MOLECULAR GENETICS OF DISEASE

IL5 08.45 – 09.30

HOST GENETICS OF TUBERCULOSIS AND LEPROSY

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Tuberculosis, caused by Mycobacterium tuberculosis, and leprosy, caused by M. leprae, are the two most medically important diseases with mycobacterial etiology. A large number of studies have established the host genetic background as critical mediator for susceptibility to both diseases. To determine the molecular identity of these mycobacterial host susceptibility genes, our group has employed both whole genome scanning and candidate gene approaches. In leprosy, we have used whole genome linkage analysis followed by high resolution association mapping for the positional cloning of major leprosy risk variants located in the shared promoter region of the PARK2 and PACRG genes. Following the same strategy we have also identified a low producing lymhotoxin-alpha allele as major susceptibility factor for early onset leprosy. For tuberculosis, our experiments have focused on applying mouse susceptibility genes to candidate gene studies in human populations. Specifically, we have investigated the contribution of the mouse Nramp1 mycobacterial susceptibility gene for its contribution to primary tuberculosis disease. These studies revealed the critical importance of host-environment interactions and their impact on the strength of genetic risk factors. Finally, in more recent studies, we have identified a major dominant acting tuberculosis susceptibility gene in multiplex Moroccan tuberculosis families. The presence of dominant major susceptibility factors raises interesting questions about the strength of selection applied against such factors by a deadly disease such as tuberculosis.

FREE PAPER SESSION 3

O17 09.30 – 09.50

STEPWISE REPLICATION IDENTIFIES A LOW-PRODUCING LYMHPOTOXIN-ALPHA ALLELE AS A MAJOR RISK FACTOR FOR EARLY-ONSET LEPROSY

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Leprosy is a chronic infectious disease caused by Mycobacterium leprae that still affects an estimated 300,000 individuals each year. Here we dissected a linkage peak (LOD=2.7) on chromosome region 6p21 identified in a previous genome-wide scan [1]. In 194 Vietnamese simplex families, an association scan of a 10.4 megabase region underlying the linkage peak targeted the lymhotoxin-alpha (LTA) gene for high-resolution association mapping. All SNPs in the bin containing the functional [2] LTA+80 variant (AA/AC vs. CC P=0.007; OR=1.74 [1.16-2.60]) were associated with leprosy. The association of LTA+80A was replicated in a second independent sample of 104 Vietnamese simplex families (P=0.003; OR=2.34 [1.27-4.31]). When stratifying on age at diagnosis, the association of LTA+80 was captured almost entirely by cases diagnosed before age 16 (P=0.00004), reflecting significant genetic heterogeneity of the LTA+80 effect between cases <16 years and those >=16 years (P=0.00054). In the second sample, the odds-ratio increased in cases <16 years (OR=5.31 [1.19-23.60]) resulting again in significant evidence for heterogeneity (P=0.04). When both Vietnamese samples were combined, the evidence for association overall and in cases <16 years was very strong (P=0.000024 and P=0.0000004, respectively).
In a third sample of 364 cases and 371 controls from Northern India, the association of LTA+80A was replicated (P=0.01; OR=1.60 [1.10-2.33]) using multivariate analysis to adjust for differences in linkage disequilibrium structure. The strength of association increased in the youngest age group (P=0.004; OR=2.95 [1.32-6.58]) replicating the age-effect and genetic heterogeneity (P=0.003) observed in the Vietnamese samples.

Our results, replicated in three samples from two ethnically diverse populations, show that the low-producing LTA+80A allele is a strong risk factor for early-onset leprosy.

References
[1] Mira MT et al. Nat Genet. 2003 Mar;33(3):412-415.
[2] Knight JC et al. Nat Genet. 2004 Apr;36(4):394-399.

O18 09.50 – 10.05
HIGH RESOLUTION MOLECULAR ANALYSIS OF A RING CHROMOSOME REVEALS UNEXPECTED ALTERATIONS: LESSONS FOR ROUTINE DIAGNOSIS

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Introduction. Ring chromosomes are rare cytogenetic findings and are associated at phenotypic level with mental retardation and congenital abnormalities. Often telomeric and coding sequences are deleted if a ring is formed, which can have a high impact on the severity of the phenotype. Due to specific immunological problems in a patient with a routinely cytogenetically detected ring chromosome 14, further molecular karyotyping was performed.

Methods and Materials and Results. FISH showed a deletion of the entire IgH locus on 14q32.33. In order to determine breakpoints, ±1 Mb spaced large clone insert array-CGH was performed and a complex interstitial duplication with terminal deletion pattern was revealed. For the exact characterization of the involved breakpoint regions further tests using higher resolution array-CGH platforms were needed. Due to unequal reporter element distribution in the breakpoint regions, we chose to compare the performance of two different platforms: the Agilent Human Genome CGH 244A oligo based platform and the Affymetrix GeneChip Human Mapping 500k SNP-typing based platform. Analysis of the data revealed an even more complex genotype with a 681 kb triplication, a 11.344 Mb duplication, a 2.641 Mb hemizygous deletion and a 27.4 kb homozygous deletion.

Conclusions. A comparison of high resolution array-CGH platforms will be shown, which demonstrates the importance of a case based choice for the platform to use.

019 10.05 – 10.20
THE IMPACT OF CDC4 MUTATIONS AND CYCLIN E INCREASE ON CHROMOSOMAL INSTABILITY

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Chromosomal instability (CIN) is characterized by an increased rate of chromosomal gains or losses resulting in a high number of aneuploid cells. CIN is typically observed in the majority of human epithelial cancers, however, at present, the origin of CIN in human cancers is unclear. Several studies suggested the existence of CIN causing mutations in specific genes, e.g. in spindle checkpoint genes such as BUB1 and MAD2. However, mutations in these genes are rarely found in human cancer. Therefore, it is a matter of debate, whether CIN can be caused by a single hit in a certain gene or whether CIN represents the consequences of several/multiple changes within a cell. Recently, several studies described a direct correlation between deregulated cyclin E and CIN. The regulation of cyclin E levels is dependent on CDC4 (FBXW7), an evolutionary conserved E3 ubiquitin ligase, which binds directly to cyclin E and is thought to target it for ubiquitin-mediated degradation. CDC4 mutant cells show persistently elevated levels of cyclin E protein (Moberg et al. 2001) and constitutive overexpression of cyclin E was shown to cause CIN (Spruck et al. 1999). The targeted disruption of both CDC4 alleles by homologous recombination in the karyotypically stable colorectal carcinoma cell lines HCT116 and DLD1 was reported to result in both increased cyclin E levels and CIN (Rajagopalan et al. 2004). However, when Kemp and co-workers (2005) screened 244 colorectal tumors and 40 cell lines for CDC4 mutations and allelic loss, a similar spectrum of
CDC4 mutations in six percent of tumors as described by Rajagopalan and co-workers were found. However, there was no association between the presence of a CDC4 mutation and chromosomal instability. To investigate this discrepancy between in vivo and in vitro observations and also to contribute to the question whether single-hits, e.g. mutations in individual genes can cause CIN, we investigated both the cyclin E levels and the chromosomal stability in several cell lines with CDC4 mutations. Our data clearly confirm that CDC4 mutations indeed result in elevated cyclin E levels. To determine chromosomal stability in the respective cell lines we used a number of different approaches such as interphase FISH, percentage of cells with micronuclei, and chromosome number in metaphase spreads. However, this plethora of methods failed to show any evidence for CIN, which questions the presumed absolute correlation between cyclin E levels and CIN. In contrast to other studies, our results suggest that constitutional cyclin E increase alone may not be sufficient to cause CIN. Our data indicate that CIN is rather the result of multiple, complex changes, than single mutations. In addition, our data has far reaching consequences for drawing conclusions from cell lines after gene disruption.

O20 10.20 – 10.40
GENOMIC PROFILING TO IDENTIFY NOVEL STROKE GENETIC RISK FACTORS

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Introduction. Stroke, a "brain attack" cutting off vital blood to the brain cells, is the second cause of death worldwide and the leading cause of death in Portugal. It is even more disabling than lethal and requires more effective prevention and treatment strategies. Stroke is a complex disease resulting from the interplay of environmental and genetic factors, but very few genetic factors for the common form of stroke have been identified. To identify additional susceptibility genes we are conducting the novel "genomic convergence" approach which combines data from whole-genome linkage screens with data from gene profiling analyses to determine which genes will be tested in association studies.

Methods and Materials. We are conducting gene expression analysis in peripheral blood mononuclear cells of carefully matched stroke cases and controls using Affymetrix GeneChip Human Genome U133 Plus 2.0 microarrays, and starting to perform association studies on candidate genes using Sequenom's technology in our complete biobank.

Results. Preliminary gene profiling studies identified 78 genes differentially expressed among both young (45-54y) and old (65-74y) cases vs. controls with a 1.5 fold-change cutoff. Phosphodiesterase 4D (PDE4D), currently the strongest genetic risk factor for stroke, emerged as one of the two genes differentially expressed and mapping to the 5q12 Icelandic linkage region. We tested for association 47 SNPs in the 5'end of PDE4D and found an association with stroke in 175 cases and 175 controls. We are currently confirming the expression studies in a larger dataset and performing association studies on genes identified through the genomic convergence approach using other human and animal model linkage studies.

Conclusions. We validated our genomic convergence approach in stroke and will present the results of expression profiling and association studies with novel candidate genes.
**021 13.15 – 13.30**
**DETECTION OF CRYPTIC GENOMIC ALTERATIONS IN BURKITT LYMPHOMAS BY GENOMEWIDE SINGLE NUCLEOTIDE POLYMORPHISM (SNP) MICROARRAY MAPPING**

Violaine Havelange; Evelyne Callet-Bauchu; Ivan Theate; Francine Mugneret; Lucienne Michaux; Carole Barin; Nicole Dastugue; Pascale Saussoy; Dominique Penther; Eric Lippert; Miikka Vikkula; Hélène A. Poirel.

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**Introduction.** Burkitt lymphomas (BL) are highly aggressive mature B-cell lymphomas characterized by MYC locus rearrangement leading to deregulation of this oncogene which plays a major role in proliferation and apoptosis. Additional chromosomal abnormalities could be involved in BL pathogenesis. A recent conventional cytogenetic study showed that del(13q), +7q and der(3q) have a negative prognostic impact in childhood B-cell mature lymphomas. Aims of the study To characterize these prognostic additional chromosomal abnormalities and to look for cryptic genomic alterations in order to reveal candidate genes and/or cellular pathways involved in Burkitt lymphomagenesis.

**Material and method.** DNA from 36 BL (adults and children) was analyzed by 50K Xba SNP arrays (Affymetrix), a genome-wide study of single nucleotide polymorphisms (SNPs). This technique allows the detection of allelic imbalances and losses of heterozygosity.

**Results and discussion.** Prognostic additional chromosomal abnormalities have been refined. +7q are homogeneous partial gains. Non random 13q and 3q abnormalities with a minimal modified region of respectively 3,1kb and 1,4kb were identified. Both regions contain candidate genes which are under study. Many cryptic imbalances have been detected. The more frequent are partial deletions of 9p, 12q and partial gains of 1q, 18q. 144 acquired partial uniparental disomies (pUPD) (defined as region of at least 50 SNPs) were found by SNP-arrays. pUPD are characterized by loss of heterozygosity without chromosomal deletion and probably result from mitotic abnormalities. The physiopathogenic role of pUPD remains unclear. Firstly, it can be polymorphisms. Secondly, random pUPD can reflect genomic instability. Thirdly, non random pUPD may have a pathogenic effect, rendering the cell homozygous for a preexisting mutation by activation of an oncogene or inactivation of a tumor suppressor gene (TSG). Study of candidate genes in pUPD is under process, to unveil mutations of oncogenes or TSG which can be involved in BL pathogenesis in cooperation with MYC deregulation.

**022 13.30 – 13.45**
**HIDDEN UNBALANCED CHROMOSOMAL ABNORMALITIES REVEALED BY TILING ARRAY-CGH IN CHILDREN WITH NORMAL G-BANDING KARYOTYPE**

Ekaterina Kuchinskaya; Ann Nordgren; Mats Heyman; Jacqueline Schoumans; Martin Corcoran; Johan Staaf; Åke Borg; Stefan Söderhäll; Dan Grandé; Mags Nordskjöld.

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**Introduction.** Cytogenetic results are of major prognostic importance in children with acute lymphoblastic leukemia. Therefore, failure to perform a correct cytogenetic investigation may lead to the wrong treatment strategy, and hence, increased risk to relapse or overtreatment.

Failure to find cytogenetic abnormalities may be due to overgrowth of normal cells and few malignant metaphases, or poor morphology and spreading of the chromosomes and low resolution of the method. Another explanation is the presence of abnormalities that are below the resolution of the existing diagnostic methods. Tiling-resolution array-CGH allows analysis of unbalanced changes in the genome at the resolution of 300 kb.

**Methods and Materials.** We have used a 33K tiling resolution BAC array to evaluate 28 children with normal or failed karyotype using G-banding. Genomic DNA was isolated from fresh frozen bone marrow cells at diagnosis and complete remission. DNA from complete remission was used as a reference in the array-CGH experiments, in order to avoid conflicting results due to normal genomic variation. Interphase FISH with labeled BAC clones from the sites of copy number alterations (CNA) was used to confirm the results.

**Results.** According to the main aberration pattern, the patients were divided into a five groups: hyperdiploidy (n=4), ETV6/RUNX1 (n=7), RUNX1 amplification (n=5), a group with small abnormalities on array-CGH (under the resolution of CC, n=4), no abnormalities on array-CGH (n=4). Patients with T-ALL (n=4) were
considered as a separate group. Most of the patients had 5-7 gains and losses of different size. In four patients we were unable to observe any CNA. This might be explained by the limitation of the method or by absence of CNA in these specific samples, e.g. balanced chromosome rearrangements.

Conclusions. Tiling resolution array-CGH reveals genetic changes in 86% of the patients with a normal or failed karyotype. In addition to larger abnormalities, most of these samples show copy number alterations that are below the resolution of G-banding.

O23 13.45 – 14.00
FAMILIAL INHERITED MICROTIA CAUSED BY A BENIGN CNV AMPLIFICATION AT CHROMOSOME 4PTER

Irina Balikova; Kevin Martens; Cindy Melotte; Steven Van Vooren; Yves Moreau;Heike Starke; David Vetrie; Heike Fiegler; Nigel Carter; Thomas Liehr; Gert Matthijs; Jean-Pierre Fryns; Ingele Casteels; Koen Devriendt; Joris Vermeesch
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Recently, large scale benign copy number variations (CNVs) were uncovered, encompassing over 12% of our genome. Deletions and duplications of these regions present in normal individuals contain genes considered to be dosage tolerant for human development. Here we present a 4 generation family with autosomal dominant inheritance of microtia, eye coloboma and lacrimal duct obstruction, a novel syndrome. This phenotype is linked (lod >3) with a cytogenetically visible alteration at 4pter but was never described in patients with 4pter deletions nor duplications. We demonstrate by array CGH, qPCR, FISH and Southern blot that the disorder is caused by the amplification of a 780kb region on 4pter, encompassing the olfactory receptor gene cluster. This is the first example in which the amplification of a well-known copy number variable region causes a phenotype and hence is a novel genetic disease mechanism causing a dominant disorder. In addition, we investigated the organization of the amplified fragment in order to understand the mechanism by which this amplification occurred. We show that perfect copies of the 780kb fragment are amplified in tandem.

IN SILICO GENOME ANALYSIS

IL6 14.00 – 14.45
TOWARDS A COMPREHENSIVE MAP OF COPY NUMBER VARIATION IN THE HUMAN GENOME

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Copy number variation (CNV) in the genome is extensive and yet is grossly under-ascertained. The resolution of CNV detection of most current technology platforms is approximately 50kb, and yet copy number variation two orders of magnitude smaller than this is likely to go undetected by exon resequencing. Furthermore, we know that smaller CNVs are far more numerous than larger CNVs, and so improved CNV detection resolution can be expected to dramatically increase the numbers of known CNVs. We have detected that CNV has a appreciable impact on gene expression and is subject to purifying selection, and this motivates the generation of a more comprehensive map of all CNV. Recent technological developments in both arrays and sequencing present opportunities to detect all common CNVs (with minor allele frequencies of 5% of more) of length 500bp and I will discuss our experiences with both of these approaches. We are also developing a robust 'gold standard' approach for optimising CNV detection parameters and comparing different platforms. We will make all these data publicly available for the benefit of the entire research community.

FREE PAPER SESSION 4
Introduction. Structural variants have recently become a popular area of research in the biomedical research community. In particular, reports of widespread copy number variation (Iafrate et al. 2004; Sebat et al. 2004) and large deletions (McCarroll et al. 2005; Conrad et al. 2005) revealed that structural variation affects a substantial portion of the human genome and is likely to play a significant role in human disease. While comparative genome hybridization (CGH) and SNP genotyping technologies have been adapted to detect structural variants, doing so at the nucleotide level remains a challenge. We have developed a method, based on the BLAST algorithm, that allows for the high-throughput identification of structural variation from sequence trace data.

Methods and Materials. Each set of sequence traces was used to create a BLAST database against which the reference genome was aligned using WU-BLAST. The BLAST results were parsed and filtered to identify reads that appear to span a molecular lesion or "breakpoint". Alignment positions and orientations were analyzed to characterize the size, type, and precise molecular boundaries of the apparent structural variant.

Results. We tested the method using data from the model organism C. briggsae. From a database of 13,632 traces we identified 966 breakpoint reads representing 901 unique arrangement events. The results were further analyzed with CrossMatch and filtered for indel events. Some 208 were identified (46 read-through insertions and 164 deletions). We chose a test set of 12 indels, and designed PCR assays for them. Nine of the 12 PCR assays were successful under uniform conditions and each of the nine reflected the predicted indel.

Conclusions. Our method is both efficient and sensitive, and when applied to the wealth of human sequence trace data, should offer a powerful approach for identification of structural variants in the human genome.
O26 15.45 – 16.05
WEIGHTED CLUSTERING OF CALLED aCGH DATA

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Array comparative genomic hybridization is a lab technique to measure chromosomal copy number changes. A clear biological interpretation of the measurements is obtained by mapping these onto an ordinal scale with categories loss/normal/gain of a copy. The pattern of gains and losses harbors a level of tumor specificity. We present WECCA (WEighted Clustering of Called aCGH data), a method for weighted clustering of the ordinal aCGH data. Two similarities to be used in the clustering and particularly suited for ordinal data are proposed, which are generalized to deal with weighted observations. In addition, a new form of linkage, especially suited for ordinal data, is introduced. In a simulation study we show that the proposed cluster method is competitive to clustering using the continuous data. We illustrate WECCA using an application to a breast cancer data set, where WECCA finds a clustering that relates better with survival than the original one.

References
[1] W.N. van Wieringen, M.A. van de Wiel, B. Ylstra (2007), "Weighted clustering of aCGH data", submitted for publication.

O27 16.05 – 16.20
CANDIDATE CANCER GENE DISCOVERY USING KC-SMART: A NOVEL METHOD FOR STATISTICAL MULTI-EXPERIMENT aCGH DATA ANALYSIS

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Introduction. Genomic aberrations in the form of regional DNA copy number alterations (CNAs) are commonly observed phenomena in most cancers, and can be readily identified in a genome-wide fashion via array-based comparative genomic hybridization (aCGH). Identifying regions of DNA that are amplified or deleted in a significant fraction of tumor samples can facilitate identification of genes that are causal in the development of cancer. Until now, no method has been described that provides a statistical framework in which these regions can be identified without prior discretization of the aCGH data. This study applies a new method of analyzing non-discretized aCGH data to identify regions that are significantly aberrant across an entire tumor set: Kernel Convolution - a Statistical Method for Aberrant Region deTecTion (KC-SMART).

Methods and Materials. KC-SMART uses kernel convolution to generate a Kernel Smoothed Estimate (KSE) of copy number alterations across the genome, aggregated over all tumors. The peaks in the KSE are tested against randomly permuted data to obtain significantly aberrant regions. By varying the width of the kernel, a scale space is created which enables the detection of aberrations varying in size.

Results. KC-SMART performs better than a comparable method, STAC, and it enriches for cancer genes in an analysis of 67 human sporadic breast tumors. Furthermore, KC-SMART identifies 18 aberrant regions in mammary tumors from p53 conditional knockout mice. These regions, when combined with gene expression microarray data, point to various known cancer genes and several potential new candidate cancer genes. We also show that incorporation of a scale space analysis in KC-SMART facilitates analysis of complex aberrations.

Conclusions. By combining an unbiased statistical approach for multi-experiment aCGH analysis with gene expression data, we are able to find known cancer genes as well as candidate genes that can be validated for their function in tumorigenesis.

O28 16.20 – 16.35
REDEFINING THE RESOLUTION OF aCGH

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Introduction. Array comparative genomic hybridization (aCGH) has rapidly become the standard technique for the analysis of gene dosage in disease. The design of an aCGH platform can incorporate uniform or highly variable element distributions, leading to bias in the
the repeat clusters in telomere and centromere regions (eg alpha and beta repeats) but the first genome wide approach was achieved with the identification of a human duplicon set1. These duplicons were not randomly spread on the genome but flank microdeletion regions associated with for example Prader Willi or DiGeorge syndrome. Many of the duplicons are pitfalls in the interpretation of genomic-arrays and a recent report of the HapMap project showed a nice correlation between duplicon regions and polymorphic regions in of two different platforms: a tiled human BAC array and the Affymetrix 500K SNP array2.

To visualize the actual complexity at array hotspots or candidate region related to specific diseases, an integrated view on genomic and experimental data must be available in a customized way. For this we developed a generic visualization tool called the 3D viewer. Here we would like to demonstrate the flexibility, customisation options, current and potential value of this 3-D viewer. In a few examples we will show the intuitive integration of experimental data from different diagnostic platforms (MLPA, Q-PCR, SNP/BAC arrays) with a selection of the currently available public data sets (eg NCBI, CNV, DECIPHER). Also for future visualization requirement, high through put expression/SNP arrays, education purposes, nuclear organization, epigenetic and “molecular” imaging this 3D viewer can be the basis of many visual concepts.

References
Bailey et al , 2002 , Science 29:1003;[1] Redon et al , 2006 Nature 444, 444

16.50 – 17.00
ANNOUNCEMENT SEPTEMBER WORKSHOP IN HELSINKI

17.00 – 17.10
ANNOUNCEMENT NEXT CONFERENCE IN BARCELONA

17.10 – 18.00
BOARD MEETING:
MEMBERS SCIENTIFIC COMMITTEE ONLY

19.00 – late
DINNER AT THE WEIGH HOUSE (DE WAAG) **
AMSTERDAM CITY CENTRE
(** Only eligible researchers)