

THE HARTWELL FOUNDATION

2007 Individual Biomedical Research Award

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A Mechanistic Study of Genetic Influences on Emotional Regulation of Behavior

The estimated rate of increase of depression among children is an astounding 23% per year. An appalling 4 % of preschool-age children may be clinically depressed. By age 19, nearly 30% of all young people will have experienced one major depressive episode, a factor in suicide being one of the three leading causes of death. Depression is also a contributory factor to fatal coronary disease. In the US population, age 18 and older, depressive disorders affect approximately 19 million American adults each year and by 2020, will be the second leading cause of death after heart disease. While genetic factors play a substantial role in the risk for major depressive disorder, genetic studies have focused on depression as a behavioral clinical entity (phenotype), rather than a biological entity (genotype) and thus considerable variability exists in interpretation of data. The molecular effects of known genetic risk factors have not yet, been specifically matched to the biological processes that contribute to depression, an approach that might allow early identification of at-risk children. On this motivation, Dr. Glatt proposes to characterize depression phenotype-genotype relationships across several levels of biological complexity. His detailed, cutting-edge approach will be to characterize the molecular nature of a common polymorphism (rs3813034) in the gene for the serotonin transporter (SERT), a prominent candidate gene for depression because of its central role in modulating behavior, emotional processing, and human psychopharmacology. Utilizing validated real-time PCR assays, he intends to quantitate the amount of the gene expressed in individual patients as a function of clinical phenotype, relating amount present to regional differences in the expression of phenotypic during adolescent brain development (stored tissue samples). In addition, he plans to characterize the effects of emotional content on adolescent (age 11-18 years) behavioral performance by functional MRI, to correlate performance with brain activity. If successful, Glatt will demonstrate how individual attributes of behavioral performance in one polymorphism relates to emotional dysregulation.