550F Frequency of gene usage and copy number variation within the rearranged Immunoglobulin Heavy-Chain Variable locus based on immune repertoire sequencing, M.J. Rieder 1, D. Williams 1, A. Sherwood 1, R. Emerson 1, C. Desmarais 1, M. Chung 1, H. Robbins 1, 2, C. Carlson 1, 2. 1) Adaptive Biotechnologies, Seattle, WA; 2) Fred Hutchinson Cancer Research Center, Seattle, WA.

The human adaptive immune system is composed of both B and T cells that undergo somatic recombination at specific loci to create rearrangements of Variable (V), Diversity (D) and Joining (J) gene segments. For the B-cell immunoglobulin receptor heavy-chain (IGH), the CDR3 regions are defined by the VDJ gene segments and nucleotide insertions/deletions at these junctions that create the vast sequence diversity of the IGH repertoire. Characterizing the germline DNA in these regions is impeded by the high sequence similarity between gene segments, mutation and copy-number variation (i.e. large insertions/deletions). Currently, there is a fundamental lack of information about the baseline IGH immune repertoire V gene usage and diversity within healthy human controls. To provide an estimate of this, we sequenced functionally recombined gene segments to infer the underlying gene structure. From a set of 132 healthy controls we sorted C19+/CD27+ B-cells from whole blood and amplified germline DNA using a highly multiplexed PCR assay that targeted the rearranged IGH receptor locus. Following DNA sequencing and data processing to assign V, D and J gene families and names, we examined the usage frequency of IGH gene segments across all individuals. We found that of the 98 V gene segments only 56 (57%) were used at a frequency > 0.1%, and ~10 showed little to no usage (present in <1% of individuals). This data also allowed us to identify two IGHV genes currently annotated as orphans (pseudogenes assigned to an alternate chromosomal location) that had non-trivial functional usage (IGHV4/OR15-8; IGHV3/OR16-09) and therefore must reside at the IGH locus on chromosome 14. Finally, by taking this functional approach we were able to screen all V gene segments for germline copy-number variation (e.g. large insertion/deletion events encompassing individual gene segments) by looking for an excess of deletion events or modal changes in gene usage. We confirmed that existence of 12 of 15 previously identified deleted IGHV gene segments. Strong deletion evidence was observed for an additional VDJ gene segment (IGHV3-33, IGKV4-04, IGKV4-41, IGKV3-35) and ten with highly likely germline deletion events. These data suggest that functional immune profiling of rearranged immune receptors provides a more robust method of identifying individual structural variation and provides insight into the immune repertoire of healthy controls.

551W Copy Number Variants near SLC2A9 Are Associated with Hyperuricemia, R.B. Scharpf 1, L. Mireles 1, E. Halper-Stromberg 1, A. Tin 1, A. Chakravarti 1, E. Boerwinkle 2, J. Coresh 2, W.H.L. Kao 1. 1) Oncology, Johns Hopkins University School of Medicine, Baltimore, MD; 2) Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD.

Hyperuricemia is associated with multiple diseases, including gout, cardiovascular disease, and renal disease. Serum urate is highly heritable suggesting a strong genetic component, yet genome-wide association studies of nucleotide polymorphisms (SNPs) and serum uric acid concentrations explain only a small fraction of the heritability. Whether common copy number variants (CNVs) contribute to uric acid levels is not known. Here, we use high-throughput genotyping arrays to assess DNA copy number on a genome-wide scale among 9,738 individuals of European ancestry who use high-throughput genotyping arrays to assess DNA copy number on a genome-wide scale among 9,738 individuals of European ancestry who.

552T Comprehensive comparison of copy number variations detection using Illumina Omni 2.5M and Affymetrix Cytoscan® arrays, C. TAM 1, 2, E. WONG 2, H. SUIT 1, S. CHERNY 1, 2, P. SHAM 1, 2, 4, 5, P. TAM 1, 2, 5, M. GARCIA-BARCELO 1, 2, 3, 5. 1) Department of Psychiatry; 2) Centre for Genomic Sciences; 3) Department of Surgery; 4) State Key Laboratory of Brain and Cognitive Sciences; 5) Centre for Reproduction, Development and Growth, the University of Hong Kong, Pokfulam, Hong Kong.

Structural variation has been recognized as a genetic risk factor contributing to human diseases, and in particular, congenital disorders. Smaller scale copy number variations (CNVs) have also been linked to a number of developmental phenotypes, including intellectual disability as well as autism spectrum disorders. The precise detection of CNVs is therefore necessary for understanding disease pathogenesis. Recently, the new generation of SNP-based arrays, Affymetrix Cytoscan® and Illumina Omni 2.5M offer an unique opportunity for improved discovery of CNVs with their special design. We explored the performance of these new platforms by genotyping in duplicate on each platform, 4 samples from patients diagnosed with a congenital disease. Performance of the CNV calling was assessed on the basis of sensitivity and specificity, both within and across platforms using various CNV detection software. Similar to previous generations of SNP-based genotyping arrays, the concordance of CNVs was found to be moderate and dependent on the calling software. In general, Cytoscan offered higher sensitivity whereas more specific calls were achieved using Omni. To conclude, multiple CNV calling methods should be employed for reliable CNV calling.

553F Characterisation of the RNU2 CNV, a bulky neighbour for BRCA1, C. Taxis 1, 2, 3, 4, 5, N. Monnet 1, 2, M. Imbert 1, 2, M. Buisson 1, L. Barjoux 1, C. Cuenin 1, C. Schluth-Bolard 1, 4, D. Sanlaville 1, 4, Z. Herceg 1, E. Cessille 1, M. Ceppi 1, L. Duret 1, OM. Sinilnikova 1, 2, S. Mazoyer 1. 1) Genetics of Breast Cancer, Cancer Research Center of Lyon, CNRS UMR5286/Inserm U1052; Université Lyon 1, Lyon, France; 2) Genomic Vision, Bagneux, France.

Structural variation has been recognized as a genetic risk factor contributing to human diseases, and in particular, congenital disorders. Smaller scale copy number variations (CNVs) have also been linked to a number of developmental phenotypes, including intellectual disability as well as autism spectrum disorders. The precise detection of CNVs is therefore necessary for understanding disease pathogenesis. Recently, the new generation of SNP-based arrays, Affymetrix Cytoscan® and Illumina Omni 2.5M offer an unique opportunity for improved discovery of CNVs with their special design. We explored the performance of these new platforms by genotyping in duplicate on each platform, 4 samples from patients diagnosed with a congenital disease. Performance of the CNV calling was assessed on the basis of sensitivity and specificity, both within and across platforms using various CNV detection software. Similar to previous generations of SNP-based genotyping arrays, the concordance of CNVs was found to be moderate and dependent on the calling software. In general, Cytoscan offered higher sensitivity whereas more specific calls were achieved using Omni. To conclude, multiple CNV calling methods should be employed for reliable CNV calling.

554W Characterisation of the RNU2 CNV, a bulky neighbour for BRCA1, C. Taxis 1, 2, 3, 4, 5, N. Monnet 1, 2, M. Imbert 1, 2, M. Buisson 1, L. Barjoux 1, C. Cuenin 1, C. Schluth-Bolard 1, 4, D. Sanlaville 1, 4, Z. Herceg 1, E. Cessille 1, M. Ceppi 1, L. Duret 1, OM. Sinilnikova 1, 2, S. Mazoyer 1. 1) Genetics of Breast Cancer, Cancer Research Center of Lyon, CNRS UMR5286/Inserm U1052; Université Lyon 1, Lyon, France; 2) Genomic Vision, Bagneux, France.

Structural variation has been recognized as a genetic risk factor contributing to human diseases, and in particular, congenital disorders. Smaller scale copy number variations (CNVs) have also been linked to a number of developmental phenotypes, including intellectual disability as well as autism spectrum disorders. The precise detection of CNVs is therefore necessary for understanding disease pathogenesis. Recently, the new generation of SNP-based arrays, Affymetrix Cytoscan® and Illumina Omni 2.5M offer an unique opportunity for improved discovery of CNVs with their special design. We explored the performance of these new platforms by genotyping in duplicate on each platform, 4 samples from patients diagnosed with a congenital disease. Performance of the CNV calling was assessed on the basis of sensitivity and specificity, both within and across platforms using various CNV detection software. Similar to previous generations of SNP-based genotyping arrays, the concordance of CNVs was found to be moderate and dependent on the calling software. In general, Cytoscan offered higher sensitivity whereas more specific calls were achieved using Omni. To conclude, multiple CNV calling methods should be employed for reliable CNV calling.

Posters: Genome Structure, Variation and Function