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Roche NimbleGen CGH Arrays Enable Characterization of Novel Genomic Disorders Associated with Psychiatric Disease in Recent Studies.

High-resolution comparative genomic hybridization (CGH) has rapidly emerged as the method of choice for molecular cytogenetic detection and characterization of chromosomal abnormalities associated with mental retardation, cancer, and other complex phenotypes. In two recent studies published in the *Journal of Medical Genetics* (1, 2), high-resolution NimbleGen CGH arrays were used to further characterize two recently identified genomic disorders (3, 4).

In the first study, van Bon and colleagues used custom NimbleGen CGH 12x135K and 4x72K arrays to precisely map chromosomal breakpoints in the 15q13 region in a series of individuals with developmental delay and normal karyotype. Initial characterization of the 15q13.3 microdeletion syndrome indicated a frequency of occurrence among mentally retarded individuals similar to Prader Willi syndrome, Angelman syndrome, and Williams-Beuren syndrome (3). In the current study analysis of an additional 18 individuals, harboring the 15q13.3 deletion, revealed highly variable intra- and inter-familial disease characteristics, with inherited deletions in at least 11 of the individuals. In addition, 7 of 10 siblings from four families also harbored the deletion and showed disease characteristics ranging from mild developmental delay, to early childhood learning problems, to no recognizable phenotype. Analysis of four individuals, with a duplication in this region, failed to identify a shared recognizable phenotype, although psychiatric irregularities were observed in two of the individuals. Interestingly, deletions in the 15q13 region were recently described in a study featuring 16 individuals with schizophrenia, one of whom also had autism (5, 6). Together, these research data associate the 15q13.3 microdeletion syndrome with broad disease characteristics, ranging from normal development to mild and severe mental retardation and psychiatric disease, and challenge the paradigm that chromosomal abnormalities inherited from an apparently normal parent are usually without clinical significance.

A second novel genomic disorder involving chromosome 17q21.31 was recently identified and to date, fourteen 17q21.31 deletions have been reported in the medical literature. In the initial report, custom NimbleGen CGH arrays were used to define a minimal critical 478 kb deletion region (4). In

the current study, Koolen and colleagues used a custom NimbleGen 385K array to precisely map chromosomal breakpoints in an additional 5 affected individuals. Results from this analysis narrowed the 17q21.31 critical region to a 424 kb region containing at least six genes, including the *MAPT* gene which is associated with several neurodegenerative diseases. In addition, the NimbleGen CGH array enabled identification of a specific polymorphism in parent samples that is associated with the pathogenic deletion.

Together, these research data establish the 17q21.31 microdeletion syndrome as a clinically and molecularly recognizable genomic disorder that occurs at a frequency of 0.64% among individuals with unexplained mental retardation and is highly under diagnosed.

The studies described above illustrate how the unique high resolution and flexible array design advantages of NimbleGen CGH arrays have enabled the identification and molecular characterization of novel microdeletion syndromes, and the realization that these syndromes can represent unpredictable and highly variable disease characteristics. Continued research focused on the identification and characterization of microdeletion and duplication syndromes will be essential to establish diagnostic criteria in the clinic.

Roche NimbleGen is a leading innovator, manufacturer, and supplier of a proprietary suite of DNA microarrays, consumables, instruments and services. Roche NimbleGen produces high-density arrays of long oligonucleotide probes that provide greater information content and higher data quality necessary for studying the full diversity of genomic and epigenomic variation. The enhanced performance is made possible by Roche NimbleGen's proprietary Maskless Array Synthesis (MAS) technology, which uses digital light processing and rapid, high-yield photochemistry to synthesize long oligonucleotide, high-density DNA microarrays with extreme flexibility. For more information about Roche NimbleGen, please visit the company's website at www.nimblegen.com

- (1) von Bon, et al. Further delineation of the 15q13 microdeletion and duplication syndromes : A clinical spectrum varying from non-pathogenic to a severe outcome. *Journal of Medical Genetics*. 2008.063412
- (2) Koolen, et al. Clinical and molecular delineation of the 17q21.31 microdeletion syndrome. *Journal of Medical Genetics*. 45:710-720 (2008)
- (3) Sharp, et al. A recurrent 15q13.3 microdeletion syndrome associated with mental retardation and seizures. *Nature Genetics*. 40:322-8 (2008).
- (4) Sharp, et al. Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome. *Nature Genetics*. 38, 1038 - 1042 (2006)
- (5) Stefansson, et al. Large recurrent microdeletions associated with schizophrenia. *Nature*. 455, 232-236 (11 September 2008)

- (6) Stone, et al. Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature*. 455, 237-241 (11 September 2008)

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For further information please contact:

Roche Diagnostics

Dr. Burkhard Ziebolz

Phone: +49 8856 604830

Email: burkhard.ziebolz@roche.com

Roche NimbleGen

Kary Staples

Phone: +1 608 218 7623

Email: kary.staples@roche.com