M, Redzić I, Nikolac M, Hercigonja VN, Curković KD, Curković M, Nedić G, Muck-Seler D, Borovecki F, Rudan I, Lauc G. Human plasma glycome in attention-deficit hyperactivity disorder and autism spectrum disorders. Mol Cell Proteomics. 2011;10:M110.004200.

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Over a half of all proteins are glycosylated, and their proper glycosylation is essential for normal function. Unfortunately, because of structural complexity of nonlinear branched glycans and the absence of genetic template for their synthesis, the knowledge about glycans is lagging significantly behind the knowledge about proteins or DNA. Using a recently developed quantitative high throughput glycan analysis method we quantified components of the plasma N-glycome in 99 children with attention-deficit hyperactivity disorder (ADHD), 81 child and 5 adults with autism spectrum disorder, and a total of 340 matching healthy controls. No changes in plasma glycome were found to associate with autism spectrum disorder, but several highly significant associations were observed with ADHD. Further structural analysis of plasma glycans revealed that ADHD is associated with increased antennary fucosylation of biantennary glycans and decreased levels of some complex glycans with three or four antennas. The design of this study prevented any functional conclusions about the observed associations, but specific differences in glycosylation appears to be strongly associated with ADHD and warrants further studies in this direction.

Pavlinac I, Pecotić R, Đogaš Z, Valic M. Role of 5-HT_1(A) receptors in induction and preservation of phrenic long-term facilitation in rats. Respir Physiol Neurobiol. 2011;175:146-52.

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The aim was to investigate the role of 5-HT_1(A) receptor activation in induction and preservation of phrenic long-term facilitation (pLTF) at two different time points, before exposures to episodic hypoxia and after pLTF was induced. Adult, male, urethane anesthetized, vagotomized, paralyzed, and mechanically ventilated Sprague-Dawley rats were exposed to an acute intermittent hypoxia (AIH) protocol. Experimental groups of animals received an intravenous injection of WAY-100635, before the onset of the first hypoxic stimulus (WAY0), and after pLTF was induced (WAY60). Peak phrenic nerve activity (pPNA), burst

frequency (f), and respiratory rhythm parameters were analyzed during the five hypoxic exposures (TH1-5), as well as at 15 min (T15), 30 min (T30), and 60 min (T60) after the end of the last hypoxic episode. In the control group, pPNA was elevated from baseline (121.6 ± 7.3%, $P < 0.001$) at 60 min after episodic hypoxia indicating pLTF. Administration of WAY-100635 prior to hypoxic stimulation prevented the induction of pLTF. Additionally, administration of WAY-100635 after pLTF developed impaired preservation of pLTF. In conclusion, there is an important role for 5-HT_1(A) receptors in induction as well as in preservation of pLTF in urethane anesthetized rats.

Vidović A, Gotovac K, Vilibić M, Sabioncello A, Jovanović T, Rabatić S, Folnegović-Šmalć V, Dekaris D. Repeated assessments of endocrine- and immune-related changes in posttraumatic stress disorder. Neuroimmunomodulation. 2011;18:199-211.

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Objective: It is assumed that stress-related changes in the endocrine and immune systems are key mediators involved in the development of diseases associated with posttraumatic stress disorder (PTSD). Evidence suggests that those changes might be related to the duration of PTSD. The aim of our study was to investigate the differences in selected endocrine- and immune-related variables between PTSD patients and control subjects, and whether these differences persist over time. Methods: We assessed 39 Croatian war veterans with PTSD and 25 healthy volunteers (civilians without traumatic experience), all men, at two time points separated by 5.6 years (median; interquartile range: 5.4-6.3). Cortisol and prolactin levels were measured by radioimmunoassays while interleukin-6 and tumor necrosis factor-α were determined by enzyme-linked immunosorbent assays. Immune function was assessed by in vitro natural killer cell cytotoxicity (NKCC). Lymphocyte counts, immunophenotype and intracellular glucocorticoid receptor expression in various lymphocyte subsets were determined by three-color flow cytometry. Results: At the first assessment, moderate to large effect size estimates of differences between patients and controls were observed for most of the measured variables. Only prolactin levels and lymphocyte counts remained significantly elevated in PTSD patients at the second assessment with low to moderate effect size estimates of differences between patients and controls in other variables. Conclusion: Observed endocrine- and immune-related changes in PTSD over time may depend on the duration of the allostatic load posed by the disorder and its impact on interactions between the endocrine and immune systems involved in stress response.

Kirin I, Jurišić D, Grebić D, Nadalin S. The advantages of humeral anteromedial plate osteosynthesis in the middle third shaft fractures. Wien Klin Wochenschr. 2011;123:83-87.

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BACKGROUND: Humeral shaft fractures account for 1.2% of all fractures and occur in a slightly younger population. Their causes include a fall from standing or from height, motor vechicle accident, but can be also pathological. In order to clarify which of both surgeries we performed in our Department for treating humeral shaft fractures had more advantages (anterolateral or anteromedial plating through anterolateral approach) we analyzed incidence of postoperative iatrogenic radial palsies and mean operation time required to complete each surgery.
METHODS: During January 1992 to December 2009 on Department of Surgery, Division for Traumatology of Clinical Hospital Center Rijeka, 420 patients (340 males and 80 females with mean age of 38.11 ± 9.29 years) were treated for middle third humeral shaft fracture by anterolateral approach and internal fixation using AO/DCP or LCP plates that was positioned on anteromedial humeral surface in 141 patients (33.57%) and on anterolateral humeral surface in 279 patients (66.43%).
RESULTS: None of the patients who had osteosynthesis by using plate on anteromedial humeral sufrace had lesions of the radial nerve. Therefore, χ(2) test revealed significantly higher frequency of postsurgical radial nerve injuries in patients who were treated by anterolateral plating than in patients where anteromedial plating was performed ($\chi^2 = 17.51$; $P< 0.05$). Anterolateral plating required longer mean operation time than anteromedial plating and the difference in its duration determined by *t*-test for independent samples showed statistically significant difference ($t= 14.57$; $P< 0.05$).
CONCLUSION: An anteromedial plating of humeral shaft fractures through anterolateral approach was determinated to be a simple, safe, effective and also fast surgical treatment and we highly recommend it as operative technique for treating humeral shaft fractures.

Dumić M, Barišić N, Rojnić-Putarek N, Kušec V, Stanimirović A, Koehler K, Huebner A. Two siblings with triple A syndrome and novel mutation presenting as hereditary polyneuropathy. Eur J Pediatr. 2011;170:393-6.

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The clinical and molecular data on triple A syndrome in two siblings (girl 3.5 years and boy 5.5 years at presentation) with early onset of neurological dysfunction are described. Both patients showed delayed developmental milestones and neurological dysfunctions (motor and sensory demyelinating neuropathy, marked hyperreflexia, calves hypothrophy, pes cavus, gait disturbance) in early childhood, when erroneously diagnosed with hereditary polyneuropathy, most likely Charcot-Marie-Tooth disease. After a severe adrenal crisis in the younger sister at the age of 3 years, the older brother aged 5.5 years was also evaluated and latent adrenal insufficiency was discovered. As both of the siblings had alacrima, hyperkeratosis of palms, cutis anserina, and nasal speech, diagnosis of triple A syndrome was considered. Sequencing of the AAAS gene detected a compound heterozygous mutation consisting of a novel mutation p.Ser296Tyr (c.887C>A) in exon 9 and a previously described p.Ser263Pro (c.787T>C) missense mutation in exon 8 in both siblings. In conclusion, triple A syndrome should be considered in patients presenting with early neurological dysfunction and developmental delay. Alacrima as the earliest and most consistent clinical sign should be investigated by Schirmer test. Patients should be regularly tested for adrenal dysfunction to prevent life-threatening adrenal crises.

Zibar L, Wagner J, Pavlinić D, Galić J, Pasini J, Juras K, Barbić J. The relationship between interferon-γ gene polymorphism and acute kidney allograft rejection. Scand J Immunol. 2011;73:319-24.

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Cytokine gene polymorphisms have been associated with modified gene expression and cytokine production. Gamma interferon (IFN-γ) plays an important role in the pathogenesis of kidney transplant rejection. This study evaluated the association between IFN-γ gene polymorphisms and the history of acute allograft rejection in 53 adult first-transplant recipients receiving cadaveric kidney grafts. They were followed up in a single centre until 2006, for a median time of 4 years after transplantation (1-22 years). IFN-γ gene polymorphisms +874 T/A (rs2430561) were determined by polymerase chain reaction (PCR). T/T high IFN-γ genotype was found in 12, intermediate T/A in 29 and low A/A in 12 patients. Twenty-six acute kidney rejection episodes were evidenced in 20 patients, of which none occurred in the 12 patients with low IFN-γ genotype A/A. Age, gender, number of HLA (human leukocyte antigen) mismatches, ABO blood groups, HLA, time after transplantation, creatinine clearance and immunosuppressive regimens were excluded as confounding factors associated with IFN-γ genotype distribution between rejectors and non-rejectors. IFN-γ gene polymorphisms could be an important risk factor for acute kidney transplant rejection, whereas the low A/A IFN-γ genotype could be protective against rejection.

Benko G, Spajić B, Demirović A, Štimac G, Kru Sbreve Lin B, Tomas D. Prognostic value of connexin43 expression in patients with clinically localized prostate cancer. Prostate Cancer Prostatic Dis. 2011;14:90-5.

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Connexins (Cxs) are a family of transmembrane proteins that build cell-to-cell channels in gap junctions. Gap junctions composed of Cxs have an essential role in intercellular communication, adhesion and cell differentiation. Several studies investigated the role of connexin43 (Cx43) in different carcinomas; however, none investigated its prognostic role in prostate cancer. Cx43 expression and relationship with established prognostic features were assessed in a cohort of 102 patients treated with radical prostatectomy for clinically localized prostate adenocarcinoma. Cx43 expression in prostate cancer was significantly associated with established features indicative of worse prognosis, such as follow-up time ($P<0.001$) and preoperative PSA ($P<0.007$). Patients with lower Cx43 expressions in tumours have shorter follow-up time, which indicated shorter disease-free survival and higher preoperative PSA values. Furthermore, tumours with positive surgical margins ($P<0.001$) showed significantly lower Cx43 expression compared with tumours without this feature. In univariate ($P<0.001$) and multivariate ($P=0.014$) analyses, decreased Cx43 expression was found to be a significant predictor of biochemical recurrence free-survival. Study results show the association of decreased Cx43 expression with prostate cancer progression. Moreover, Cx43 could serve as an additional prognostic marker and used together with traditional prognostic markers might help in further stratifying the risk of disease progression in patients with prostate cancer.