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The *Drosophila foraging* gene human orthologue *PRKG1* predicts individual differences in the effects of early adversity on maternal sensitivity

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ABSTRACT

There is variation in the extent to which childhood adverse experience affects adult individual differences in maternal behavior. Genetic variation in the animal *foraging* gene, which encodes a cGMP-dependent protein kinase, contributes to variation in the responses of adult fruit flies, *Drosophila melanogaster*, to early life adversity and is also known to play a role in maternal behavior in social insects. Here we investigate genetic variation in the human foraging gene (*PRKG1*) as a predictor of individual differences in the effects of early adversity on maternal behavior in two cohorts. We show that the *PRKG1* genetic polymorphism rs2043556 associates with maternal sensitivity towards their infants. We also show that rs2043556 moderates the association between self-reported childhood adversity of the mother and her later maternal sensitivity. Mothers with the TT allele of rs2043556 appeared buffered from the effects of early adversity, whereas mothers with the presence of a C allele were not. Our study used the Toronto Longitudinal Cohort (N = 288 mother-16 month old infant pairs) and the Maternal Adversity and Vulnerability and Neurodevelopment Cohort

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(N = 281 mother-18 month old infant pairs). Our findings expand the literature on the contributions of both genetics and gene-environment interactions to maternal sensitivity, a salient feature of the early environment relevant for child neurodevelopment.

1. Introduction

It is a universal finding that there are individual differences in how people behave and respond to adversity and advantage (Boyce, Robinson, & Sokolowski, 2012; Rutter, 2012). However, the source(s) of this heterogeneity in behavior continues to be debated. Historically it was thought that these individual differences could be attributed to variation in nature (genes) *or* nurture (environment) *or* an additive function of both (G + E).

Research over the past several decades has led to the concept of gene by environment interaction (G x E) (Bagot and Meaney, 2010; Caspi and Moffitt, 2006; Manuck and McCaffery, 2014; Rutter, 2010, 2012, 2015; Sokolowski and Wahlsten, 2001). Gene by environment interaction (G x E) can arise when individuals who carry a certain genetic variant are more buffered to environmental adversity (or to advantage by positive environments) than those who do not carry the variant. G x E is pervasive in the animal and human literature (Kendler and Greenspan, 2006).

More recently, the notion of gene-environment interplay has appeared in the literature (Rutter, 2006, 2010; Boyce et al., 2012). In this iteration of the gene-environment perspective, the "genetic" contribution is not static or deterministic. Rather the genes are "listening" to the environment over the lifetime of the individual and responding to experience; changes in gene expression give rise to individual differences in behavior. The idea here is that the genome is responsive, allowing it to mount nimble responses to environmental stimuli during development. It is now well accepted that social adversity can become embedded into an individual's biology (Bagot and Meaney, 2010; Turecki and Meaney, 2016; Boyce et al., 2012; Boyce and Kobor, 2015). Several recent studies suggest that there can be interactions between early adversity and genetic variants such as single nucleotide polymorphisms (SNPs), which can predict DNA methylation (Klengel et al., 2013; Chen et al., 2015; Ursini et al., 2016).

In the present study we investigate if genetic variants in the human *PRKG1* gene interact with childhood adversity of the mother to affect maternal sensitivity towards her infant in two independent cohorts.

The human cGMP dependent protein kinase gene, *PRKG1*, encodes the soluble I-alpha and I-beta isoforms of PRKG1 through alternative splicing (Ostravik, Natarajan, Tasekn, Jahnsen, & Sandberg, 1997). PRKG1 proteins are best known for their cardiovascular and neuronal functions. PRKG1 is expressed in cerebellar Purkinje cells, hippocampal neurons, and the lateral amygdala as well as smooth muscle and platelets. PRKG1 is a serine/threonine protein kinase, a key regulator of the nitric oxide (NO)/cGMP signalling pathway. PRKG1 phosphorylates the serotonin transporter (Steiner et al., 2009; Zhang and Rudnick, 2011). In mammals, PRKG1 phosphorylated proteins are known to regulate cardiac function, gene expression, feedback of the NO-signalling pathway, and processes in the central nervous system including axon guidance, hippocampal and cerebellar learning, circadian rhythm and nociception (Feil et al., 2005).

We choose to study genetic variants in *PRKG1* in the G x E context because of the extensive literature on the *foraging* gene, the animal orthologue of *PRKG1*. The *foraging* gene affects individual differences in behavior and is environmentally sensitive (Reaume and Sokolowski, 2009). *foraging* plays multiple roles in the behavior of the following organisms ranging from nematodes (Fujiwara, Sengupta, & McIntire, 2002; Raizen, Cullison, Pack, & Sundaram, 2006; Kroetz, Srinivasan, Yaghoobian, Sternberg & Hong, 2012), the fruit fly *Drosophila melanogaster* (see below), social insects including honey bees (Ben-Shahar, Robichon, Sokolowski, & Robinson, 2002; Ben-Shahar, Leung, Pak, Sokolowski, & Robinson, 2003; Ben-Shahar, 2005; Thamm and Scheiner, 2014), bumble bees (Tobback, Mommaerts, Vandersmissen, Smagghe, & Huybrechts, 2011) and ants (Ingram, Oefner, & Gordon, 2005; Lucas & Sokolowski, 2009; Oettler, Nachtigal, & Schrader, 2015) as well as mice (Kleppisch et al., 1999, 2003; Feil, Hofmann, & Kleppisch, 2005; Feil et al., 2009; Paul et al., 2008; Paul, Stratil, Hofmann, & Kleppisch, 2010).

In the fruit fly *D. melanogaster*, the *foraging* gene encodes the rover and sitter natural allelic variants (Osborne et al., 1997; Sokolowski, 2001; Sokolowski, 2010). These variants differ in their predisposition to move and feed (Sokolowski, 1980; Kaun, Chakaborty-Chatterjee, & Sokolowski, 2008), learn and remember (Mery, Belay, Sokolowski, & Kawecki, 2007; Kaun, Hendel, Gerber, & Sokolowski, 2007; Reaume, Sokolowski, & Mery, 2011; Kohn et al., 2013; Donlea et al., 2012; Wang et al., 2008; Kuntz, Poeck, Sokolowski, & Strauss, 2012), endure stress (Dawson-Scully et al., 2010; Dawson-Scully, Armstrong, Kent, Robertson, & Sokolowski, 2007; Donlea et al., 2012) as well as in their tendency to interact with others in a social environment. Briefly, rover larvae move more while foraging for food, have longer short-term memory, are less resistant to heat, hypoxia and starvation stress, but are more resistant to sleep deprivation. Sitters aggregate more than rovers (Philippe et al., 2016) and learn better when in groups (Kohn et al., 2013; Foucaud, Philippe, Morenco, & Mery, 2013). Thus, the *D. melanogaster foraging* gene has multiple functions in physiology and behavior.

Despite these genetic predispositions, the *foraging* gene is itself responsive to the environment resulting in G x E. For example, after a 4-h period of acute food deprivation rover larvae behave like sitters and rover cGMP-dependent protein kinase enzyme activity falls to a sitter level (Kaun, Riedl et al., 2007) resulting in a G x E interaction that predicts both behavior and gene activity. In another example, chronic food deprivation early in life differentially affects adult rover and sitter exploratory behavior in an open field demonstrating a *foraging* genetic variant by early experience interaction (Burns