THE IMPACT OF WNT1-INDUCIBLE SIGNALLING PATHWAY PROTEIN 1 POLYMORPHISM ON HEPATOCELLULAR CARCINOMA SUSCEPTIBILITY

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Material and methods 6 SNPs of WISP1 were analysed with real-time polymerase chain reaction in 332 patients with HCC and 664 cancer-free controls.

Results and discussions The results exhibited that the WISP1 rs2977530 polymorphism carriers were susceptible to HCC. Patients with higher frequencies of WISP1 rs62514004 (AG +GG) and rs16893344 (CT +TT) variants were at a lower risk to reach a later clinical stage compared with the wild-type carriers. Furthermore, individuals who carried WISP1 rs62514004 and rs16893344 haplotype G-T revealed a higher synergistic effect combined with alcohol drinking on HCC development (AOR=26.590, 95% CI=9.780–72.295).

Conclusion Our results indicated that the HCC patients with WISP1 SNPs are associated with HCC susceptibility. The WISP1 SNPs may serve as markers or therapeutic targets for HCC.

CANCER-PREDISPOSING VARIANTS IN THE IMPACT OF WNT1-INDUCIBLE SIGNALLING PATHWAY PROTEIN 1 POLYMORPHISM ON HEPATOCELLULAR CARCINOMA SUSCEPTIBILITY

GENETIC INTERACTION AND PATHWAY BASED DISCOVERY OF KEY REGULATORS IN MULTIPLE MYELOMA

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Introduction Multiple myeloma (MM) is a plasma cell dyscrasia characterised by proliferation of monoclonal plasma cells. As one of the most prevalent haematological malignancies, MM is genetically heterogeneous. Although 17 individual MM susceptibility loci have been identified, their inherent biological mechanism is sparsetly understood. We carried out a polygenic interaction analysis with published whole-genome association studies (GWASs) to further characterise MM susceptibility with inflated genomic resolution in order to locate seemingly aberrant variations having temporal aggregation of risk.

Material and methods Single nucleotide polymorphisms data from two MM GWAS representing 3999 cases and 7266 controls were subjected to genome-wide interaction analysis and followed-up with a meta-analysis. The identified loci were used for consequent gene set enrichment and tissue expression prioritisation to obtain functional evidence. Causal dependency between sentinel loci and functional variants was then interrogated with expression quantitative trait loci subject to summary data-based Mendelian randomization. Patient samples and relevant clinico-pathological information was obtained conditional on written informed consent and was subject to approval of corresponding ethical review boards at respective study centres in accordance with the tenets of Declaration of Helsinki.

Conclusion Our polygenic interaction analysis renders novel insight into genetic susceptibility in MM. Related pathways provide some basic understanding of functional relation between discovered candidates as well as a biological basis of predisposition.

CANCER-PREDISPOSING VARIANTS IN ALTERNATIVELY SPliced TP53 EXONS

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Introduction Germline pathogenic variants in the canonical TP53 gene cause Li-Fraumeni, a severe cancer predisposition syndrome characterised by early onset of multiple tumours, particularly breast cancer, brain tumours, soft-tissue sarcomas, osteosarcomas and leukaemia. Genetic variation in the alternatively spliced TP53 exons 9B and 9Y, each encoding a different carboxy-termini, have been poorly studied. Therefore, the clinical significance of germline variation in these alternative exons remains unknown. In the search for novel colorectal cancer susceptibility genes, we identified a germline variant in an alternative TP53 exon 9 and we show that this variant is associated with a predisposition to multiple cancer types.

Material and methods Exome sequencing was performed on 118 unexplained familial and/or early-onset colorectal cancer patients. Somatic TP53 and cancer hotspot mutations were assessed in tumour tissues of carriers. TP53 isoform expression and non-sense mediated decay were studied in cell lines from colorectal cancer patients using (allele specific) qPCR and Western blotting.

Results and discussions We identified a germline heterozygous variant in an alternative TP53 exon 9 in twelve individuals.
from three families severely affected by colorectal cancer and multiple other cancer types. The carriers developed one or more primary tumours after 40 years of age, including colorectal cancer, breast cancer, thyroid cancer and Non-Hodgkin lymphoma. Only two out of eleven tumours harboured a somatic TP53 mutation and a single tumour showed loss of heterozygosity of the alternative exon 9 variant. The cell line carrying the TP53 variant showed (i) an allelic imbalance towards the expression of variant containing transcripts and (ii) a higher expression of the alternative TP53 exon 9 isoforms compared to wild-type cell lines. Increased protein expression of the alternative exon 9 isoforms could be confirmed in the cell line using Western blotting. The increased expression was not caused by disturbance of non-sense mediated decay mechanisms.

Conclusion We have identified a variant in an alternative TP53 isoform that predisposes carriers to multiple cancers. Carriers presented at a slightly older age and with a different spectrum of tumours compared to classical Li-Fraumeni syndrome patients. Therefore we recommend the screening of the alternative exons 9 of the TP53 gene in all unexplained cancer-prone families.

Introducing Rhabdomyosarcomas (RMS) are the most prevalent form of paediatric soft tissue sarcomas. They arise from skeletal muscle progenitor cells and are divided predominantly into two subtypes, embryonic and alveolar, with relatively poor prognosis. The alveolar subtype appears to be driven by an oncogenic fusion gene protein, typically but not exclusively FOXO1-PAX3 or FOXO1-PAX7. Fusion negative tumours better define the embryonal subtype, with occasional RMS cases where both subtypes histologically appear to coincide. Previously published work on somatic RMS variants associate embryonal RMS with hits in the RAS/AKT pathway (KRAS, NRAS, HRAS, NF1, PIK3CA, PTEN) alongside other cancer-related genes (TP53, FGFR4, FBXW7, BCOR). In this study we generate new whole exome sequencing data and integrate with previously published datasets to study germline predisposition to RMS.

Material and methods The study includes 3 published datasets (Shen 2014 – 120 samples; Seki 2015 – 16 samples and Zhang 2015 – 30 samples) in addition to our in-house set (36 tumour-normal pairs of both RMS subtypes, collected in collaboration with the Children’s Cancer and Leukaemia Group tissue bank). Our primary samples were processed using Illumina’s Nextera Rapid Capture kit and sequenced on HiSeq NGS machines. The combined analysis cohort consists of 202 cases of paediatric RMS.

Results and discussions A customised bioinformatics pipeline was used for integration of the studied datasets: from raw fastq through BWA-MEM alignment and GATK-HC joint variant calling. Germline variants passing several quality control filters were pruned for a MAF <0.05 compared to the 1000 genomes project controls. Protein affecting variants (loss of function and predicted deleterious missense variants) were aggregated per gene for delineating candidate RMS predisposition genes. Genes with recurrent germline variants were found in DNA-repair, RAS/AKT, RMS-specific and other cancer-related pathways.

Conclusion We explored the potential for germline predisposition to RMS as genetic inheritance is common in a number of paediatric cancers. The relative rarity of paediatric RMS prevents sufficiently powered single-centre studies and requires the consolidation of all available data to make meaningful conclusions. We employ this approach to identify new candidate predisposition genes. Expanding our understanding of genes predisposing to rhabdomyosarcomas, could assist earlier diagnosis and therapy for these children, ultimately improving their survival.