MUTATION DETECTION 2011

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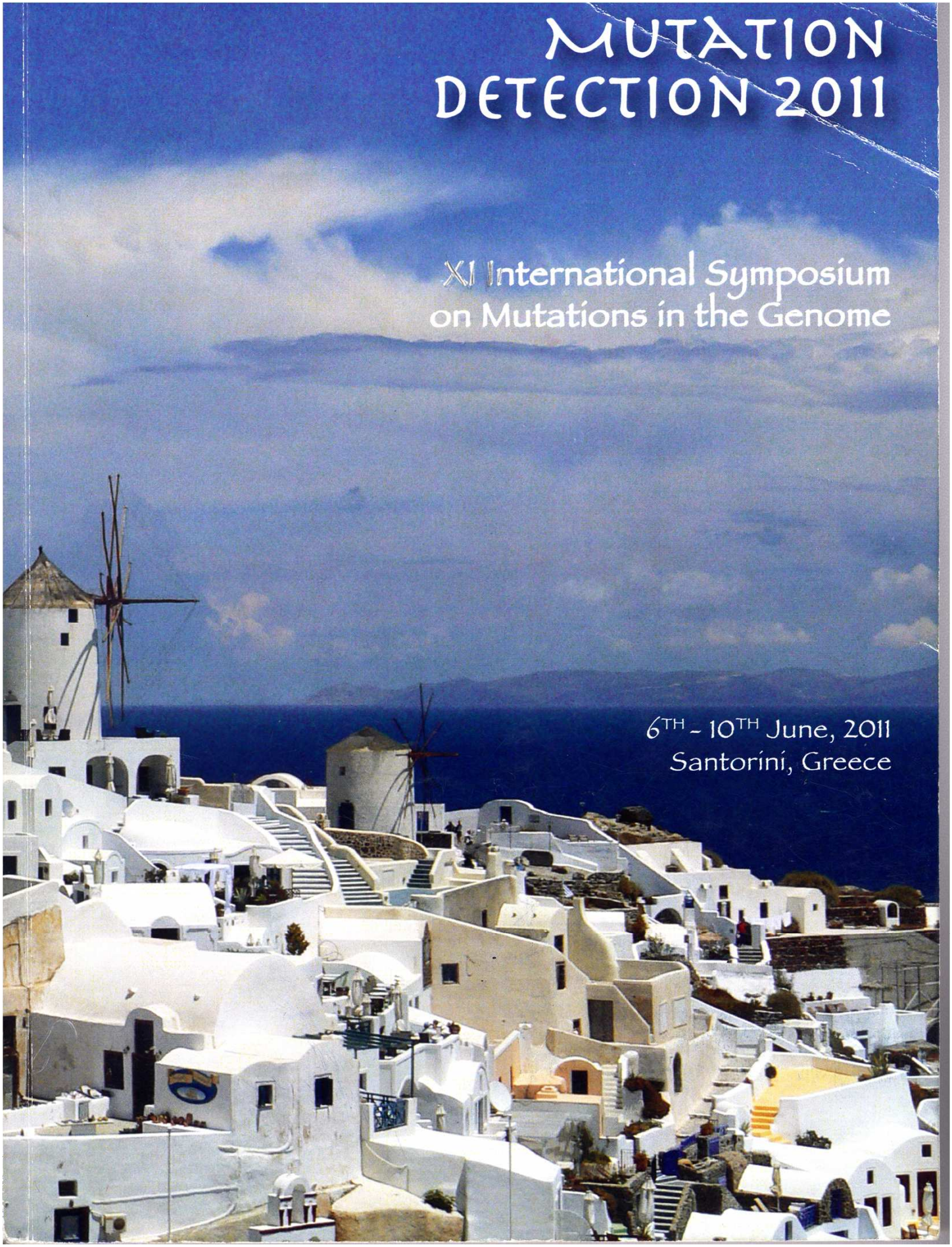

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Poster 20

Prediction of deleterious nsSNPs in human UGT1A1 gene by web available algorithm tools

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The uridine diphosphate glucuronosyltransferase (UGT1A1) belongs to the class of phase II enzymes involved in the metabolism and detoxification of numerous xenobiotic and endogenous compounds (e.g. bilirubin). Genotyping data lead to the discovery of over 100 single nucleotide polymorphisms (SNPs) within the UGT1A1 gene. Some of the non-synonymous (ns) SNPs (nsSNPs) of the human UGT1A1 gene variants have been associated to hyperbilirubinemia in Gilbert's and Crigler-Najjar syndromes, as well as altered drug clearance and/or drug response. In UGT1A1, and other genes, there are many nsSNPs which genotype-phenotype correlations were not established, since the study of the functional impact of all SNPs is time consuming and expensive. Alternatively, bioinformatics tools have gained an increased importance with the prospect of reducing the totality of detailed studies at protein level.

The aim of this study was to investigate the potential of bioinformatics approaches, using five web available algorithms [Sorting Intolerant from Tolerant (SIFT); polymorphism phenotyping-2 (PolyPhen-2); Align Grantham Variance/Grantham Difference (Align-GVGD); Multivariate Analysis of Protein Polymorphism (MAPP); Block Substitution Matrix score 62 (BLOSUM62)], to predict the phenotype of 28 human UGT1A1 nsSNPs, previously characterized at protein level by in vivo and in vitro studies. From those, 24 SNPs were confirmed as responsible for changes in protein function and in 4 there were no detected impact. Information describing the UGT1A1 variants was obtained from mutation database websites: http://www.polydoms.cchmc.org/polydoms, http://www.mutdb.org, and http://www.ncbi.nlm.nih.gov/sites/entrez.

Results from in silico analysis showed a correct prediction rate of 85.7% for Polyphen-2, 82.0% for both BLOSUM62 and SIFT, 60.7% for MAPP and 32.1% for Align-GVGD. In the total of 28 studied variants, 78.6% (n=22) had concordant results using Polyphen-2 and SIFT algorithms and 57.1% (n=16) using Polyphen-2, SIFT and BLOSUM62. Concordance in variants prediction, between the five used methods and with results obtained at protein levels, was observed in 14.3% (n=4) nsSNPs. In conclusion, our results showed that SIFT and Polyphen together, were the best predictor methods of nsSNPs phenotype in human UGT1A1 gene. These tools have the advantage of directing and complement functional assays. However, the observed discrepancy in variants prediction phenotype may be improved with a method combining all currently available criterions.

Poster 21

Rapid Aneuploidy Detection by QF-PCR: Comparison between Aneufast™ v2 and QST*RplusV2

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Background. QF-PCR allows the rapid and efficient detection of the common aneuploidies in at-risk pregnancies. With this assay, targeted chromosome or locus copy number is determined by assessment of peak area ratios for each heterozygous and therefore informative STR marker tested. Our experience to date with 161 samples established that Aneufast™ v1 (MolgentixSL) required a relatively high rate of additional reflex testing to resolve uninformativeness of STRs markers or because of inconclusive ratios: 10.2% of the chromosome pairs tested did not have at least two