Keynote Lecture XVII

Genome Architecture, Rearrangements, Evolution and Genomic Disorders

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James R Lupski is the Cullen Professor of Molecular and Human Genetics and a Professor of Pediatrics at Baylor College of Medicine. He received his MD, PhD training in the MSTP at NYU School of Medicine where his PhD research focused on bacterial genetics. After training in pediatrics and medical genetics Dr Lupski's laboratory began investigations on the molecular genetic basis of Charcot-Marie-Tooth disease and related inherited peripheral neuropathies. In addition, a portion of the laboratory continued to work on basic bacterial genetics and helped develop a technology for fingerprinting bacteria which has had widespread utility in molecular epidemiologic investigation of nosocomial infections, food borne outbreaks, and various uses in agriculture.

Through studies of Charcot-Marie-Tooth disease, a common autosomal dominant trait, and Smith-Magenis syndrome, a contiguous gene deletion syndrome, his laboratory delineated the concept of "genomic disorders." Viewing genetic information in the context of the entire genome his work recognized that the mechanism of some genetic disease is best understood not at the level of gene or chromosome, but instead at a genomic level. An increasing number of human diseases are recognized to result from recurrent DNA rearrangements involving unstable genomic regions. Other novel mechanisms for disease transmission described in his laboratory include the concept of triallelic inheritance wherein manifestation of disease phenotype within a family may require three mutant alleles. Triallelic inheritance may represent a transmission model that bridges classic Mendelian disorders with complex traits.

Dr Lupski has co-authored over 325 articles published in professional journals and co-edited one book entitled Bacterial Genomes Physical Structure and Analysis. *In 2002, he received the Curt Stern Award from the American Society for Human Genetics recognizing the most significant achievement in human genetics in the previous decade for delineating the concept of genomic disorders. He also received the Outstanding Investigator Award in Clinical Science for 2001 from the American Federation for Medical Research and the E Mead Johnson Award for Pediatric Research in 1998 from the Society for Pediatric Research for the investigation of molecular genetics of Charcot-Marie-Tooth disease and related demyelinating neuropathies. Dr Lupski is a Fellow of the American Association for the Advancement of Science, a Fellow of the American Academy of Pediatrics, and a Fellow of the American College of Medical Genetics and was elected to the Institute of Medicine of the National Academies of Science in 2002. He has been granted 14 different patents for inventions related to clinical applications of DNA diagnostic technologies.*

The term "genomic disorder" refers to a disease that is caused by an alteration of the genome that results in complete loss, gain, or disruption of the structural integrity of a dosage sensitive gene(s). In most of the common chromosome deletion/duplication syndromes, the rearranged genomic segments are flanked by large (usually >10kb), highly homologous low copy repeat (LCR) structures that can act as recombination substrates. Recombination between non-allelic LCR copies, also known as non-allelic homologous recombination (NAHR), can result in deletion or duplication of the intervening segment. Recent findings suggest that other chromosomal rearrangements, including reciprocal, Robertsonian, and jumping translocations, inversions, isochromosomes and small marker chromosomes, may also involve susceptibility to rearrangements related to genome structure or architecture. In several cases, LCRs, AT-rich palindromes and pericentromeric repeats are located at such rearrangement breakpoints. Analysis of the products of recombination at the junctions of the rearrangements reveals both homologous recombination and non-homologous end joining (NHEJ) as causative mechanisms. Thus, a more global concept of genomic disorders emerges in which susceptibility to rearrangements occurs due to underlying complex genomic architecture. Interestingly, this architecture plays a role not only in disease etiology through constitutional rearrangements, but also in somatic rearrangement events associated with cancers and in primate genome evolution.