

doi: 10.3325/cmj.2009.50.421

CROATIAN INTERNATIONAL PUBLICATIONS

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Barbalić M, Narančić NS, Škarić-Jurić T, Salihović MP, Klarić IM, Lauc LB, et al. A quantitative trait locus for SBP maps near KCNB1 and PTGIS in a population isolate. *Am J Hypertens.* 2009;22:663-8.

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BACKGROUND: Population isolates are characterized by simplified genetic background and as such present promising opportunities for studying complex diseases. We performed a genome-wide linkage analysis for systolic (SBP) and diastolic blood pressure (DBP) followed up by the association analysis in the Croatian isolated island of Vis, where a very high prevalence of hypertension was reported (75%). **METHODS:** Variance-components linkage analysis was used to map quantitative trait loci (QTL) for SBP and DBP in 125 families with 1,389 members. Follow-up association analysis was performed in a sample of 421 subjects from the island of Vis. The 15 top-ranking single nucleotide polymorphisms (SNPs) were selected and tested for the association by in silico replication in the British 1958 Birth Cohort DNA Collection. **RESULTS:** Linkage results showed evidence for a QTL influencing DBP (lod = 1.89) on chromosome 7p14.2 and two QTL influencing SBP (lod = 2.03 on chromosome 1p36 and lod = 1.75 on chromosome 20q13). For the association results, the replication was observed for the rs237484 polymorphism on chromosome 20 that was associated with SBP with the effect size beta = -5.2 (P = 0.001; per A allele) in Vis population and beta = -1.1 (P = 0.04) in the British 1958 Birth Cohort. rs237484 is in proximity to the potassium voltage gate channel gene (KCNB1) and close to the prostaglandin I2 (prostacyclin) synthase gene (PTGIS). **CONCLUSIONS:** These results provide evidence of a QTL influencing blood pressure (BP) variability in this region and support the notion that the isolated population of the island of Vis is a suitable population for conducting linkage and association analyses of cardiovascular-related phenotypes.

Skerk V, Roglić S, Čajić V, Markotić A, Radonić A, Skerk V, et al. Comparison of clinical symptoms scored according to the National Institutes of Health chronic prostatitis symptoms index and assessment of antimicrobial treatment in patients with chronic prostatitis syndrome. *J Chemother.* 2009;21:181-7.

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We examined a total of 194 patients over 18 years of age with chronic prostatitis syndrome and no evidence of structural or functional lower genitourinary tract abnormalities. The following data were obtained for each patient: clinical history--the severity of chronic prostatitis symptoms scored by a Croatian translation of the NIH CPSI questionnaire, clinical status including digitorectal examination, urethral swab specimens, and selective samples of urine and expressed prostatic secretion, according to the 4-glass localization test (meares and Stamey localization technique). Patients were treated orally with antimicrobial agents in doses and duration according to clinical practice in Croatia. An infectious etiology was determined in 169 (87%) patients. Chlamydia trachomatis was the causative pathogen in 38 (20%), Trichomonas vaginalis in 35 (18%), Enterococcus in 36 (19%) and Escherichia coli in 35 (18%) patients. In the remaining 25 patients the following causative pathogens were found: Ureaplasma urealyticum, Proteus mirabilis, Klebsiella pneumoniae, Streptococcus agalactiae and Pseudomonas aeruginosa. Comparison of symptoms scores and effect on quality of life has shown that the most severe clinical presentation of disease was recorded in patients with chronic bacterial prostatitis caused by E. coli and Enterococcus (p<0.001). Clinical success was paralleled by bacteriological eradication in chronic bacterial prostatitis caused by C. trachomatis, Enterococcus and E. coli (kappa >0.2<0.5), but not in inflammatory chronic pelvic pain syndrome caused by T. vaginalis.

Boraska V, Torlak V, Škrabić V, Kačić Z, Jakšić J, Stipančić G, et al. Glycosyltransferase B4GALNT1 and type 1 diabetes in Croatian population: clinical investigation. Clin Biochem. 2009;42:819-22.

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OBJECTIVES: Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by destruction of pancreatic beta cells. Gangliosides are thought to be a target of a variety of anti-islet autoantibodies. The formation of gangliosides is catalyzed by addition of sugar residues to complex glycoconjugate molecules by glycosyltransferases. Beta-1,4-N-acetyl-galactosaminyl transferase 1 is the enzyme involved in the synthesis of asialo, a, b and c-series gangliosides and it is coded by B4GALNT1 gene. **DESIGN AND METHODS:** We genotyped 2 B4GALNT1 tagSNPs, designed to capture 100% of common variation in the region, in 202 families and 199 controls from the Croatian population. **RESULTS:** Transmission disequilibrium test and case-control analysis did not detect an association of B4GALNT1 gene with T1DM. **CONCLUSIONS:** Expression of gangliosides requires coordinated work of many genes. There is enough evidence showing that gangliosides are plausible contributors to T1DM pathological processes and, therefore, future studies on different glycosyltransferase genes are necessary.

Kraljević Pavelić S, Sedić M, Hock K, Vučinić S, Jurišić D, Gehrig P, et al. An integrated proteomics approach for studying the molecular pathogenesis of Dupuytren's disease. J Pathol. 2009;217:524-33.

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Dupuytren's disease (DD) is a fibromatosis characterized by non-malignant transformation of palmar fascia leading to permanent contraction of one or more fingers. Despite the extensive knowledge of its clinical pathogenesis, the aetiology of this disease remains obscure. In the present paper, we report for the first time on the proteomic profiling of diseased versus unaffected patient-matched palmar fascia tissues from DD patients using two-dimensional gel electrophoresis coupled with mass spectrometry analysis. The herein identified proteins were then used to create the protein-protein interaction network (interactome). Such an integrated approach revealed the involvement of several different molecular processes related to DD progression, including extra- and intra-cellular signalling, oxidative

stress, cytoskeletal changes, and alterations in cellular metabolism. In particular, autocrine regulation through ERBB-2 and IGF-1R receptors and the Akt signalling pathway have emerged as novel components of pro-survival signalling in Dupuytren's fibroblasts and thus might provide a basis for a new therapeutic strategy in Dupuytren's disease.

Rajić Z, Butula I, Zorc B, Kraljević Pavelić S, Hock K, Pavelić K, et al. Cytostatic and antiviral activity evaluations of hydroxamic derivatives of some non-steroidal anti-inflammatory drugs. Chem Biol Drug Des. 2009;73:328-38.

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Non-steroidal anti-inflammatory drugs (NSAID) pharmacophores are interesting in designing potential anticancer drugs. Indeed, numerous experimental, epidemiologic and clinical studies suggest that NSAIDs are promising anticancer drugs. Herein, NSAID hydroxamic acids 3a-i were prepared by a new synthetic procedure and evaluated for their antiviral and cytostatic activity against malignant tumor cell lines and normal human fibroblasts (WI38). Antiviral activity evaluation results indicated that 3f had only a minor activity against the influenza virus A/H1N1 subtype with a selectivity index of 7-10. On the other hand, the results of the in vitro cytostatic activity evaluations revealed that the majority of NSAID hydroxamic acid derivatives 3a-i exhibited a strong non-specific antiproliferative effect at the highest concentration (100 microM) on the tested cell line panel. Only compounds 3b, 3e and 3i exerted a differential dose-dependent inhibitory activity against the growth of HeLa cells ($p < 0.05$) at concentration 10 microM. Among those three compounds, only compound 3b showed a selective cytostatic effect on HeLa in comparison with normal fibroblasts.

Čaleta I, Kralj M, Marjanović M, Bertoša B, Tomić S, Pavlović G, et al. Novel cyano- and amidinobenzothiazole derivatives: synthesis, antitumor evaluation, and X-ray and quantitative structure-activity relationship (QSAR) analysis. J Med Chem. 2009;52:1744-56.

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Synthesis of a series of novel cyano- and amidinobenzothiazole derivatives 3-31 is described. All studied amidino

derivatives showed noticeable antiproliferative effect on several tumor cell lines. Cyano derivatives 11-17 showed considerably less pronounced activity because of their poor solubility in aqueous cell culture medium, which was confirmed by the principal components (PC) analysis. Compounds 21, 22, 28, and 29 were tested for their effects on the cell cycle and apoptosis, whereby 22 and 29, having methyl group at the C-6 position in pyridine ring, showed drastic cell cycle perturbations that were both concentration- and time-dependent and induced apoptosis. The QSAR modeling, based on the physicochemical descriptors and on the measured biological activities, indicated the relevance of molecular polarizability and particular distribution of pharmacophores on the molecular surface for activity. In conclusion, benzothiazoles containing either isopropylamidino or imidazolyl groups will be considered as starting compounds for further investigation on lead identification.

Dorević G, Matusan-Ilijaš K, Babarović E, Hadžisejdić I, Grahovac M, Grahovac B, et al. Hypoxia inducible factor-1alpha correlates with vascular endothelial growth factor A and C indicating worse prognosis in clear cell renal cell carcinoma. J Exp Clin Cancer Res. 2009;28:40.

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BACKGROUND: The role of angiogenesis in the pathogenesis of renal cell carcinoma is well recognized, however, the influence of tumor cells in this activity has not yet been fully clarified. The aim of this study was to analyze the expression of hypoxia inducible factor-1alpha (HIF-1alpha), a regulatory factor of angiogenic switch, in comparison to vascular endothelial growth factor A and C (VEGF-A and VEGF-C), recognized to be involved in blood and lymph vessel neoangiogenesis, with potential association in the prognosis of patients with renal cell carcinoma. **METHODS:** Ninety-four patients with diagnosis of clear cell renal cell carcinomas (CCRCC), all clinicopathological characteristics and overall survival were unrolled in this study. Immunohistochemically VEGF-A, VEGF-C, HIF-1alpha and Ki67 were detected on tumor cells and the staining was performed on tissue microarrays (TMA). The staining was evaluated as a percentage of cytoplasmic or nuclear positive tumor cells. **RESULTS:** Variable expression of all three proteins was confirmed. Both an-

giogenic factors demonstrated perimembranous or diffuse cytoplasmic staining, with diffuse pattern positively associated ($p < 0.001$). Nuclear HIF-1alpha expression (nHIF-1alpha) showed inverse correlation with diffuse cytoplasmic VEGF-A ($p = 0.002$) and VEGF-C ($p = 0.053$), while cytoplasmic HIF-1alpha expression (cHIF-1alpha) showed positive correlation with diffuse staining of both angiogenic factors ($p < 0.001$; $p < 0.001$, respectively). In comparison to clinicopathological characteristics, a higher nuclear grade ($p = 0.006$; $p < 0.001$, respectively), larger tumor size ($p = 0.009$; $p = 0.015$, respectively), higher stage ($p = 0.023$; $p = 0.027$, respectively) and shorter survival ($p = 0.018$; $p = 0.024$, respectively) were associated with overexpression of cHIF-1alpha and diffuse cytoplasmic VEGF-A expression. In contrary, overexpression of nHIF-1alpha was associated with better diagnostic parameters i.e. lower nuclear grade ($p = 0.006$), smaller tumor size ($p = 0.057$), and longer survival ($p = 0.005$). **CONCLUSION:** Overexpression of VEGF-A and cHIF-1alpha in tumor cells highlights a more aggressive subtype of CCRCC that might have some clinical implications. The significance of nHIF-1alpha expression associated with better differentiated tumors should be further elucidated.

Perica MC, Šola I, Urbas L, Smrekar F, Krajačić M. Separation of hypoviral double-stranded RNA on monolithic chromatographic supports. J Chromatogr A. 2009;1216:2712-6.

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A procedure based on BIA Separations CIM DEAE anion-exchange chromatography was developed to separate double-stranded (ds) RNA of hypovirus infecting phytopathogenic fungus *Cryphonectria parasitica*. Using a linear gradient of 25 mM 4-morpholinepropanesulfonic acid (MOPS), pH 7.0 as a binding buffer, and 25 mM MOPS, 1.5 M NaCl, 0.1 mM EDTA, 15% isopropanol (v/v), pH 7.0 as an elution buffer, hypoviral dsRNA was additionally purified from nucleic acid species present in preparations partially purified by standard CF-11 cellulose chromatography. Moreover, crude phenol/chloroform extracts of the fungal tissue were also applied to monolithic supports and CIM DEAE chromatograms revealed clear evidence for hypoviral presence without CF-11 chromatography, nucleic acid precipitation, and electrophoresis.