

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

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### A B S T R A C T

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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microRNA  
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cGMP-dependent protein kinase

(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

et al., 2012). Finally, food deprivation of rover and sitter adult flies shows G x E patterns in gene expression and metabolomics (Kent, Daskalchuk, Cook, Sokolowski, & Greenspan, 2009). A predominant finding in the animal literature is that the *foraging* gene interacts with the environment to affect molecular, physiological and behavioral phenotypes.

Most relevant to the current study is that the *foraging* gene in social insects plays a role in the transition from nursing inside compared to foraging outside the hive. Within the lifetime of the individual, *foraging* gene expression changes depending on whether the worker honey bee, ant or wasp is nursing the larvae or foraging for food. The role of the *foraging* gene in social behavior and the social interactions between the care giving nurse bees and their young larvae suggests the hypothesis that the *foraging* gene plays a role in maternal behavior (Sokolowski, 2010).

In humans, maternal sensitivity involves the warm, timely, and appropriate response to infant signals (Ainsworth, Blehar, Waters, & Wall, 1978). Traditional attachment theory holds that maternal sensitivity is strongly influenced by the mother's representations of her own early attachment experiences, and the conscious and unconscious rules that organize information relevant to her early attachment experiences (Main, Kaplan, & Cassidy, 1985). However, while the relation between maternal representations and maternal sensitivity is significant, it is unexpectedly small (van IJzendoorn, 1995; Verhage et al., 2016) highlighting the need to identify other determinants of maternal sensitivity and their moderators (Atkinson et al., 2005).

Individual differences in susceptibility to early adversity (Mileva-Seitz et al., 2011, 2013; Rutter, 2012) result in some mothers being better buffered from their early adversity than others (Mileva-Seitz, Bakermans-Kranenburg, & van IJzendoorn, 2016). There are many routes through which early experiences can affect mothers' care for their babies. Adverse early experiences can affect mothers' cognitive and executive functions, including their working memory, decision-making, and attention to the environment, including infant cues (Gonzalez et al., 2012; Pawluski, Lambert, & Kinsley, 2016; Plamondon et al., 2015). Early adversity also affects mothers' stress regulation and responsivity (Pereira et al., 2012) through dysregulation of the hypothalamic-pituitary-adrenal axis (Gonzalez et al., 2012) and regulation of neurochemistry and brain function important for mothering (Lomanowska and Melo, 2016).

Mothering is regulated by multiple hormonal (Bridges, 2016), neurochemical (Pereira and Ferreira, 2016; Lonstein, Levy, & Fleming, 2015) and brain factors (Kim, Strathearn, & Swain, 2016). Multiple environmental factors including mothers' age and education as well as infant age, sex, and temperament, also influence mothering (Lonstein et al., 2015; Fleming, Lonstein, & Levy, 2016; Gonzalez et al., 2009). The quality of the maternal response to her offspring is affected by her experiences during pregnancy and after the birth of her infant (Drury, Sánchez, & Gonzalez, 2016; Fleming et al., 2016; Gonzalez et al., 2009; Lonstein et al., 2015). Additionally, how mothers were mothered during their early development can also affect the quality of their maternal behavior and the sensitivity exhibited to her offspring (Belsky, Conger, & Capaldi, 2009; Neppl, Conger, Scaramella, & Ontai, 2009; Drury et al., 2016). Thus, negative experiences of parenting can be transmitted across generations (Belsky et al., 2009; Champagne and Meaney, 2001; Gonzalez, Lovic, Ward, Wainwright, & Fleming, 2001).

Genetic variation and G x E also contribute to individual differences in parenting (Mileva-Seitz et al., 2016; Wazana et al., 2015). Briefly, genetic variants in the serotonin, dopamine, oxytocin and vasopressin systems affect individual differences in maternal behavior and some of these interact with early adversity (reviewed in Mileva-Seitz et al., 2016). Genetic variants in the serotonin transporter gene affect measures related to maternal sensitivity (Bakermans-Kranenburg & van IJzendoorn, 2008; Cents et al., 2014; Mileva-Seitz et al., 2011; Pender-Tessler et al., 2013). The *foraging* gene has not been investigated in the context of parenting despite its links to behavioral and physiological outcomes that are known to affect mothering including sociability, reward processing, stress endurance and cognitive function. Interestingly, the *foraging* gene *PRKG1* is known to regulate the serotonin transporter (Steiner et al., 2009; Zhang and Rudnick, 2011) suggesting a link between the serotonin system and *PRKG1* in maternal behavior.

Here, we assess whether the human *foraging* gene *PRKG1* associates with maternal sensitivity and if early adversity of the mother interacts with genetic variation within *PRKG1*, to affect maternal sensitivity towards their infants.

## 2. Methods

### 2.1. Cohorts

#### 2.1.1. Toronto longitudinal cohort (Toronto cohort)

The Toronto Longitudinal cohort is described in Atkinson et al. (2013). Research Ethics Boards at the Centre for Addiction and Mental Health and Ryerson University approved the ethics. Participants were recruited using community centre postings, in person visits to mother-infant activity centers and consumer baby shows across Toronto, a large urban and suburban area. The sample includes approximately 300 mother-infant pairs. The study began when infants were 16 months of age. Inclusion criteria were maternal age 18 years or older at the birth of the child, and full-term, healthy birth of infants. Self reported ancestries were Caucasian (74.8%), Asian (8.5%), African American (3.5%), Hispanic (2.2%) and Other (including Mixed, East Indian, Middle Eastern, Persian; 13.06%). The present study investigates maternal sensitivity with 16-month-old infants on 288 mother-infant pairs.

#### 2.1.2. Maternal adversity, vulnerability and neurodevelopment (MAVAN) cohort

The Maternal Adversity, Vulnerability and Neurodevelopment (MAVAN) study is a longitudinal birth cohort described in O'Donnell et al. (2014). MAVAN's sample consists of mothers recruited in Montréal (Québec) and Hamilton (Ontario), Canada, at 13–20 weeks' gestation. Babies were born at >37 weeks and weighed >2000 g with APGAR scores >7. Mothers were 18

years or older at the birth of their child. They were first assessed at 26 weeks of pregnancy and followed with written consent at multiple time points using home visits and laboratory sessions. Ethics approval was obtained from Douglas Mental Health University Institute (McGill University, Montreal, Quebec), St-Joseph Healthcare/McMaster University, Hamilton, Ontario and the Centre for Addiction and Mental Health, Toronto, Ontario, Canada. 86.5% of the sample was Caucasian (European-Canadian), 2.7% was African descent/African American, 3.1% was Hispanic/Latino and 6.2% other self-report ethnicities. The present study investigates maternal sensitivity with 18-month-old infants on 281 mother-infant pairs.

## 2.2. DNA collection and extraction

We collected DNA from both cohorts using buccal swabs. Additional collections for MAVAN were done using saliva samples (~2 mL) collected from subjects using the Oragene OG-500 DNA kit (DNA Genotek, Ottawa, ON). All DNA extraction was done as per manufacturer's instructions at the Neurogenetics Laboratory at the Center for Addiction and Mental Health (CAMH), Toronto, Ontario, Canada.

The *PRKG1* gene is found on Chromosome 10, cytological location 10q11.23-21.1 and its molecular location in base pairs is 50,991,358–52,298,350. We selected SNPs within the *PRKG1* gene to affect function of the *PRKG1* product(s). SNPs chosen were located in the protein coding regions of *PRKG1*. In addition, the SNP rs2043556 was chosen because it is located both within an intron between *PRKG1*'s exons 3 and 4 and also within a non-coding transcript exon variant for a microRNA embedded in *PRKG1*. The SNPs in the exonic regions of *PRKG1* were monomorphic in both cohorts and are not further discussed. In contrast, rs2043556 showed significant variation across individuals. rs2043556 is on chromosome 10, location 53,059,406 and has a minor allele frequency (MAF) in our sample of  $C = 0.222$  which was not different than the global MAF of  $C = 0.2596/1300$  (1000 genomes). The rs2043556 polymorphism generates three genotypes TT, CT and CC.

## 2.3. DNA extraction and polymorphism determination

SNP sequence information was obtained from NCBI or other databases and optimal primer binding locations were determined. Primers were designed using MassArray Assay design software (version 3.1) and Assay Design Site v2.0. Oligos were ordered from IDT in plate format (for PCR 10 nM scale standard desalted; for EXT 50 nM scale standard desalted). All PCR and EXT primers were normalized to 500 uM with sterile H<sub>2</sub>O and working solutions were mixed for each multiplex reaction (5000 nM for each PCR primer). DNA samples were normalized and 2ul of each sample was dispensed into 384-well plates. A total of 20 ng of genomic DNA was used for each multiplex reaction. PCR conditions were as follows: 1 cycle 95 °C for 15 min (Taq Activation), followed by 45 cycles of 95 °C (20 s), 56 °C (30 s), 72 °C (60 s), and a final extension of 72 °C for 3 min. To dephosphorylate excess deoxyribonucleotide triphosphates, 0.3 units shrimp alkaline phosphatase (iPLEX Reaction Kit; Sequenom) was added to the PCR reaction followed by incubation at 37 °C for 40 min (dephosphorylation). Shrimp alkaline phosphatase was then denatured for 5 min at 85 °C. All pipetting was done using the Innovodyne Nanodrop Dispenser. For the extension reaction, primers were designed using MassArray design software. Extension primers were balanced by mixing a small test volume (100 ul) with EXT primers grouped into one of the following tiers: 7 uM, 9.33 uM, 11.67 uM, and 14 uM. The test mixture is then spotted onto a primer-test chip in triplicate and MALDI-ToF Mass Spectrometry was performed. Peak intensities were evaluated and the EXT primer concentrations were adjusted by either decreasing or increasing their concentration. Concentrations were adjusted so that no primer peak was less than 50% of neighbouring peaks resulting in a uniform primer peak spectrum. The reaction mix consisted of 0.2 X iPLEX buffer, 0.1 X iPLEX termination mix, 0.0205 X iPLEX enzyme (iPLEX Reaction Kit; Sequenom), and either 7 uM, 9.33 uM, 11.67 uM, or 14 uM primer. The EXTiPlex extension reaction was performed under the following conditions: 1 cycle at 94 °C (30 s) to denature, followed by 40 cycles of 94 °C (5 s) each containing 5-sub cycles (looped back to 94 °C (5 s)) of 52 °C (5 s) annealing and 80 °C (5 s) extension. A total of 200 cycles annealing and extension cycles were thus performed. A final extension was completed at 72 °C (3 min) for 1 cycle. Each reaction was desalted by the addition of 16 ul of Milli-Q water to each well of the 384-well reaction plate followed by 6 mg clean resin. Plates were then sealed and rotated at room temperature for a minimum of 30 min. Following rotation, plates were centrifuged at 5000 rpm for 5 min. Water dispensing was carried out using Innovodyne Nanodrop Dispenser. Samples were spotted onto a 384-SpectroCHIP Array. The CHIP was then loaded into the Agena Compact mass spectrometer. Chips were scanned using the iPlex parameters for SNP genotyping. Spectra acquisition was performed using Spectroacquire (Sequenom) and data analysis was performed using the MassArray Typer software version 3.4. Data was checked for clustering, assay quality, blanks. Poorly performing SNPs/assays were disqualified.

## 2.4. Maternal sensitivity and early experience

In the Toronto Longitudinal cohort, two female research assistants observed mother-infant interactions when the infants were 16 months old while taking detailed notes over a two-hour period in the home. Much of this observation occurred during unstructured activity (mothers were simply instructed to go about their day, as they typically would), although interactions were also observed for 20–30 min while mothers completed questionnaires in the presence of their infants who were otherwise unattended. This latter condition was introduced to divide mothers' attention between infant and inventories (Smith and Pederson, 1988) as this likely reveals variability between mothers that is not evident in relatively low-demand situations (Atkinson et al., 2000; Behrens, Parker, & Kuldofsky, 2014; Pederson et al., 1990).



Post-visit, the research assistants coded maternal sensitivity according to the Maternal Behavior Q-sort (MBQS; Pederson et al., 1990). The MBQS consists of 90 items, each describing a particular maternal behavior, which observers sort into 9 piles of 10, with piles denoting “most like” to “least like” mother. The items themselves were derived from the extensive observations of Ainsworth et al. (1978) and subsequent work by the authors (Pederson and Moran, 1995). The MBQS distills numerous aspects of maternal sensitivity, including “contingent pacing in response to communicative signals, prompt and effective reactions to distress, . . . maternal availability, [and] knowledge and enjoyment of the infant” (p. 1982) into a single metric, varying from  $-1.0$  to  $+1.00$  (the lower the score, the less sensitive the mother; this metric is actually the correlation between the sort of the observed mother and the sort of a hypothetical “prototypically sensitive mother”). Meta-analytic data indicate that MBQS observations are associated with infant attachment security at  $r=0.48$ , significantly larger than the effect size linking traditional observations to infant attachment security ( $r=0.21$ ; Atkinson et al., 2000); Behrens et al. (2014) refer to the MBQS as a “breakthrough in the measurement of maternal sensitivity” (p. 349). The success of the MBQS, with its divided attention component has been partially attributed to its executive function demands, insofar as it assesses maternal sensitivity in the context of two concepts central to neo-Piagetian theorizing, attention regulation and integration of information (Atkinson et al., 2000). In the Toronto Longitudinal Cohort, inter-observer agreement (intraclass correlation) was  $0.88$ ,  $p < 0.0005$ . We used the mean score across both observers as the measure of sensitivity.

In the MAVAN cohort, research assistants visited the homes when the infants were 18 months and videotaped interactions during: 10 min of free play, divided attention for 10 min while the mother completed questionnaires with the infant in the room, free-play without toys for 5 min, and free play with toys provided by the MAVAN research assistant for 10 min. These videotapes were coded centrally using the 25-item short form of the MBQS (MBQS-25), designed for briefer observations. Here, items are sorted into 5 piles of 5 and correlated with a prototypically sensitive sort. The MBQS-25 is significantly correlated with the MBQS and infant cognitive development and attachment security (Tarabulsy et al., 2009). Inter-observer reliability (intraclass correlation based on 18 tapes coded independently by two coders) was  $0.94$ ,  $p < 0.0005$ .

The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994) was used as a retrospective self-report questionnaire to assess the early experience of the mother. We used an integrated measure of CTQ that assesses the following five types of childhood trauma: physical, emotional, and sexual abuse as well as emotional and physical neglect. Each trauma subscale produces scores from 5 to 25. Scores were averaged across the 5 subscales to derive a total mean score. Although CTQ is a retrospective report of early adversity, it has good psychometric properties and predictive validity (Bernstein et al., 1994).

## 2.5. Statistical analyses

Hardy–Weinberg equilibrium (HWE) tests on the *PRKG1* rs2043556 SNP were assessed in the Toronto Longitudinal and MAVAN cohorts. The results showed that the SNP was in linkage equilibrium (Chi squared test,  $p > 0.05$ ) in both cohorts. Linkage disequilibrium (LD) calculations were from the 1000 Genomes Project.

Residuals from regression models were plotted using a histogram and Normal–P–P plot of regression standardized residuals. When the maternal sensitivity measures (MBQS) were ln transformed all residuals were normally distributed. We therefore used the ln transformed MBQS as our measure of maternal sensitivity for all analyses.

We used a multiple linear regression model to test for the effect of SNP, CTQ and the interaction of SNP and CTQ (G x E) on maternal sensitivity score (MBQS). Model 1 included SNP and CTQ as predictor variables. Model 2 included SNP and CTQ as well as an interaction term between SNP and CTQ. This analysis was run for the rs2043556 SNP in the Toronto Longitudinal cohort as well as in the replication sample, the MAVAN cohort. Finally, the covariates maternal age and education were introduced in a stepwise forward regression model to adjust our analyses for these covariates. When sample sizes were  $N < 20$  for a given genotype, that genotype was dropped from the analysis. A 2-tailed test was used for our main cohort, the Toronto Longitudinal cohort. The replication sample, the MAVAN cohort was used to test the following specific 1-tailed hypotheses. Mothers with the CT genotype showed a negative relationship between maternal sensitivity and CTQ and the TT genotype buffered this relationship making the slope of the line for mothers with the TT genotype significantly less negative.

## 3. Results

We began our investigation of whether *PRKG1* SNP rs2043556 associates with maternal sensitivity by analyzing genetic variants in the Toronto Longitudinal cohort of mothers. We first used the Toronto cohort to test the hypotheses that rs2043556 associates with maternal sensitivity and can act as a moderator between early experience and subsequent parenting. Both cohorts used similar measures of maternal sensitivity (MBQS see methods) and the same measure of early experience (CTQ). However as mentioned in the methods, in MAVAN the mother–infant interactions were measured when the infants were 18 months old, whereas in the Toronto Longitudinal Cohort, the infants were 16 months old. We ran two 2-tailed regression models: Model 1 included CTQ and SNP as predictors whereas model 2 included CTQ, SNP and their interaction as predictors. The results shown in Table 1 demonstrate that in the Toronto Longitudinal cohort, polymorphism rs2043556 exhibited a main effect of SNP (model 2, SNP,  $p=0.013$ ), of CTQ ( $p=0.001$ ) and an interaction between SNP and CTQ (model 2, SNP x CTQ,  $p=0.005$ ) (Table 1). The analyses adjusted for maternal age ( $B=0.001$ ;  $SE=0.006$ ;  $p=0.844$ ) and maternal education ( $B=0.151$ ;  $SE=0.063$ ;  $p=0.017$ ) yielded comparable results (interaction term adjusted for maternal age:  $B=0.013$ ;  $SE=0.005$ ;  $p=0.003$ ; interaction term adjusted for maternal education:  $B=0.013$ ;  $SE=0.004$ ;  $p=0.005$ ).

**Table 1**

Toronto Cohort: Summary of hierarchical regression analyses for the effect of rs2043556 (SNP), Early Experience (CTQ), and their interaction on maternal sensitivity (MBQS).

	<i>B</i>	<i>SE</i>	$\beta$	<i>t</i>	<i>p-value</i>
Model 1					
SNP <sup>a</sup>	0.025	0.061	0.025	0.418	0.676
CTQ	-0.025	0.011	-0.135	-2.309	0.022
	R <sup>2</sup> = 0.019, F(2, 285) = 2.745, p = 0.066				
Model 2					
SNP	-0.424	0.169	-0.409	-2.505	0.013
CTQ	-0.127	0.037	-0.694	-3.385	0.001
SNP x CTQ	0.012	0.004	0.728	2.840	0.005
	R <sup>2</sup> = 0.046, F(3, 284) = 4.564, p = 0.004				

*Abbreviations:* B: unstandardized regression coefficient;  $\beta$ : standardized regression coefficient; MBQS = Maternal Behaviour Q-sort; CTQ: Childhood Trauma Questionnaire; SE: Standard Error of Regression coefficient; SNP: single nucleotide polymorphism.

<sup>a</sup> Sample sizes for rs2043556 (CT and CC = 105, TT = 183), 2 tailed *p*-value.

**Table 2**

MAVAN Cohort: Summary of hierarchical regression analyses for the effect of rs2043556 (SNP), Early Experience (CTQ), and their interaction on maternal sensitivity (MBQS).

	<i>B</i>	<i>SE</i>	$\beta$	<i>t</i>	<i>p-value</i>
Model 1					
SNP <sup>a</sup>	0.122	0.076	0.100	1.616	0.054
CTQ	-0.009	0.014	-0.041	-0.664	0.254
	R <sup>2</sup> = 0.012, F(2, 262) = 1.656, p = 0.193				
Model 2					
SNP	0.584	0.241	0.476	2.426	0.008
CTQ	0.006	0.016	0.026	0.373	0.355
SNP x CTQ	-0.066	0.033	-0.395	-2.019	0.022
	R <sup>2</sup> = 0.028, F(3, 261) = 2.476, p = 0.062				

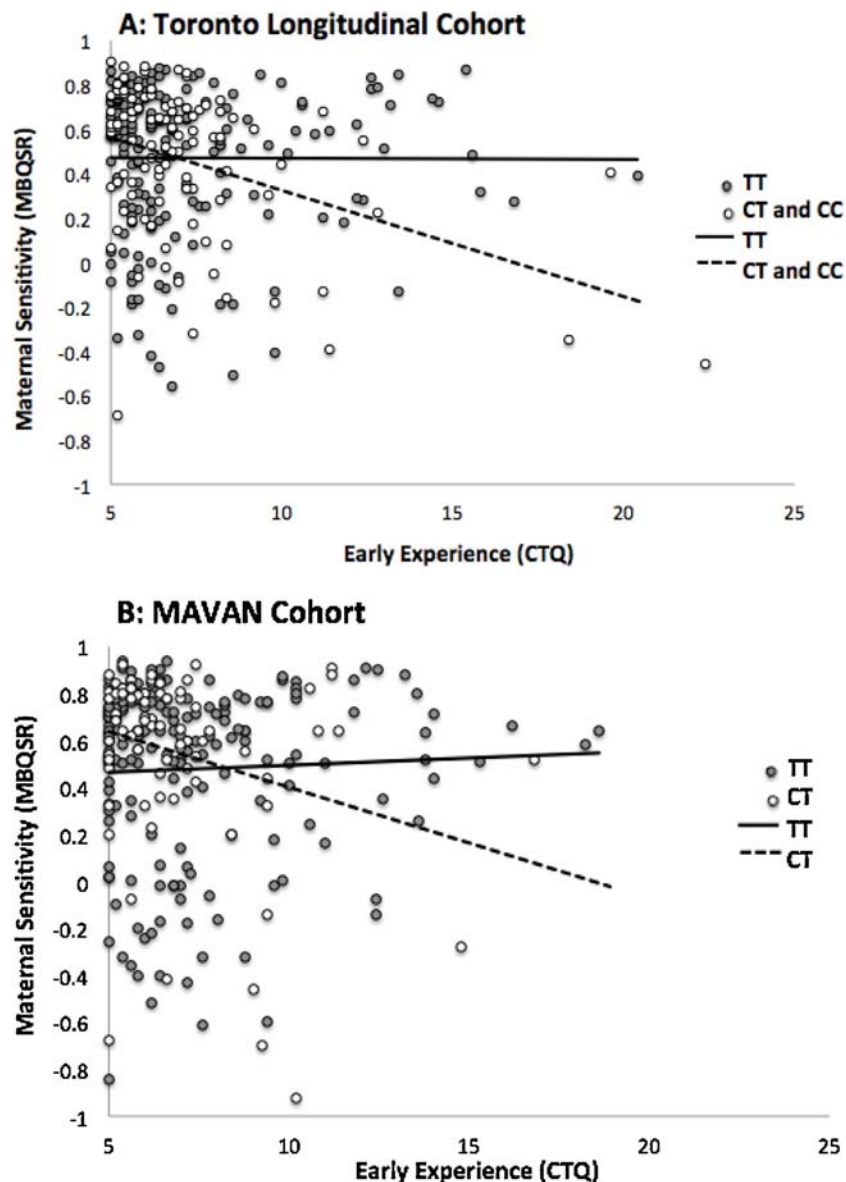
*Abbreviations:* B: unstandardized regression coefficient;  $\beta$ : standardized regression coefficient; MBQS = Maternal Behaviour Q-sort-Revised; CTQ: Childhood Trauma Questionnaire; MAVAN: Maternal Adversity Vulnerability and Neurodevelopment Project; SE: Standard Error of Regression coefficient; SNP: single nucleotide polymorphism.

<sup>a</sup> Sample sizes for rs2043556 (CT = 83, TT = 182), 1 tailed *p*-value.

We next investigated the *PRKG1* SNP rs2043556 in the MAVAN replication sample cohort. We tested the 1-tailed hypotheses that mothers with the CT genotype showed a negative relationship between maternal sensitivity and CTQ and that the TT genotype buffered this relationship making the slope of the line for mothers with the TT genotype was significantly less negative. We ran two 1-tailed regression models: Model 1 included CTQ and SNP as predictors whereas model 2 included CTQ, SNP and their interaction as predictors. Again, the SNP rs2043556 showed a main effect on maternal sensitivity (model 2,  $p = 0.008$  for rs2043556). In model 2, rs2043556 showed a SNP by early adversity interaction ( $p = 0.022$ ). Regression analyses are provided in Table 2. The analysis adjusted for maternal age ( $B = 0.014$ ;  $SE = 0.007$ ;  $p = 0.0275$ ) and maternal education ( $B = 0.193$ ;  $SE = 0.072$ ;  $p = 0.004$ ) revealed comparable results (interaction term adjusted for maternal age:  $B = -0.063$ ;  $SE = 0.033$ ;  $p = 0.0265$ ; interaction term adjusted for maternal education:  $B = -0.061$ ;  $SE = 0.033$ ;  $p = 0.033$ ). Since the change in the regression coefficient and *p*-value is small, it is likely due to reduced power related to decreased sample size and a change in degrees of freedom in the covariate analysis.

Together, these findings support the hypothesis that genetic variation within the human *foraging* gene, *PRKG1*, plays a role in maternal behavior and that it moderates early experiences (CTQ) in a G x E. The direction of the effects in the replication sample, the MAVAN cohort parallel the findings described above for the Toronto cohort.

In Fig. 1 we illustrate the results of the regression analyses for SNP rs2043556 in interaction with CTQ. The Toronto Cohort is shown in Fig. 1A and the MAVAN Cohort is shown in Fig. 1B. The Toronto Longitudinal Cohort shows the regression lines for rs2043556 TT genotypes versus CT and CC genotypes. As described above, we found a main effect of SNP ( $p = 0.013$ ), CTQ ( $p = 0.001$ ) and SNP x CTQ interaction ( $p = 0.005$ ) on maternal sensitivity. Mothers with the TT genotype exhibit a horizontal line and are well buffered to early adversity whereas those with the CT and CC genotype with a line of negative slope are not. As CTQ increases maternal sensitivity decreased in mothers who have the C allele.



**Fig. 1.** *PRKG1* SNP rs2043556 by maternal early experience (CTQ) interactions on maternal sensitivity (MBQS) in the Toronto Longitudinal and MAVAN cohorts. MBQS and CTQ are plotted for individual mothers ( $N=288$ ) for the Toronto cohort and ( $N=281$ ) for MAVAN (A) The Toronto cohort: maternal genotype is provided for TT as dark circles ( $N_{TT}=183$ ) and CT and CC open circles ( $N_{CT\&CC}=103$ ). TT mothers are well buffered to a history of adversity when they were children (solid line). In contrast, C-carriers (CT or CC) at rs2043556 exhibit a decreasing slope (dotted line) reflecting the sensitivity of these mothers to early adversity as measured by CTQ. (B) The MAVAN cohort: maternal genotype is provided for TT as dark circles ( $N_{TT}=182$ ) and CT open circles ( $N_{CT}=83$ ). The flat regression line shown for TT (solid line) suggests that TT is well buffered from early adversity (CTQ) whereas the CT genotype (dotted line) is not.

Fig. 1B shows the regression lines for the MAVAN Cohort for the mother's TT and CT genotypes (main effect of SNP,  $p=0.008$  and SNP  $\times$  CTQ interaction,  $p=0.022$  on maternal sensitivity). As was the case for the Toronto cohort, the MAVAN figure (Fig. 1B) shows that mothers with the TT genotype at rs2043556 exhibit a horizontal line and are well buffered to early adversity with respect to maternal sensitivity to their infant whereas those with the CT genotype have a line of negative slope and are not. Thus, as CTQ increased, maternal sensitivity decreased in mothers with the CT genotype. The MAVAN CC genotype was not included in the analysis in Table 2 and Fig. 1B because of the lower sample size ( $N=16$ ) of the group. However, the same patterns were found when the 16 CC genotypes were combined with the CT genotypes (see supplemental Fig. S1 and Table S1). CT mothers with an early history of abuse tended to be less sensitive towards their own infants. The effect of SNP was significant at  $p=0.032$  while the interaction term showed a trend towards significance at  $p=0.088$ .

#### 4. Discussion

In this paper we assessed whether genetic variation in the human *foraging* gene, *PRKG1*, associates with maternal sensitivity and if early adversity of the mother interacts with genetic variation in *PRKG1* to affect maternal sensitivity. As described in the introduction to this paper, this hypothesis arose from the animal literature on *PRKG1*'s orthologue, the *foraging* gene. We found that the polymorphism rs2043556 in *PRKG1* significantly associated with maternal sensitivity in two cohorts and that this SNP interacted with CTQ to affect maternal sensitivity in the primary sample and approached significance in the replication sample. That we were able to replicate our finding in two cohorts provides strong support for our hypotheses (Rutter, 2015). Our study also shows how findings from the animal literature can guide hypotheses about G x E in human populations. Even simple model organisms such as *Drosophila* and social insects can provide ample hypotheses for human research in genes, environment and behavior (Sokolowski, 2010).

Intriguingly as discussed below, the *PRKG1* intronic SNP rs2043556 found to be significant in the present study can affect the transcriptional regulation of *PRKG1*. An interesting aspect of rs2043556 is that it sits within both *PRKG1* and *miR-605*, a microRNA gene hosted by *PRKG1* (Lee et al., 2009; Xiao et al., 2011). MicroRNAs are short RNA regulators that due to their small size can be rapidly produced; they function as efficient tools for regulating the production of many proteins and as a result of their actions they can change entire biological pathways. MicroRNAs are important in regulating suites of genes relevant for various phenotypes, some of these involving stress responses (Soreq, 2015). *miR-605* is arranged in the same orientation as *PRKG1* and is coexpressed with it (Xiao et al., 2011). Thus, both genes are polymorphic for rs2043556 and the effects found in the present study could have arisen from rs2043556 affecting maternal sensitivity through genetic variation in *PRKG1*, *miR-605* or both of these genes. Future experiments will need to distinguish between these possibilities. Another possibility is that rs2043556 acts as a marker of another polymorphism found in the same linkage group that alters *PRKG1*'s regulation. Linkage disequilibrium groups in humans can be large and each linkage group in *PRKG1* has multiple SNPs (Reich et al., 2001; Wall and Pritchard, 2003).

How rs2043556 affects *PRKG1* or *miR-605* or both is currently unknown. However, the position of the SNP in the microRNA lends itself to speculation. SNPs occurring in microRNA genes can affect microRNA function by altering the transcription or processing of the microRNA, or by affecting microRNA-mRNA interactions through a change in the complementarity between the microRNA and its target (Ryan, Robles, & Harris, 2010). rs2043556 is located in the pre-microRNA hairpin stem of *miR-605* and therefore could affect processing and maturation of the microRNA and lead to changes in its expression (Gong et al., 2012; Cammaerts, Strazisar, De Rijk, & Del Favero, 2015). In the case of SNP rs2043556 the energy of the hairpin is lowered by the SNP ( $\Delta \Delta G = -2.6$  kcal/mol). This suggests that the SNP could cause the hairpin to be more stable and improve microRNA maturation, consequently increasing microRNA expression (Gong et al., 2012). Because rs2043556 is not located in the mature microRNA sequence, it will not affect the binding of target genes. rs2043556 has been implicated in aspects of human health and disease risk (Hu et al., 2014; Huang et al., 2014; Said and Malkin, 2015; Zhang et al., 2012). The present paper is the first to report an association between variation at rs2043556 and individual differences in maternal behavior.

*PRKG1* is associated with post-traumatic stress disorder (Ashley-Koch et al., 2015), schizophrenia (Zhao et al., 2013) and attention deficit hyperactivity disorder (Neale et al., 2010) although *PRKG1* did not reach genome wide significance in any of these studies. *PRKG1* plays a role in neurodevelopment where it is known to regulate neuronal migration, dendrite development, forebrain development, long-term potentiation, and signal transduction (Calabresi et al., 2000; Demyanenko et al., 2005; Kleppisch et al., 2003; Werner et al., 2005). In addition, as mentioned above, *PRKG1* is known to phosphorylate the serotonin transporter (Steiner et al., 2009; Zhang and Rudnick, 2011) associated with maternal care in a number of studies (Bakermans-Kranenburg & van IJzendoorn, 2008; Cents et al., 2014; Mileva-Seitz et al., 2011; Pener-Tessler et al., 2013). Thus, *PRKG1* genetic variants might interact with the serotonergic system to affect maternal sensitivity. Specifically, genetic variants in both *PRKG1* and the serotonin transporter gene may contribute to differences in sensitivity to early adversity of the mother (the present study; Mileva-Seitz et al., 2011). This hypothesis could be addressed from the perspective of maternal sensitivity and early experience using gene interaction (G x G) and G x G x E studies in the MAVAN and Toronto cohorts. The functional aspects of this interaction could be addressed by measuring gene expression/activity differences arising from different combinations of *PRKG1* and serotonin transporter genetic variants in cell culture. Recent rat studies show a role for the serotonin system in regulation of maternal behavior and in the effect of maternal licking on serotonin-based pup development (Yang et al., 2015; Ragan, Harding, & Lonstein, 2016). Hence, regulation of the serotonin transporter by *PRKG1* and its interaction with early adversity provides one potential biological mechanism for the effects observed in the present study.

This paper provides a glimpse into the factors that may affect maternal sensitivity. The relationships we found here were for mother-infant pairs with 16–18 month old infants; it is not known if these results extend to mothers' interacting with different age infants. The effect of specific genes and their interactions with early adversity (G x E) may be developmental stage specific as G x E's can change during development. Our findings show that the TT genetic variant at rs2043556 within *PRKG1* buffers the exposure to early adversity of the mother thereby maintaining maternal sensitivity at a comparable level across gradients of adversity. In contrast, mothers with a C allele of rs2043556 and a history of early adversity have reduced maternal sensitivity. Thus, the mother's early adversity predicted sensitivity towards her infant in a genotype dependent way. Our findings revise our current understanding of the pathways that may underlie the intergenerational transmission of risk associated with maternal adversity.



A powerful metaphor describes differential sensitivity to the environmental context: sensitive individuals (orchids) thrive in positive enriching environments and flounder when raised in adverse circumstances (Boyce and Ellis, 2005; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011). Meanwhile, less sensitive individuals (dandelions) are buffered in both of these environmental contexts. Had we sampled maternal sensitivity in a highly positive environment, we would predict that the *PRKG1* mother with the C allele would be more sensitive to both adverse and positive environments compared to the well-buffered TT genotype dandelion mothers. This would have resulted in higher maternal sensitivity for mothers with the C allele at the very low end of the adversity scale. We also are in the process of investigating functional consequences of rs2043556 and early life experiences in relation to patterns of DNA methylation, which might explain why carriers of one allele are more sensitive to environmental cues.

Genetic variants provide predispositions for behavior that are modified by experience. This experiential modification of the mother's behavior can be a consequence of her childhood experience as measured by CTQ. Thus, one stage of development has consequences for another and this interacts with genetic predisposition. In addition, the aforementioned genes do not act alone; the finding of a single gene association with maternal sensitivity does not imply that *PRKG1*, and/or *miR-605*, is the only gene important for individual differences in this behavior. By virtue of having different variants of *PRKG1* (TT or presence of a C), gene expression could differ in many down stream genes, some of which might lead to effects on developmental and/or physiological time scales. *PRKG1* is an important signalling molecule whose primary role is to phosphorylate proteins in multiple tissues including the nervous system in neurons and glia, the muscle, the gut, and adipose tissue (Reaume and Sokolowski, 2009; Feil et al., 2005). Because of its important role in cell signalling, *PRKG1* is thought to influence the activity of a range of genetic networks. Layered upon this is that these gene networks are also affected by the environment throughout development giving rise to individual differences in behavior. The fact that we can identify a gene of importance whose genetic variants (TT or presence of a C) act as a main effect and in interaction with early adversity in two independent cohorts testifies to the importance of *PRKG1* in individual differences in maternal sensitivity which has important consequences for infant and childhood wellbeing. Mothers who carry the *PRKG1* SNP genotype CT/CC identified in this study may be at a higher risk for early adversity to affect their maternal sensitivity. Thus, together with other genetic markers, *PRKG1* might be useful in identifying vulnerable women in the future. Mothers' who carry the particular *PRKG1* SNP genotype TT identified in this study may be better buffered from the well-documented effect of early adversity on maternal sensitivity.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.cogdev.2016.11.001>.

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