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The National Centre for Suicide Research and Prevention of Mental Ill-health (NASP) at the Department of Learning, Informatics, Management, and Ethics (LIME)

Gene-environment interactions between HPA axis regulatory genes and stressful life events in suicide attempts

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Suicide is a leading cause of death. In the future, treatment for suicidal behavior, as well as public health prevention and/or intervention efforts, may be guided by genetic epidemiology. This research is informed by biological alterations which have been previously observed in suicidal behavior. Such alterations include dysregulation of the cortisol response to psychosocial stress, which is in large part mediated by the hypothalamic-pituitary-adrenal (HPA) axis. HPA axis functioning is influenced e.g. by heritable variation in regulatory genes, by exposure to stressful life events (SLEs), and/or by gene-environment interactions (G x Es) of regulatory genetic variants with SLEs. Using a family-based design of proband offspring who have made a suicide attempt (SA) and their parents, we tested and characterized associations of transmitted variants in candidate genes that regulate HPA axis activation, as well as G x Es of these variants with SLEs, with SA and secondary outcomes.

In Study 1, we showed a G x E between a variant in corticotropin releasing hormone receptor type-1 (*CRHR1*), a gene which has a major role in mediating HPA axis activation, and physical assault in childhood/adolescence. We further observed a novel and independent G x E between another unlinked variant and physical assault in adulthood. These findings confirmed and extended previous findings on adulthood depressive symptoms, cortisol response, and alcohol misuse by other groups.

In Study 2, we investigated 98% of currently known common single nucleotide polymorphisms (SNPs) and certain low-frequency SNPs in serotonin receptor type-2a (*HTR2A*), a gene involved in serotonergic system modulation of HPA axis activation, and showed novel genetic linkage/association of a promoter SNP and a low frequency exon 2 SNP, as well as a novel G x E between a well-studied exon 1 SNP and exposure to cumulative lifetime SLEs. We further characterized this G x E, revealing a complex parent-of-origin effect in females, which may partly explain inconsistent findings in the literature.

In study 3, we investigated twenty-four genes in the glutamatergic, γ-aminobutyric acid (GABA)-ergic, and polyaminergic systems that are known to link several brain areas involved in emotional processing with HPA axis activation. We showed linkage/association of 3 SNPs in an *N*-methyl-D-aspartate (NMDA) receptor subunit type-2B gene (*GRIN2B*), and 2 SNPs and 1 haplotype in a gene which codes for a rate limiting enzyme in polyamine biosynthesis (*ODC1*). A G x E was also observed between another *ODC1* SNP and physical assault in childhood/adolescence.

In study 4, we investigated 100% of currently known common SNPs and a low frequency SNP in arginine vasopressin receptor type-1B (*AVPR1B*), a gene involved with *CRHR1* in partially overlapping roles in HPA axis activation. We showed linkage/association of two SNPs and a corresponding major allele haplotype across the gene predominantly on current depressive symptoms in SA. Interestingly, we found no evidence of a G x E between *AVPR1B* variants and SLEs, or any gene-gene interaction effects with *CRHR1* variants.

In all studies, the findings were complemented with case-control re-analysis of SA offspring with healthy volunteers; characterized with SA-concomitant outcomes, as well as lifetime psychiatric diagnoses, and/or other descriptive variables; and discussed with regard to previous findings by our group or others, and to potential mechanistic roles. These findings support a stress-diathesis model of suicidal behavior, and a potential etiological role in the suicidal process for novel genetic variants and variants that have previously associated with stress-related HPA axis dysregulation, maladaptive behaviors and neuropsychiatric outcomes. The strength of these results is supported by the family-based design, which is robust to population substructure, and relatively comprehensive investigations of genetic variation, signaling pathway, and/or G x E. Further investigation and consistent replication across samples are warranted before utility in clinical diagnosis, treatment and/or public health efforts.