**Ljubojević M, Balen D, Breljak D, Kušan M, Anzai N, Bahn A, et al. Renal expression of organic anion transporter OAT2 in rats and mice is regulated by sex hormones. Am J Physiol Renal Physiol. 2007;292: F361-72.**

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The renal reabsorption and/or excretion of various organic anions is mediated by specific organic anion transporters (OATs). OAT2 (Slc22a7) has been identified in rat kidney, where its mRNA expression exhibits gender differences [females (F) > males (M)]. The exact localization of OAT2 protein in the mammalian kidney has not been reported. Here we studied the expression of OAT2 mRNA by RT-PCR and its protein by Western blotting (WB) and immunocytochemistry (IC) in kidneys of adult intact and gonadectomized M and F, sex hormone-treated castrated M, and prepubertal M and F rats, and the protein in adult M and F mice. In adult rats, the expression of OAT2 mRNA was predominant in the outer stripe (OS) tissue, exhibiting 1) gender dependency (F > M), 2) upregulation by castration and downregulation by ovariectomy, and 3) strong downregulation by testosterone and weak upregulation by estradiol and progesterone treatment. A polyclonal antibody against rat OAT2 on WB of isolated renal membranes labeled a approximately 66-kDa protein band that was stronger in F. By IC, the antibody exclusively stained brush border (BB) of the proximal tubule S3 segment (S3) in the OS and medullary rays (F > M). In variously treated rats, the pattern of 66-kDa band density in the OS membranes and the staining intensity of BB in S3 matched the mRNA expression. The expression of OAT2 protein in prepubertal rats was low and gender independent. In mice, the expression pattern largely resembled that in rats. Therefore, OAT2 in rat (and mouse) kidney is localized to the BB of S3, exhibiting gender differences (F > M) that appear in puberty and are caused by strong androgen inhibition and weak estrogen and progesterone stimulation.

**Belužić R, Ćuk M, Pavkov T, Fumić K, Barić I, Mudd SH, et al. A single mutation at Tyr143 of human S-adenosylhomocysteine hydrolase renders the enzyme thermosensitive and affects the oxidation state of bound cofactor nicotinamide-adenine dinucleotide. Biochem J. 2006;400:245-53.**

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Recently, the authors have described the first human case of AdoHcyase (S-adenosylhomocysteine hydrolase) deficiency. Two point mutations in the AdoHcyase gene, the missense mutation p.Y143C (AdoHcyase in which Tyr143 is replaced by cysteine) and the truncation mutation p.W112stop (AdoHcyase in which Trp112 is replaced by opal stop codon) were identified [*Baric et al., Proc. Natl. Acad. Sci. U.S.A. 2004;101:4234-9*]. To elucidate the molecular and catalytic properties of AdoHcyase, they have made recombinant wild-type and mutant p.Y143C (AdoHcyase in which Tyr143 is replaced by cysteine) enzymes for a comparative analysis. The catalytic rates of p.Y143C protein in the directions of S-adenosylhomocysteine synthesis or hydrolysis are decreased from 65% to 75%. Further, the oxidation states of coenzyme NAD differ between mutant and wild-type protein, with an increased NADH accu-

mulation in the mutant p.Y143C enzyme of 88% NADH (wild-type contains 18% NADH). Quantitative binding of NAD is not affected. Native polyacrylamide gel electrophoresis showed, that mutant p.Y143C subunits are able to form the tetrameric complex as is the wild-type enzyme. CD analysis showed that the p.Y143C mutation renders the recombinant protein thermosensitive, with an unfolding temperature significantly reduced by 7 degrees C compared with wild-type protein. Change of Glu115 to lysine in wild-type protein causes a change in thermosensitivity almost identical with that found in the p.Y143C enzyme, indicating that the thermosensitivity is due to a missing hydrogen bond between Tyr143 and Glu115. The authors emphasize involvement of this particular hydrogen bond for subunit folding and/or holoenyzme stability. In summary, a single mutation in the AdoHcyase affecting both the oxidation state of bound co-factor NAD and enzyme stability is present in a human with AdoHcyase deficiency.

**Tomas D, Krušlin B, Rogatsch H, Schafer G, Belicza M, Mikuz G. Different types of atrophy in the prostate with and without adenocarcinoma. Eur Urol. 2007;51:98-103.**

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The purpose of this study was to evaluate, according to a classification proposed by a working group, the extent and type of atrophy lesions in radical prostatectomy specimens obtained from patients with prostatic carcinoma and benign prostatic hyperplasia (BPH), and to compare the prevalence and types of atrophy between two investigated groups. Histologic analysis of 1096 slides from 50 patients with carcinoma and 277 slides from 31 patients with BPH was performed to evaluate, according to the new prostatic atrophy classification, the number of foci and type of atrophic lesions. Age, Gleason grade, and TNM showed no significant correlation with the number of proliferative atrophy (PA) and proliferative inflammatory atrophy (PIA) foci ($p>0.05$). PIA was significantly more frequent in prostates with carcinoma (1.63 *vs.* 1.27 atrophic lesions per slide) ($p<0.001$), whereas PA displayed an increased frequency in BPH (2.28 *vs.* 0.76 atrophic lesions per slide) ($p<0.001$). In conclusion, the authors have confirmed that PA and PIA are common findings in prostates with and without carcinoma, but the question of whether inflammation produces tissue damage and PA or whether some other insult induces the tissue damage and atrophy directly, with inflammation occurring secondarily, is still unresolved.

**Šimunić V, Tomić V, Tomić J, Nižić D. Comparative study of the efficacy and tolerability of two vaginal progesterone formulations, Crinone 8% gel and Utrogestan capsules, used for luteal support. Fertil Steril. 2007;87:83-7.**

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The aim of this study was to compare the efficacy and tolerability of two different types of vaginal progesterone (P), Crinone 8% gel (Fleet Laboratories Ltd., Watford, United Kingdom) and Utrogestan capsules (Laboratories Besins International, Paris, France), used for luteal support after in vitro fertilization (IVF) cycles. The study included a total of 285 women aged < or =37 years undergoing IVF-embryo transfer treatment. Patients were treated with either Crinone 8% vaginal P gel (90 mg) administered daily, or Utrogestan vaginal capsules (2 x 100 mg) administered three times daily. Progesterone was administered from the day of oocyte retrieval (day 0) to menses or, in a case of pregnancy, until week 12. The tolerability and acceptability of both preparations were determined by a questionnaire given to patients. The similar rates of clinical pregnancies (33 [1%] *vs.* 30 [9%]) were obtained by using either Crinone 8% vaginal P gel or Utrogestan vaginal capsules. Overall tolerability and acceptability were significantly better in the Crinone group than in the Utrogestan group. In conclusion, the efficacy of the two vaginal P formulations was nearly the same, but the tolerability and acceptability of Crinone 8% gel were superior, in the opinion of patients.

**Bilić E, Bilić E, Rudan I, Kušec V, Zurak N, Delimar D, Žagar M. Comparison of the growth hormone, IGF-1 and insulin in cerebrospinal fluid and serum between patients with motor neuron disease and healthy controls. Eur J Neurol. 2006;13:1340-5.**

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Neurotrophic effects of the growth hormone (GH), insulin-like growth factor-1 (IGF-1) and insulin on the central nervous system have become more apparent in the past decade. In this study, the authors measured serum and cerebrospinal fluid (CSF) concentrations of GH, IGF-1 and insulin in 35 patients with motor neuron disease (MND) [24 patients with definite amyotrophic lateral sclerosis (ALS) and 11 patients with progressive bulbar palsy] and in 40 healthy controls. Levels of serum concentrations of GH and IGF-1 did not significantly differ between the MND patient

group and the healthy controls, while the level of insulin was significantly decreased (p=0.0033) in the MND patient group. However, levels of all three examined parameters in CSF were significantly lower in the MND group than in the healthy controls with the statistical significance for IGF-1 and insulin of p<0.001. This finding has not been reported previously, and further investigations into its association with ALS should establish whether it can be used as an early marker of the disease, or whether it merely represents a consequence of ALS development.

**Grubić Z, Štingl K, Žunec R, Car H, Čečuk-Jeličić E, Brkljačić-Kerhin V. Linkage disequilibria between human leucocyte antigen-B and closely linked microsatellites in the Croatian population. Tissue Antigens. 2007;69:86-94.**

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The aim of the present study was to investigate polymorphism of D6S2927, STR_MICA, D6S2793, TNFa (D6S2792), TNFb and TNFd (D6S2789) microsatellites and linkage disequilibria between these loci and human leucocyte antigen (HLA)-B (previously tested) for better characterisation of extended HLA haplotypes. A total of 176 healthy unrelated Croatians were studied using polymerase chain reaction amplification and electrophoresis on 6% polyacrylamide gel in ALFexpress sequencer. Eight HLA-B/D6S2927 haplotypic associations (B*07/D6S2927-4, B*08/D6S2927-3, B*18/D6S2927-3, B*27/D6S2927-1, B*35/D6S2927-5, B*38/D6S2927-4, B*51/D6S2927-2 and B*61/D6S2927-1) showed strong association (p<0.001, D>0.5). Among 88 different HLA-B/STR_MICA haplotypic associations, seven combinations (B*07/STR_MICA-A5.1, B*08/STR_MICA-A5.1, B*15/STR_MICA-A5, B*18/STR_MICA-A4, B*27/STR_MICA-A4, B*38/STR_MICA-A9 and B*51/STR_MICA-A6) demonstrated high linkage (D>/=0.3) with significant P value (p<0.001). Strong associations were also observed for five HLA-B/D6S2793 haplotypes (B*07/D6S2793-CA17, B*08/D6S2793-CA24, B*13/D6S2793-CA18, B*14/D6S2793-CA14 and B*27/D6S2793-CA14). HLA-B*08/TNFb3 and HLA-B*50/TNFb7 were the strongest associations for HLA-B/TNFb. Nine HLA-B/TNFa combinations were observed with significant P value (B*07/TNFa11, B*08/TNFa2, B*13/TNFa7, B*18/TNFa10, B*27/TNFa6, B*37/TNFa9, B*38/TNFa10, B*39/TNFa13 and B*44/TNFa4). Out of six HLA-B/TNFd haplotypic associations with strong D value, HLA-B*08/TNFd2 and B*37/TNFd3 showed the highest statistical significance (p<0.0001). These results provide data on the region around the HLA-B that is very attractive because of its contribution to genetic susceptibility for many HLA-associated diseases and therefore this information will help in all further HLA-B locus-associated disease studies.

**Radić M, Martinović Kaliterna D, Ljutić D. The level of anti-topoisomerase i antibodies highly correlates with metacarpophalangeal and proximal interphalangeal joints flexion contractures in patients with systemic sclerosis. Clin Exp Rheumatol. 2006;24:407-12.**

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Antibodies against DNA topoisomerase I (anti-topo I abs) are detected almost exclusively in systemic sclerosis (SSc). These antibodies are predictors of pulmonary fibrosis and peripheral vascular disease. Metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints flexion contractures are assessed as markers of active SSc. The aim of this study was to find out is there any relationship between anti-topo I abs and MCP and PIP joints flexion contractures. Twenty-eight patients with active disease who fulfilled the American College of Rheumatology criteria for SSc were included in this study. Twenty eight healthy control subjects were also investigated. Clinical and radiological assessments of the hands were carried out. The flexion ranges in the 8 finger joints by goniometric measurement were obtained. Anti-topo I abs were measured by ELISA. MCP and PIP joints flexion contractures and the levels of anti-topo I abs were significantly higher in patients with SSc than in healthy control. Anti-topo I abs were found in 16 of 28 patients with SSc. Sixteen of 28 patients with active disease had MPC and proximal PIP joints flexion contractures. In 16 SSc patients with anti-topo I abs, 13 had metacarpophalangeal and proximal interphalangeal joints flexion contractures. In only 3 patients of 16 with the flexion contractures the levels of anti-topo I abs were negative. The patients with MPC and PIP joints flexion contractures had higher mean value of anti-topo I abs titers (53.718±50.977 vs 8.127±8.915, p<0.0001) than did those with no contractures. Furthermore, the titers of anti-topoisomerase I antibody positively correlated with the flexion contractures (r=0.4252, p=0.0241). Radiologically, joint space narrowing and flexion contractures of the fingers were seen significantly more frequently in the SSc patients with anti-topo I abs (p<0.05). In conclusion, serum level of anti-topoisomerase I antibodies is in direct relationship with MPC and PIP joints flexion contractures.

**Janjanin N, Dumić M, Škrabić V, Kušec V, Grubić Z, Špehar Uroić A. Five patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency (one with associated neuroblastoma) discovered in three generations of one family. Horm Res. 2006;67:111-6.**

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Most patients with 21-hydroxylase deficiency (21-OHD) are compound heterozygous carriers. Their phenotype usually reflects a less severe allelic mutation, although discordance between the genotype and the phenotype has been observed. The authors present 5 patients with congenital adrenal hyperplasia (CAH) due to 21-OHD belonging to the 3 generations of the same family (grandmother, parents and their 2 children). As each patient carries at least one mild mutation of the CYP21 gene, their genotypes correspond to nonclassical CAH. The propositus is the older brother, who is compound heterozygous with a mild and severe CYP21 mutation (P30L/R356W). In spite of one mild CYP21 mutation, he presented with the clinical picture of a simple virilizing form of 21-OHD and required glucocorticoid replacement therapy from the age of 4. Both probands' parents are compound heterozygous carriers of different CYP21 gene mutations causing various degrees of enzymatic activity impairment, which explains the different genotypes and phenotypes in their offspring. The probands' mother, besides the nonclassical 21-OHD, also had neuroblastoma of the adrenal gland. In conclusion, the potential discordance between the genotype and the phenotype in some patients with CAH is emphasized. The existence of a mild CYP21 mutation P30L in a compound heterozygous with CAH might be associated with progressive virilization requiring glucocorticoid therapy from early childhood. The occurrence of neuroblastoma with 21-OHD may support the hypothesis that an impairment in the synthesis and secretion of glucocorticoids may play role in the development and functioning of the adrenal medulla.