2002 CURT STERN AWARD ADDRESS
Introductory Speech for James R. Lupski*

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It is my honor to introduce the 2002 Curt Stern Awardee, Dr. James R. Lupski, for his ground-breaking work in the initial identification and subsequent characterization of genomic disorders. Jim first coined the term "genomic disorders" to refer to those genetic diseases in which the basis is a chromosome structural alteration due to homologous recombination between flanking low-copy repeat (LCR) sequences (Lupski 1998). These LCRs, also called "duplicons" to distinguish them from dispersed, common repetitive elements and short tandem repeat elements in the genome (Eichler 1998), are region specific and derived by local genomic duplications that have been evolutionarily fixed. In most instances, the phenotypic consequences of genomic disorders arise due to deletion or duplication of one or more dosage-sensitive genes within the chromosome region undergoing rearrangement, and Jim's work has illustrated this for several genomic disorders associated with chromosome 17p subregions.

Clearly, the significance of this group of disorders is illuminated by the recognition that duplicons comprise ~5%–10% of human genome sequence distributed in a nonrandom pattern within all human chromosomes (Bailey et al. 2002) and that there are dozens of different genetic diseases that are genomic disorders (table 1; Lupski 1998; Ji et al. 2000; Emanuel and Shaikh 2001; Stankiewicz and Lupski 2002). Indeed, at least 1 of every 1,000 births is a new mutation due to this recombination mechanism (Ji et al. 2000; Shaffer and Lupski 2000). With completion of the human genome sequence and with future directed analysis of genes surrounded by duplicons and their potential involvement in developmental disorders and psychiatric conditions, these numbers are likely to increase further. Nevertheless, the current wealth of knowledge began with just one disease and the identification of one small duplicon (or LCR) barely 1 decade ago, and it is for his major role in the key discovery of the chromosome 17p12 duplication in Charcot-Marie-Tooth syndrome type 1A (CMT1A) (Lupski et al. 1991; Pentao et al. 1992), as well as for his subsequent outstanding work in the field of genomic disorders, that Jim is being recognized with this award.

Table 1

Genomic Disorders

- Duplicons comprise ~5%–10% of human genome sequence
- Many current gaps in sequence may be duplicons
- Dozens of genetic diseases are genomic disorders
- Genetic disease load due to genomic disorders: at least 1/1,000 births as de novo events
- Many more genomic diseases to be identified by directed approaches
- Wealth of knowledge began as 1 disease and 1 small, local segmental duplication, barely 1 decade ago

James R. Lupski, M.D., Ph.D., is the Cullen Professor of Molecular and Human Genetics and Professor of Pediatrics at Baylor College of Medicine in Houston, Texas, where he has built a distinguished career since 1986. In his award presentation, Dr. Lupski will elaborate upon the paths that led him and his colleagues to their discoveries in genomic disorders (Lupski 2003). True to the goals of the award, the 2002 Curt Stern Award is presented to Dr. James R. Lupski for his insight and body of work illuminating the importance of genomic disorders and the mechanisms underlying homologous recombination events due to genomic architecture that explain many human diseases.

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