618 Five vertebrate ChIP-seq reveals the evolutionary dynamics of transcription factor binding

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Mammalian transcription factor binding evolves rapidly, yet tissue-specific transcription is highly conserved. To explore this apparent paradox, we experimentally determined the genome-wide occupancy of two transcription factors (TF) CEBPA and HNF4A in livers of multiple vertebrates. Although each TF has highly conserved DNA binding preferences, most binding is species-specific and ultra-shared events are rare. Functional target genes are associated with an enrichment of shared TF binding, yet collectively, the binding events near functional targets show no increase in sequence constraint. Most lineage-specific lost TF binding can be explained by sequence mutations of the binding motif, and only half of the apparently lost binding events appeared to have turned over to a nearby location. Our results reveal the plasticity of vertebrate TF binding and the complex evolutionary dynamics of transcriptional regulation.

619 Blood based breast cancer molecular signatures

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Strategies to achieve personalized medicine and improve public health encompass assessment of an individual's risk for disease, early detection and molecular classification of disease resulting in an informed choice of the most appropriate treatment instituted at an early stage of disease development. A major contribution of proteomics in this field is the development of blood based tests to achieve the goals of personalized medicine. An integrated cooperative effort is currently under way for the identification of biomarkers of breast cancer risk, early detection of breast cancer and identification of altered signaling pathways based on serum and plasma analysis. The effort encompasses analysis of specimens collected before onset of symptoms for the identification of risk and early detection markers and elucidation of signatures in plasma for altered signaling pathways in tumours. This overarching effort also benefits from the availability of subject cohorts and from the availability of engineered mouse models and cell lines that inform with respect to proteins involved in altered signaling pathways. Such an effort requires and benefits from the availability of in-depth quantitative proteomics methods, bioinformatics resources and integration with other broad based molecular profiling technologies.

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620 Adjuvant diet to prevent cancer recurrence

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Background: There is increasing evidence that the same factors that influence cancer incidence may effect cancer prognosis. In the case of breast cancer, for instance, sedentary lifestyle, overweight, fatty diet, metabolic syndrome, and high serum levels of insulin and sex hormones, are associated with both incidence and the risk of recurrences. In the case of colon cancer the same is true for westerd dietary pattern, sedentary lifestyle, overweight, and serum levels of C-peptide.
Material and Methods: We carried out several dietary intervention trials to test the effect of a comprehensive dietary modification, aimed at reducing insulin levels, based on Mediterranean and macrobiotic dietary traditions, on metabolic and endocrine biomarkers of breast cancer incidence and progression. DIANA-1 randomized 104 healthy but hyperandrogenic postmenopausal women into a 5-month intervention and control group; DIANA-2 randomized 110 postmenopausal breast cancer patients into a 3-month intervention and control wroup, and subsequently offered the intervention to both groups for 9 months. DIANA-3 randomized 90 premenopausal healthy women to a 12-month insulin lowering intervention, with or without protein restriction, and to a control group.
Results: In postmenopausal women randonized in the intervention groups body weight, metabolic syndrome factors, serum insulin, testosterone, and estradiol decreased, while SHBG and IGFBP1 and 2 increased significantly. Before menopause we observed a decrease in IGF-I levels but no change in sex hormones.
Conclusion: Dietary intervention may improve breast cancer prognosis.

621 Individualized prediction of prostate cancer using genetic markers

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Background: Prostate cancer (PCa) has the highest heritability of all cancers. During the last 3 years over 35 risk-associated single nucleotide polymorphisms (SNPs) have been identified. Each SNP only confers to a 1.1−1.5 increased risk and the clinical used of these new genetic markers has been questioned. In PCa there are three possibilities to use these new markers:
1. To identify men at high risk before diagnosis.
2. To increase the sensitivity and specificity of the PSA test in the diagnosis of PCa.
3. To distinguish between men with aggressive and non-aggressive disease.

Here we present data in the ability to identify men at high risk and the impact of increasing numbers of SNPs and the predictive performance of family history of PCa and SNPs.
Methods: Absolute risk for PCa was estimated in a population-based case-control study in Sweden (2,899 cases and 1,722 controls) using family history and three sets of sequentially discovered PCa risk-associated SNPs. Their performance in predicting PCa was assessed by positive predictive values (PPV) and sensitivity.
Findings: SNPs and family history were able to differentiate individual risk for PCa and identify men at higher risk; ~18% and ~8% of men in the study had 20-year (55−74 years) absolute risks that were two-fold (0.24) or three-fold (0.36) greater than the population median risk (0.12), respectively. When predictive performances were compared at absolute risk cutoffs of 0.12, 0.24 or 0.36, PPV increased considerably (~20%, ~30% and ~37%, respectively) while sensitivity decreased considerably (~55%, ~20% and ~10%, respectively). In contrast, when increasing numbers of SNPs (5, 11 and 28 SNPs) were used in risk prediction, PPV approached a constant value while sensitivity increased steadily.
Interpretation: PCa risk-associated SNPs have better predictive performance for men at higher risk. SNPs discovered to date are suitable for risk prediction while additional SNPs discovered in the future may identify more subjects at higher risk. Men identified as high-risk by SNP-based testing may be targeted for PCa screening or chemoprevention.

622 Genetics of familial cancer

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Background: By early this year some 30 genes (high risk genes) have been linked to cancer syndromes and over 100 loci have been associated with cancer, mostly in unselected populations using genome-wide association studies (GWASs). These loci convey low risk but they are common and most of them have no known function. In this presentation I will review the population impact of these to types of gene variants by cancer type.
Material and Methods: Population attributable fractions (PAF) and familial relative risk (FRR) are calculated for the susceptibility genes/loci. PAFs have been used extensively for environmental risk factors of cancer in order to rank them and to assess the prospective gains in disease prevention. Their use in cancer genetics is relatively new, probably because the mutant variants of the 'classical' high penetrant cancer genes are so rare that their contribution to the population burden is low compared to the high individual risks.
Results: As an example on breast cancer, the nine established loci give a joint PAF of >60%, but explaining only some 8% of the empirical FRR. The GWASs on colorectal cancer include the chromosome 8 locus, represented by SNP rs6983267 and shared by prostate cancer, accounting for 0.4% of the empirical FRR of 2.7. Another locus close to *SMAD7* confer a marginally lower risk and it accounts for 0.3% of the empirical excess FRR. The joint PAF for these two loci is 27.8%; their FRR would be 1.01, accounting for 0.7% of the empirical excess FRR of colorectal cancer. Examples are given on several other cancers. Differences between high penetrant (relative risk some 5 or more) and low penetrant (relative risks below 1.5 or 2.0) genes have recently been illustrated by 'molecular landscaping'. The PAF of a gene variant integrates any unmeasured gene-gene and gene-environment interactions for the particular study population. With the current volume of genetic data on susceptibility genes, PAFs are useful in putting the findings into an etiologic perspective. The calculation of joint PAFs for several genes gives a progress report into the limits of understanding of the genetic basis of a disease.
Conclusions: The GWASs have identified a new repertoire of cancer susceptibility genes and loci which are characterized by a high frequency of the risk allele and a low relative risk, in line with the common disease-common variant paradigm. A reason for these apparent discrepancies is that the SNP platforms used have been built for relatively common variants (minor allele frequency >0.1) constraining the results to variants with high PAF and low FRR. However, once the true functional varaiants are found the FRRs