1375/W/Poster Board #1033

Frequency and inheritance of CNVs less than 1 Mb in a clinical cohort. How do we interpret these? *A. Patel, S-H.L. Kang, S. Neill, M. Strivens, C.A. Shaw, P. Stankiewicz, S.R. Lalani, C.A. Bacino, S.W. Cheung.* Dept Molecular & Human Gen, Baylor Col Medicine, Houston, TX.

Application of Microarray analysis for detection of copy number variation (CNV) has revealed that the human genome is awash with structural variation. The locus specific mutation rate for these structural variations is two to four orders of magnitude greater than single nucleotide changes (NG 39:S43-47,2007). An enormous amount of data has been deposited in various databases for structural variations but the basic question of what role, if any, do they play in human disease remains to be elucidated. These databases have been routinely used by clinical laboratories to guide the interpretation of CNVs less than 1 Mb in size in non-disease regions. We reviewed CNVs of less then 1 Mb in a cohort of 4186 consecutive patients examined using a custom chromosomal microarray (CMA V7 105K OLIGO) that interrogates the whole genome at an average resolution of 30 Kb with increased coverage at disease loci . Included in the CMA are probes for all the known microdeletion/duplication syndromes (>270) while excluding repetitive sequences through a combination of bioinformatics and computation. Excluding clinically significant CNVs (>1 Mb), small CNVs in clinical significant regions, and known polymorphic regions, the frequency of these CNVs was 14% (586 patients). Of these, parental analyses were available in 42% of the cases. Forty six percent of these CNVs were maternally inherited, 43% were paternally inherited and 10% were de novo. Interestingly, when the CNV was present only once (i.e. unique to that patient) in our cohort, the likelihood that the CNV contained a gene was 72%. The detailed collected data will be presented. Compiling these data may lead to a more clinically relevant interpretation of smaller CNVs and identification of new genomic syndromes.

1376/W/Poster Board #1034

CHRNA7 15q13.3 Interstitial ~ 500 kb Deletion/Duplication Associated with Speech Delay, ADHD, Autism and Agressive Behavior. *J.H. Tepperberg[1], S. Schwartz[1], R. Pasion[1], R.D. Burnside[1], V. Jaswaney[1], I.K. Gadi[1], H. Risheg[2], E. Keitges[2], C. Bullen[1], B. Williford[1], P.R. Papenhausen[1].* 1) Dept Cytogenetics, Lab Corp America, Res Triangle Pk, NC; 2) Dept Cytogenetics, Lab Corp America, Seattle, WA.

The recurrent 15q13.3 microdeletion/microduplication has been reported to cause mental impairment, autism spectrum disorder, facial dysmorphism, seizures and epilepsy. The 1.5 Mb 15q13.3 critical region (chr:15:28,719,136-30,298,264) contains 6 reference sequence genes and three OMIM annotated genes (TRPM1, KLF13 and CHRNA7). This region appears to have an unequal exchange mediated by segmental duplication breakpoints 4 and 5 (BP4 and BP5). We identified 22 individuals using the Affymetrix 6.0 SNP microarray with 15q13.3q13.3 interstitial microdeletions/duplications - 12 individuals with the commonly reported ~1.5 Mb deletion or duplication, and 11 cases with a smaller ~ 500 kb microdeletion or duplication (chr15:29,754,362-30,298,264). The latter only includes the involvement of the nicotinergic acetycholine receptor gene, CHRNA7, a neuronal ion channel gene, which has been implicated as a candidate gene associated with seizures and epilepsy. The smaller 15q deletion/duplication has, to the best of our knowledge, not been previously reported. Many of the classical clinical phenotypic features of the larger 1.5 Mb deletion and duplication were observed in some these patients, including seizures and epilepsy. The smaller 15q13.3 deletion/duplication region appears to be flanked by a 109 kb segmental duplication between BP4, (BP4a - 29,806,912-29,697,285) and the distal segmental duplication BP5 (30,540,143-30,232,699). Eight of the 11 ~500 kb CHRNA7 cases were duplications and three cases were deletions, one of which was inherited from a reportedly unaffected mother. Some of the common clinical features of the BP4a - BP5 ~500 kb deletion were speech delay, developmental delay, ADHD, aggressive behavior, ADHD, and hearing loss. None of the three deletion cases were reported to have either seizures or epilepsy. Phenotypic features of individuals with the ~500 kb duplication include growth delay, midface hypoplasia, speech delay, mild autism and one case exhibiting seizures. Further studies are needed to determine whether CHRNA7 duplications are more likely polymorphic variants with little clinical significance or possibly causative with incomplete penetrance and/or variable expressivity. These results suggest that the deletion/duplication of the CHRNA7 gene by itself may not be sufficient by itself to cause seizures and epilepsy, and may instead be a susceptibility gene related to speech delay, ADHD, autism and aggressive behavior.

1377/W/Poster Board #1035

DNA array-based copy number analysis in chorionic villus samples (CVS) of spontaneous abortions with normal karyotypes. *T. Yamada[1,3], T. Ohta[3], K. Hosoki[2,3], S. Shimada[1], M. Morikawa[1], T. Yamada[1], K. Yoshiura[4], H. Minakami[1], N. Niikawa[3], H. Yamada[5].* 1) Dept. Obstet. Gynecol., Hokkaido Univ., Sapporo, Japan; 2) Dept. Pediatr., Hokkaido Univ., Sapporo, Japan; 3) Res. Inst. Personalized Health Sci., Health Sci. Univ. Hokkaido, Tobetsu, Japan; 4) Dept. of Hum. Genet., Nagasaki Univ., Nagasaki, Japan; 5) Dept. of Obstet. Gynecol., Kobe Univ., Kobe, Japan.

A half of spontaneous abortions (SA) in the first trimester are caused by chromosome abnormalities. There is a group of patients whose pregnancies end in recurrent spontaneous abortions (RSA). Environmental factors in uterus may also contribute to RSA/SA. To investigate reasons of RSA/SA with normal karyotypes, we analyzed on whether they have a microdeletion/duplication using DNA arrays. We collected 40 chorionic villus samples (CVS) (26 from RSA and 14 from SA) with normal karyotypes. Genomic DNA from 20 CVS was directly applied to DNA arrays, while whole genome amplification (WGA) was performed in the other 20 samples before array analysis as the amount of DNA was not enough. Consequently, we detected copy-number changes at 69 loci on 22 chromosomes. Of the 69 loci, 8 and 61 were those unregistered and registered in UCSC database, respectively. As all the 8 unregistered loci contain structural genes, we focused our attention on them for further analysis, and detected two deletions in one SA sample. As one of them was also found in a parent, it is likely to be a copy-number variant (CNV), whereas the other deletion, i.e., a de novo 11-Mb deletion at 5p14 may directly contribute to SA. Although 32 of the 61 registered loci contain genes, 20 (14 registered and 6 unregistered) loci were those detected after WGA, and thus they remain inconclusive.

1378/W/Poster Board #1036

The effect of large *de novo* chromosomal deletions on gene expression. *M. Ghahramani Seno[1,2], C. Marshall[1,2], P. Hu[1,2], J. McDonald[1,2], T. Paton[1,2], G. Casallo[1,2], S. Scherer[1,2].* 1) Programme in Genetics and Genome Biology, Hospital for Sick Children, Toronto, Ontario, Canada; 2) The Centre for Applied Genomics, Hospital for Sick Children, Toronto, Ontario, Canada.

In a study of a cohort of 427 individuals with autism we identified that ~7% carried *de novo* CNVs, some of which encompassed megabase-sized genomic regions. In order to study the effect of these large *de novo* CNVs (~3-20 MB) on the expression levels of genes they encompass and also on global genes expression, we carefully selected 8 individuals with large *de novo* deletions. The criteria for selection included: 1) having *de novo* deletions confirmed by qPCR on blood DNA, 2) presence of functionally interesting genes and/or miRNAs at the CNV region, and 3) presence of ultra conserved elements with potential regulatory functions at the CNV region. Included in this study is an individual with ~2.8 Mb *de novo* deletion at chromosome 22q11.21 region. This genomic segment and the genes it harbours have been associated with Schizophrenia in a number of studies. Lymphoblstoid cell lines from the selected individuals and their available parents and siblings were cultured under controlled conditions in three biological replicates. RNA was extracted and run on Illumina gene and miRNA expression arrays. Statistic analysis of the data indicated approximately one-half reduction in gene expression of the majority of the expressed genes directly encompassed by the deletion. Moreover, several genes located distant to the deletions and on different chromosomes also showed significant variation in individuals carrying the deletions compared to their family members. For instance, in the individual with deletion of 22q11.21, genes involved in the TP53 network were found dysregulated as indicated by Ingenuity pathway analysis tool. The data is further being mined to evaluate/identify gene networks affected by these large CNV alterations.