Voxels were defined hypoxic when the signal was up to 1.2 fold the contralateral value. Image analysis was performed with Image J.
Results: Our results show the efficiency of the anti-angiogenic treatment despite a delayed administration (i.e. 17 Days) with a decrease in tumour volume by 51% in the Sunitinib group as compared to the Control group ($p < 0.01$). Along with this anti-tumour effect, we observe an increase in CBV (Control: 4.6±0.7%; Sunitinib: 5.9±1.03%; $p < 0.05$) and VSI (DR2*/DR2; Control: 1.13±0.13; Sunitinib: 1.22±0.14; $p < 0.05$) but also a reduction of hypoxia (Mean = Control: 1787±348 nCi/cc, Sunitinib: 1512±134 nCi/cc; Max = Control: 3134±1099 nCi/cc, Sunitinib: 2181±414 nCi/cc; $p < 0.05$) detected following the Sunitinib treatment.
Conclusions: Using both MRI and PET imaging, we present data demonstrating a vascular normalization following an anti-angiogenic treatment in a rat glioma model. We are currently trying to elucidate mechanisms associated with these vascular effects which may reflect a better vascular supply (high CBV, low hypoxia) paradoxically to a slowdown of tumour growth.
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83 Colorectal cancer susceptibility loci on chr 8q23.3 and 11q23.1 as modifiers for disease expression in Lynch syndrome

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Background: Recently, six colorectal cancer (CRC) susceptibility loci have been identified and two SNPs; rs16892766 (8q23.3) and rs3802842 (11q23.1) have been found to be significantly associated with an increased CRC risk in Lynch syndrome patients. In the current study we have genotyped 9 SNPs within these six loci to confirm previous finding and investigate whether they act as modifiers of disease risk in Lynch syndrome patients.
Methods: The patient cohort consisted of 684 mutation positive Lynch syndrome patients from 298 Australian and Polish families. A total of 9 SNPs were genotyped: rs16892766 (8q23.3), rs7014346 and rs6983267 (8q24.21), rs10795668 (10p14), rs3802842 (11q23.1), rs10318 and rs4779584 (15q13.3) and rs4939827 and rs4464148 (18q21.1). The data was analysed to investigate possible associations between the presence of variant alleles and risk of developing disease.
Results: An association between SNPs rs3802842 on chromosome 11q23.1 and rs16892766 on chromosome 8q23.3 and the risk of developing CRC and age of diagnosis was found in MLH1 mutation carriers. Female MLH1 mutation carriers harbouring the homozygous variant genotype for SNP rs3802842 have the highest risk of developing CRC. When analysing the number of risk alleles for the two SNPs combined, a difference of 24 years can be detected between individuals carrying 3 risk alleles compared to 0 risk alleles.
Conclusion: In conclusion, we were able to replicate the association between the CRC susceptibility loci on chromosome 8q23.3 and 11q23 and the risk of developing CRC in Lynch syndrome patients but the association could only be detected in MLH1 mutation carriers in the current study.

84 Genomic rearrangements in BRCA1/2 and CHEK2 genes in Czech high-risk breast/ovarian cancer patients

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Background: *BRCA1* and *BRCA2* are major breast cancer predisposing genes. Large genomic rearrangements (LGRs) represent substantial proportion of pathogenic mutations in the *BRCA1* gene. On the contrary, the frequency of rearrangements in the *BRCA2* gene is low in many populations. The deletion of 5395 bp in *CHEK2* gene has been described in the Czech breast cancer patients.
Material and Methods: LGRs in the *BRCA1/2* genes 5395 bp del in *CHEK2* and were examined in 558 unrelated patients, previously tested negative for *BRCA1/2* point mutations and small deletions or insertions, selected from 700 Czech high-risk breast and/or ovarian cancer patients. For mutation screening and characterization multiplex ligation-dependent probe amplification (MLPA), long range PCR, and genomic sequencing were used. Location of several deletions was disclosed using chromosome 17-specific oligonucleotide-based array comparative genomic hybridization (aCGH).
Results: We identified 15 patients with 8 different LGRs in the *BRCA1* gene that accounted 12.2% (15/123) of all pathogenic *BRCA1* mutations. Among 268 patients from hereditary cancer cases, we found 12 large deletions (4.5%), whereas in 290 non-familial cancer cases 3 deletions were revealed (1.0%). Deletions of exons 1−2, 5−14, and 21−22 were already described in the Czech Republic or in other populations. Five LGRs were novel, namely, deletions of exons 1−17, 5−10, 13−19, 18−22, and 21−24. Deletions of exons 1−17 and 5−14 were both identified in four families, and represented two Czech-specific founder mutations. LGRs at the *BRCA1* locus explained 2.14% (15/700) of all cancer cases in the study group. No LGRs were found in the *BRCA2* gene, but BRCA2-specific MLPA revealed 5 carriers of 5395bp deletion in *CHEK2* gene.
Conclusions: Our results indicate that screening for genomic rearrangements in *BRCA1* gene should include patients from breast/ovarian cancer families as well as patients with non-familial cancer, in particular cases with early-onset breast or ovarian cancer. On the contrary, our analyses do not support the need to screen for rearrangements in the *BRCA2* gene. Chromosome-specific oligonucleotide-based aCGH accurately located deleted regions, which markedly facilitated the design of primers for amplification and sequence analysis of junction fragments.
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85 Risk of non-Hodgkin lymphoma development in patients carrying mutations in CHEK2 gene or polymorphism R72P in P53 gene

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Background: The risk of non-Hodgkin lymphoma (NHL) development is modified by genetic background. Checkpoint kinase 2 protein (CHK2) participates in regulation of DNA double-strand break repair and among others phosphorylates P53 protein. Functions of these proteins could be negatively influenced by gene alterations. Not only *P53* gene, but also *CHEK2* gene has been reported as a cancer susceptibility gene in different types of cancer (e.g. breast, colorectal or prostate), but the relevance to the NHL remains unclear. The aim of our study was to determine the frequencies of *CHEK2* alterations and *P53* R72P polymorphism in NHL patients in order to evaluate their impact on the risk of NHL development.
Material and Methods: Mutation analysis of the whole coding sequence of *CHEK2* gene and of *P53* gene exon 4 was performed in 340 NHL patients. Genomic DNA was isolated from peripheral blood of patients that signed approved informed consent prior genetic testing. Individual exons and intron-exonic boundaries were PCR-amplified and analyzed by denaturing high-performance liquid chromatography (DHPLC; WAVE3500; Transgenomic). Samples with aberrant elution profiles were sequenced from independent amplification (ABI 3100; Applied Biosystems). The population frequencies of alterations were estimated in group of non cancer controls.
Results: The *CHEK2* region (exons 2 and 3) coding for highly conservative forkhead-associated (FHA) domain was shown to contain the majority of gene alterations [e.g. c.470T>C (I157T), c.542G>A (R181H), IVS1−5T>A, IVS2+1G>T]. Frequency of alterations in FHA region was significantly higher in NHL patients (5.6%; 19/340) compared to controls (2.8%; 19/683) with OR = 2.1 (95% CI 1.1−3.9; $p = 0.03$). The frequencies of polymorphisms in exon 1 [c.122C>T (S41F), c.252A>G (E84E), IVS1+39dupA] and in exon 4 (IVS4−78_-100dup23) were the same in NHL cases and controls. Alterations in other exons of *CHEK2* gene were rare (with minor allele frequency <1%). Several *CHEK2* alterations found in NHL patients has not been described previously [e.g. c.1067C>T (p.S356L), c.1201A>G (p.T401A), IVS10+1G>C, IVS10+28A>G, c.1336A>G (p.N446D), c.1421G>A (p.R474H)]. The frequency of *P53* R72P polymorphism was similar in NHL cases as in controls (21.8% and 22.4% of alleles, respectively).
Conclusions: We conclude that inherited alterations of *CHEK2* gene, but not R72P in *P53* gene, could modify the risk of NHL development.
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