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The association between perinatal hypoxia exposure and externalizing symptoms and children's decision making in conditions of uncertainty is moderated by DRD2 genotype

Roisin White[1] | Lisa M. Gatzke-Kopp[1] | Patrick J. Ryan[1] | David M. Lydon-Staley[2]

[1]Department of Human Development and Family Studies, The Pennsylvania State University, University Park, Pennsylvania

[2]Department of Bioengineering, The University of Pennsylvania, University Park, Pennsylvania

Correspondence
Lisa M. Gatzke-Kopp, Department of Human Development and Family Studies, The Pennsylvania State University, University Park, PA.
Email: lmk18@psu.edu

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Abstract

Variants of the DRD2 Taq1A polymorphism, which have been shown to result in functional differences in dopamine D2 receptors (D2R), have been linked to various externalizing outcomes in adults. However, the neurobiological processes that contribute to these associations are not well understood. The current study investigates gene × environment effects on teacher-rated externalizing behaviors and probabilistic decision making in a sample of 333 children (age 9) enrolled in an ongoing longitudinal study. Findings indicate that externalizing behaviors increased as a function of hypoxic exposure only among individuals carrying the A1 (A1+) allele. Results also indicate that willingness to pursue reward under conditions of maximum uncertainty (50% probability) decreased as a function of hypoxic exposure only among A1− individuals. Among A1 carriers, no association between probability decision making and hypoxic exposure emerged. These findings suggest that hypoxia could influence neural development through different biological pathways depending on D2 receptor genotype, and provide insight into the development of individual differences in behavior and decision making.

KEYWORDS
antisocial, hypoxia, probabilistic decision making, uncertainty intolerance

1 | INTRODUCTION

Following evidence that altered functionality in dopaminergic networks contributes to externalizing behaviors, studies have examined whether genetic variants associated with the function of dopamine receptors are associated with externalizing profiles. Perhaps the most consistently examined genetic factor to date has been the ANKK1/DRD2 Taq1A polymorphism, which has two well-documented variants that produce D2 dopamine receptors with different levels of binding sensitivity (Eisenstein et al., 2016; Jönsson et al., 1999; Pohjalainen et al., 1998; Ritchie & Noble, 2003). Studies have found associations between Taq1A genotype and substance use disorders (Munafò, Matheson, & Flint, 2007; Noble, 1998), as well as other disorders on the externalizing spectrum such as conduct disorder, ADHD, and borderline personality disorder (Esposito-Smythers, Spirito, Rizzo, McGeary, & Knopik, 2009; Nemoda et al., 2010; Nyman et al., 2007). However, studies using rigorous replication standards suggest that main effects for the influence of candidate genes on clinical disorders are not robust (Samek et al., 2016). Given the vast developmental distance between the specific protein encoded by a given gene and the complex, multifaceted, syndrome of behaviors that comprise a clinical diagnosis, it may be more appropriate to identify discrete psychological processes, or *endophenotypes*, associated with genetic variance that enhance vulnerability for psychopathological outcomes (Gottesman & Gould, 2003). Furthermore, across development, there are innumerable factors that could moderate or modify the neurodevelopmental implications of genotype on behavioral outcomes and/or moderate the implications of intermediate behavioral traits in ways that could exacerbate or mitigate the potential of developing psychopathology (Beauchaine & Gatzke-Kopp,

2012). This study examines the implications of A1+ allele status in a sample of children to determine whether this genetic marker is associated with (a) evidence of emerging externalizing psychopathology and/or (b) specific psychological traits (risky decision making) that could serve as intermediate phenotypes associated with psychiatric outcomes, and (c) whether environmental disruption, specifically perinatal hypoxia, interacts with genotype to alter the functionality of the dopaminergic systems thought to underlie externalizing behaviors.

1.1 | Intermediate phenotypic indicators of externalizing problems

The A1 allele of the DRD2 Taq1A polymorphism (rs1800497) has been shown to be associated with lower levels of D2 receptor binding and signaling in the striatum relative to the A2 allele (Eisenstein et al., 2016; Jönsson et al., 1999; Pohjalainen et al., 1998; Ritchie & Noble, 2003). While the Taq1A polymorphism does not reside on the DRD2 gene itself, an extensive body of research suggests that it is in linkage disequilibrium with a number of functional variants spanning into the DRD2 gene, such as rs2283265 and rs6277 (Markett, Montag, & Reuter, 2010; Zhang et al., 2007), which together have been linked to individual differences in D2 receptor binding (Hirvonen et al., 2009) and trait impulsivity (Markett, Montag, Diekmann, & Reuter, 2014). Although the Taq1A polymorphism is only one component of the genetic contributions to dopamine receptor functionality, a multitude of studies have found significant differences in the prevalence of externalizing disorders in association with A1 allele status (Esposito-Smythers et al., 2009; Munafò et al., 2007; Nemoda et al., 2010; Noble, 1998; Nyman et al., 2007). Additional studies have sought to identify possible personality traits associated with Taq1A status in an effort to better understand the relationship between A1+ status and vulnerability for externalizing behavior. However, despite the expectation that effects would be stronger for an intermediate phenotype than for a diagnostic outcome, many of these studies have failed to identify associations with personality traits such as novelty seeking/impulsiveness, harm avoidance, or reward dependence (Burt, McGue, Iacono, Comings, & MacMurray, 2002; Young, Lawford, Nutting, & Noble, 2004). Although there is a literature base associating personality dimensions with variation in the functionality of different brain regions or neurotransmitters, it is important to recognize that personality dimensions have been defined entirely at the behavioral level and were thus not conceptualized to reflect the expected manifestation of specific neural mechanisms. As such, personality may be a less effective level of analysis for the search for targeted phenotypes.

Several targeted psychological processes have been proposed to contribute to vulnerability for externalizing psychopathology. Specifically, externalizing behavior is associated with impulsive decision making in which individuals pursue reward without accounting for associated probabilistic risks, that is, the probability of not receiving said reward (Bechara, 2003). Typically, individuals are less inclined to pursue rewards that have a low probability of being received, reflecting the extent to which the expected value of a potential reward is discounted by its probability (e.g., the decision not to purchase a lottery ticket despite the desirability of the jackpot). Substantial individual variation in how steeply reward is discounted as a function of probability has been documented (Du, Green, & Myerson, 2002; Green & Myerson, 2010; Myerson, Green, Hanson, Holt, & Estle, 2003; Olson, Hooper, Collins, & Luciana, 2007). Blunted sensitivity to probabilistic risk leads individuals to pursue rewards even when the probability of success is quite low, and may lead to maladaptive behaviors associated with impulsivity, such as addiction (Fishbein et al., 2005), pathological gambling (Bechara, 2003; Holt, Green, & Myerson, 2003), and childhood externalizing disorders (Drechsler, Rizzo, & Steinhausen, 2008; Fairchild et al., 2009).

The majority of behavioral paradigms used to assess probabilistic decision making may fail to distinguish between distinct psychological processes that underlie the decision. For instance, research has demonstrated that an individual who pursues a low-probability/high-reward opportunity may be doing so because they are less sensitive to probabilistic risk or because they are more sensitive to reward (Bechara, Dolan, & Hindes, 2002). Although under certain conditions, these two processes lead to an equifinal outcome (risky decision); evidence indicates that estimations of probabilistic risk and reward are computed in neurobiologically dissociable pathways (Schultz, 2002; 2004; Smith et al., 2009).

Furthermore, recent research has sought to differentiate the effects of probabilistic risk from the effects of uncertainty on decision processes. In decision tasks where the probability of outcomes is known, risk reflects the chances of a successful outcome and thus increases linearly as probability of receipt decreases (e.g., from 100% to 10%). In contrast, uncertainty reflects the purely probabilistic component of the decision without regard to the value of the outcome. In other words, a 10% chance of winning $100 is highly *risky* precisely because it is fairly *certain* that the money will not be won (90% chance of losing). As such, uncertainty follows a quadratic function wherein uncertainty is maximal in the middle (50%) and decreases in both directions. Aversion to conditions of uncertainty is often associated with pathological worry, a signature characteristic of generalized anxiety disorder and depression (Carleton et al., 2012; Dugas, Laugesen, & Bukowski, 2012; Ladouceur, Gosselin, & Dugas, 2000). Because probabilistic risk, uncertainty, and reward are estimated in distinct dopaminergic networks (Fiorillo, Tobler, & Schultz, 2003), it is possible that A1+ allele status is associated with variance in a single component of decision making. Thus, examining the implications of specific dopamine processes for individual differences in probabilistic decision making should involve assessing the separate contributions of individual differences in sensitivity to uncertainty, risk, and reward on the decision outcome (Gatzke-Kopp, Ram, Lydon-Staley, & DuPuis, 2018).

1.2 | The role of the dopamine D2 receptor in probabilistic decision making

Pharmacological studies demonstrate a selective role for the D2 receptor subtype in encoding probabilistic outcomes. Activation of D2 receptors is associated with conservative decision making by reducing the tendency to select low-probability/high-reward options without altering sensitivity to reward (Simon et al., 2011). The reduction in selection of low-probability rewards may be a function of the role of D2 receptors in unfavorable outcomes from past probabilistic decisions (Zalocusky et al., 2016). Thus, D2 receptor activation appears to enhance the saliency of loss outcomes relative to win outcomes in probabilistic trials, increasing the extent to which the individual develops an aversion to uncertainty.

Although very little research has examined decision making as a function of DRD2 genotype, one study found that A1− individuals were more efficient at learning to avoid actions with negative consequences than A1+ individuals (Klein et al., 2007), consistent with previously observed effects for striatal D2 receptor activation (Zalocusky et al., 2016). Thus, A1+ individuals may be more tolerant of uncertainty and/or less averse to probabilistic risk. One study examined this hypothesis in a sample of 143 participants, and although there was no observed main effect for A1+ status, A1+ status was associated with the lowest levels of risk aversion in a gambling task where probabilities were known and winnings could be lost among individuals who were also carriers of the 66Met allele of the BDNF polymorphism (Voigt, Montag, Markett, & Reuter, 2015).

1.3 | Developmental influences on dopaminergic systems

The sensitivity of the dopaminergic system to environmental factors could create a mechanism by which individual's decision making preferences are calibrated to indicators of environmental adversity in ways that are adaptive for more threatening environments (Gatzke-Kopp, 2011). In adult animals, exposure to chronic uncontrollable stress conditions results in a change in decision strategies. Relative to both their pre-stress baseline and to nonstressed controls, animals exposed to chronic stress developed a conservative decision strategy that favored certainty, even under conditions where the expected value of uncertain options was higher (Morgado et al., 2015). Very little research has examined whether exposure to developmental stressors is associated with decision making preferences in children.

Although human brain development remains highly experience-dependent throughout childhood, research indicates that environmental inputs during prenatal development are especially critical in establishing initial tone, particularly in the dopaminergic system (Gatzke-Kopp, 2011). One of the more common stressors during human pregnancy is a reduction in the maternal supply of oxygen to the fetus, which can occur when blood flow is restricted such as in the case of high blood pressure or maternal smoking, as well as a variety of other complications during pregnancy or delivery (Newby, Myers, & Ducasay, 2015). How hypoxic exposure affects brain development remains unclear, but two possible pathways exist. The first is through the direct effects of oxygen deprivation, which initiates a process of cell death, particularly among dopaminergic neurons (Vannucci, 2000; Webster & Abela, 2007). Experimental induction of hypoxic conditions indicates a significant reduction in both D1 and D2 receptor density, attributed to a loss of striatal neurons (Przedborski, Kostic, Jackson-Lewis, Cadet, & Burke, 1991). Over time, however, there appears to be recovery that is specific to D1 receptors, whereas the reduction in D2 receptor density remains into adulthood (Kostic, Przedborski, Jackson-Lewis, Cadet, & Burke, 1991). Given the implications of hypoxia for D2 receptors, it is possible that DRD2 genotype could moderate the effect of hypoxic exposure. For example, D2 receptors have been shown to serve a neuroprotective role in instances of ischemia and other instances of hypoxic insult by maintaining dopaminergic homeostasis (Bozzi & Borrelli, 2006; Decker and Rye (2002). In particular, A1+ individuals, who already demonstrate less efficient D2 receptor function, may be more significantly impacted by hypoxic insult, leading to greater tolerance for risk/uncertainty.

The second pathway by which perinatal hypoxia affects brain development is through the release of cortisol in response to the hypoxic stressor (Groothuis, Müller, Engelhardt, Carere, & Eising, 2005). Cortisol release in response to hypoxia may have neuroprotective effects, with the amount of circulating cortisol negatively correlated with the extent of hypoxia-induced brain injury in experimental models (Harris, Healy, Colditz, & Lingwood, 2009). In the context of low-grade hypoxic exposure, it is possible that cortisol release will reduce the extent of neuronal damage, while still altering the sensitivity of the developing dopamine system (Gatzke-Kopp, 2011). Prenatal chronic stress exposure has been shown to lead to more conservative behavioral phenotypes in rodents (Weinstock, 2017), and this effect appears to be associated with a significant and selective upregulation of D2 receptors (Rodrigues et al., 2012). If stress exposure induces D2 receptor expression, A1− individuals may show a greater tendency toward conservative decision making in response to hypoxia exposure due to their ability to produce more efficient receptors.

1.4 | The current study

This study examines a sample of children whose families enrolled in an ongoing longitudinal research study at the time of the child's birth. Children participated in a probabilistic decision making task during the summer before entering 4th grade. This task is designed to estimate individual differences in sensitivity to uncertainty, risk, and reward separately in order to determine whether genetic and/or environmental factors differentially affect these component processes that underlie decision making. Children were classified as having one or more A1 alleles (A1+) or being homozygous for the A2 allele (A1−), and exposure to perinatal hypoxia was assessed from maternal report at the initial intake assessment. Children's externalizing

behaviors were assessed by teacher report across the early elementary school years. The following hypotheses were examined:

1. Children carrying an A1 allele (A1+) will have a greater tendency to display externalizing behaviors.
2. This will be associated with a tendency for A1+ individuals to be more tolerant of probabilistic risk and/or uncertainty, rather than more sensitive to reward.
3. Exposure to hypoxic conditions during fetal development will be associated with decision making preferences.
4. Individual differences in decision making related to uncertainty and/or probabilistic risk will mediate the associations between hypoxia exposure and externalizing behavior.

Given that evidence from animal models indicates at least two different pathways by which hypoxia could alter dopaminergic function (D2R cell loss, cortisol release) with different implications for the phenotypic outcome, no directional a priori hypothesis can be made for Hypothesis 3. If a significant association is detected, the nature of this association will contribute evidence toward understanding the possible mechanisms by which prenatal risk influences behavioral outcomes.

2 | METHODS

2.1 | Sample and procedure

Participants were drawn from the Family Life Project (FLP), an ongoing epidemiological study of the effects of poverty and rurality on early child development. Information regarding the recruitment and maintenance of the entire FLP sample is detailed elsewhere (Vernon-Feagans et al., 2008; Vernon-Feagans & Cox, 2013). The FLP followed 1,292 families recruited at the time of the child's birth, in regions of Pennsylvania (n = 519) and North Carolina (n = 773). During the summer between 3rd and 4th grades, participants from the Pennsylvania cohort were invited to participate in a study examining decision making behaviors in children. More details about the specific recruitment and participation for the decision making assessment have been reported elsewhere (Gatzke-Kopp et al., 2018). Briefly, n = 403 of the original Pennsylvania subsample remained in assessment proximity and agreed to participate in the study (Mean age = 9.20 years, SD = 0.28, range = 8.67–9.92). Consistent with the demographics in the regions from which this sample was drawn, 93% of parents identified their child as primarily White, 6% identified their child as primarily Black, and the remaining 1% did not indicate a race. Of the 403 children who participated in the assessment, n = 1 did not complete the probability portion of the decision making task due to time constraints, n = 5 did not have maternal IQ data, n = 54 had not provided genetic data, and n = 10 provided genetic data but were missing Taq1A single nucleotide polymorphism (SNP) data due to laboratory error, leaving a final sample of n = 333 for the current investigation.

2.2 | Decision making task

Complete details regarding the decision making task assessment protocol can be found in Gatzke-Kopp et al. (2018). Software for the decision making task can be downloaded at https://github.com/dkdupuis/aceTask#acetask. Briefly, a trained research assistant administered the decision making assessment on a laptop computer in each participant's home. Prior to the assessment, parents signed an informed consent form and children provided verbal assent. All procedures were approved by the local IRB. Families were provided a $50 gift card for their time, and children were awarded a prize in conjunction with the task (described below).

2.2.1 | Task administration

Children were told they would be playing a computer-based card game in which they would earn points that could be redeemed for a prize. Prior to the start of the game, children were shown a large selection of prizes (each worth approximately $20) including toys, art projects, games, and play equipment and told that if they got "enough" points during the game, they would be able to choose any prize, but if they did not earn enough points, they would only be allowed to select from a bin of small, relatively unappealing, plastic farm animals.

The decision making task consisted of three blocks, with each block representing a specific cost domain: effort, delay, and probability. Block order was randomly determined by the computer at the start of each session. Only the probability block (illustrated in Figure 1) will be examined here. For each card, points were represented numerically as well as visually (number of stars) as with a typical deck of cards and could range from 1 to 10. Each card had an associated probability, which indicated the chances of actually

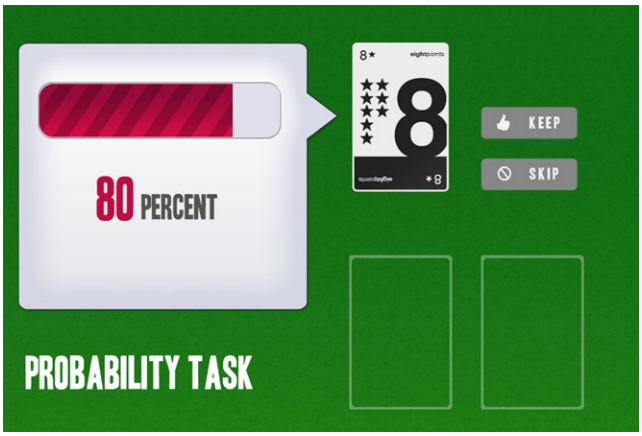

FIGURE 1 Graphical user interface screenshot from the probability block of the Assessing Cost Estimation decision making task. Each card has an associated point value and associated cost value; in this example, the participant has an 80% probability of receiving 8 points. The red-shaded bar depicts the risk associated with the current trial relative to the full range of potential probabilities

receiving the points on the card. Probability was presented on the left side of the screen, numerically as a percentage, and visually as the proportion of a rectangle that was shaded red. Probability ranged from 10% to 100% in 10 equally spaced increments and was subsequently recoded so that the lowest level of risk (1) represented the highest probability (100%) and the highest level of risk (10) represented the lowest probability (10%).

For each card, children decided if they wished to keep the card based on the reward/probability properties, or skip the card and move to the next card. Children were told there would be a limited number of cards and that the game would end without warning in order to prevent children from assuming that there was an unlimited number of future chances for a better card. If a child elected to keep the card, points were awarded at the true probability indicated. In order to ensure that children fully understood the probabilistic nature of the task, a practice session was provided before the task began. During the practice session, outcomes were programmed to ensure that children would experience a high-value/high-probability option that was not awarded. Because it was unclear to the child how task duration would be determined, no inherent strategy could be deduced for how to proceed. For instance, if the task ended after a certain number of cards were accepted, a strategy of only accepting the highest reward/probability pairings would result in the highest gain. However, if the task ended after a certain number of cards were rejected, a far more conservative approach would be warranted. This ambiguity left children to determine a decision strategy based on their own intuition and preferences, maximizing the ability to detect individual differences.

2.2.2 | Task scoring

In order to maximize information and minimize demands on the participant, an adaptive algorithm was used such that the child's decision on one card informed the computer's selection of the next card (see Gatzke-Kopp et al., 2018). Essentially, the algorithm assumed a 10 (reward) × 10 (probability) decision space, and the initial five cards presented strategically sampled each quadrant, such that all participants responded to the same choice combinations. From these decisions, the algorithm populated portions of the decision space that could be assumed rather than sampled. For instance, if a child accepted a card of 8 points at an 80% probability, it was assumed that they would also accept cards worth more than 8 points at this probability, as well as this level of points at higher probabilities. Once the decision space was populated from the initial five cards presented, the algorithm randomly selected reward/probability pairings from the unsampled decision space. The task ended once the entire space was estimated.

Decision preferences were modeled using a "measurement model" that was structured as a person-specific logistic regression. Each individual *i*'s binary decisions across *t* = 0–100 possible trials were modeled in order to determine the log odds of the decision to keep a card as a function of the associated *risks* and *rewards* (each variable centered in a range from −4.5 to +4.5).

$$\log\left(\frac{P\left(\text{keepcard}_t=1\right)}{1-P\left(\text{keepcard}_t=1\right)}\right)=\beta_0+\beta_1\text{risk}_t+\beta_2\text{reward}_t$$

In this equation, β_0 is the intercept term and reflects the individual's general *uncertainty tolerance*. The intercept represents the log odds of the child's willingness to accept a card at the median levels of risk and reward, essentially a point value of 5 at a 50% probability. Scores on this parameter ranged from −11.29 to 22.73 (*M* = 4.28, *SD* = 5.58) indicating a wide range of tolerance to decisions of maximum uncertainty. More positive tolerance scores indicate greater willingness to accept an uncertain offer, whereas more negative tolerance scores indicate greater disinclination to accept an uncertain offer (i.e., less tolerance of uncertainty).

The β_1 parameter represents a *risk-sensitivity* coefficient that quantifies how sensitive the child's decisions were to increases in risk (i.e., decreases in probability). All individuals had negative β_1 values indicating that for all children an increase in risk was associated with a lower likelihood of accepting the card. The magnitude of risk sensitivity varied across the sample from −6.14 to −0.34 (*M* = −2.92, *SD* = 1.62).

Finally, the β_2 parameter is a *reward-sensitivity* coefficient that indicates how sensitive the child's decisions were to increases in reward. All children had positive β_2 values such that an increase in potential reward was associated with a greater likelihood of accepting the card. The magnitude of reward sensitivity varied across the sample from 0.34 to 5.67 (*M* = 1.41, *SD* = 0.87).

Modest correlations were observed between greater tolerance for uncertainty and greater sensitivity to reward ($r(331) = 0.24$, $p < 0.001$) and to a lesser degree between greater sensitivity to reward and less sensitivity to risk ($r(331) = 0.15$, $p = 0.006$). No correlation was observed between uncertainty tolerance and risk sensitivity ($r(331) = -0.06$, $p = 0.25$). Furthermore, none of the probability decision parameters (i.e., uncertainty tolerance, risk sensitivity, reward sensitivity) were correlated with children's IQ, executive function, or verbal ability (Gatzke-Kopp et al., 2018). Boys (*n* = 181) and girls (*n* = 152) did not differ with regard to decision preferences in the probability block (Uncertainty tolerance: $t = -1.18$, $p = 0.24$; Risk sensitivity: $t = -0.87$, $p = 0.38$; and Reward sensitivity: $t = -0.29$, $p = 0.77$).

2.3 | Externalizing behaviors

Teachers completed the age-appropriate version of the Strengths and Difficulties Questionnaire (Goodman, 1997) each year the child was in formal schooling from preschool through 3rd grade. The 5-item conduct problems subscale was used as an index of externalizing behaviors. Items included the following: often loses temper; generally well behaved and usually does what adults request (reverse coded); often fights with other children or bullies them; often argumentative (SDQ ages 2–4)/often lies or cheats (SDQ ages 4–10); can be spiteful (SDQ 2–4)/steals from home, school, or others (SDQ 4–10); and each of which was rated dichotomously as 0 (not present

in/characteristic of the child) or 1 (present in/characteristic of the child). Children's scores were averaged across all available years to reflect both the presence and the chronicity of the behaviors. Scores could range from 0 (no symptoms present at any time point) to 5 (all symptoms present at all time points). Observed scores ranged from 0 to 4.4, with boys rated higher in conduct problems overall (M = 1.10, SD = 1.11) relative to girls (M = 0.65, SD = 0.95) (t = −4.01, p < 0.0001). Although essentially the full range of symptom severity was observed in this sample, scores were not normally distributed owing to the disproportionate number of cases with scores of zero. In order to accommodate the distribution, scores were multiplied by 10 to convert into integers and a Poisson regression was applied.

2.4 | Maternal IQ

Mothers completed the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955) during the home visit when the child was aged approximately 36 months. Scores on this measure ranged from 65 to 138 (Mean = 97.74, Median = 97, SD = 14.11). This measure was included as a covariate in all models to control for the potential contribution of maternal characteristics on child's hypoxia risk score.

2.5 | Genotyping

During a home visit when the child was approximately 36 months, saliva samples were collected using Oragene DNA Self-Collection kits (DNA Genotek, Ottawa, ON, Canada) in accordance with the manufacturer instructions. Parental consent was obtained on behalf of the child. DNA extraction and genotyping were performed at the Genome Core Facility in the Huck Institutes for Life Sciences at Penn State University under the direction of Deborah S. Grove, Director for Genetic Analysis. Genotypes were processed for quality control in the Laboratory of Dr. Christopher Bartlett, located in The Research Institute at Nationwide Children's Hospital. ANKK1 genotyping was conducted with the appropriate probes for a TaqMan SNP Genotyping Assay using an Allelic Discrimination Assay protocol (Applied Biosystems, Foster City, CA, USA). Forty nanograms of DNA was combined in a volume of 5 ml with 2× Universal PCR Mix (Applied Biosystems) and 1/20 the volume of the TaqMan SNP assay in a 384-well plate. A Pre-Read was performed and then PCR as follows: a 10 min hold at 95°C, followed by 40–45 cycles of 15 s at 92°C, and then 1 min at 60°C in a 7900HT PCR System. After amplification, a Post-Read was performed to analyze. Automatic and manual calls were made (Haberstick & Smolen, 2005).

Frequencies for ANKK1/DRD2 Taq1A genotype were as follows: 219 individuals were A2/A2 homozygous, 98 were A1/A2 heterozygous, and 16 were A1/A1 homozygous. The observed allele frequencies did not differ from Hardy–Weinberg equilibrium, $\chi^2(1, 332) = 1.34$, $p = 0.20$. Given the very low number of participants who were A1/A1 homozygous, and following the approach used in previous studies (e.g., Eisenberg et al., 2007; Li et al., 2006; Munafò, Timpson, David, Ebrahim, & Lawlor, 2009), A1 homozygous and heterozygous individuals were combined to create an A1+ group for comparison with individuals who were A2/A2 homozygous (A1−). Boys and girls did not differ with regard to A1 status, $\chi^2(1, 332) = 0.65$, $p = 0.42$.

2.6 | Hypoxia exposure

Pre- and perinatal hypoxic exposures were assessed via maternal self-report at the study intake visit, which took place when the infant was approximately 2 months old. Mothers completed a questionnaire regarding their own health during pregnancy, complications during the delivery, and other indicators of fetal and newborn health. Based on the previous literature (Socol, Manning, Murata, & Druzin, 1982; Vannucci, 2000), the following items were considered to indicate an increased risk of perinatal hypoxia exposure and combined into a composite risk score: Mother had high blood pressure during pregnancy, mother reported smoking during pregnancy, infant was delivered via Cesarean section, infant was born breech, infant was not breathing on his/her own at birth, infant displayed fetal distress requiring medical intervention, and infant required a tube or machine to help with breathing following birth. Out of possible range of 0–7, sample scores ranged from 0 to 4 (Mean = 0.87, Median = 1, SD = 0.91, skewness = 1.04). Hypoxic exposure did not differ by sex, $F(1, 346) = 0.09$, $p = 0.74$, or genotype, $F(1, 341) = 0.64$, $p = 0.38$. Lower maternal IQ was significantly associated with higher hypoxic exposure scores, r = −0.22, p < 0.001.

2.7 | Data analysis

In order to examine whether allelic variation in the Taq1 polymorphism, perinatal hypoxic exposure, or their interaction predicted individual differences in behavior, separate regressions were run with externalizing behaviors and decision making parameters as outcomes. Because externalizing behavior was characterized by a sizeable proportion of participants with no symptoms (i.e., zero inflated), and symptoms were treated as a count variable, data were analyzed using a stepwise Poisson regression model (Long, 1997), specified as follows:

$$\text{Externalizing} = \beta_0 + \beta_1 \text{sex} + \beta_2 \text{maternalIQ} + \beta_3 \text{taq1Agenotype} + \beta_4 \text{hypoxia} + \beta_5 \text{taq1Agenotype*hypoxia}$$

Because boys and girls were shown to differ on the measure of externalizing behavior, sex was included as a control variable in a first step along with maternal IQ, with Taq1A genotype and hypoxia included in a second step, and the genotype × hypoxia interaction in a third step.

Separate linear regression models were conducted for each decision making parameter, (a) uncertainty tolerance, (b) sensitivity to risk, and (c) sensitivity to reward. Because previous analyses indicated that individuals who were randomly presented the probability block first in the three-block decision making task displayed more cautious behavior than those who were presented the

probability block 2nd or 3rd, task presentation order was coded to reflect whether the probability block came 1st or not 1st and entered as a control variable along with participant sex and maternal IQ in the first step of the regression model. Genotype and hypoxia score were entered into the second step, and the genotype × hypoxia interaction was entered into the third step. Models were specified as follows:

$$Y = \beta_0 + \beta_1 \text{prob.order} + \beta_2 \text{sex} + \beta_3 \text{maternalIQ} + \beta_4 \text{taq1Agenotype} + \beta_5 \text{hypoxia} + \beta_6 \text{taq1Agenotype} \times \text{hypoxia}$$

where *Y* represents either uncertainty tolerance, risk sensitivity, or reward sensitivity. Task scoring and analyses were run using SAS 9.4 (SAS Institute, Cary, NC, USA) and R (R Core Team, 2015) software, specifically, the proc logistic SAS procedure and the lm and glm R procedures. All models were also conducted including two-way interactions between sex and hypoxia score as well as Taq1A genotype; no evidence was found for the existence of significant interactions between sex and the predictor variables; hence, the simpler models are referred to hereafter.

3 | RESULTS

Means and standard deviations of the teacher-rated externalizing behaviors, hypoxia risk score, and decision parameters by genotype group are presented in Table 1. Although A1+ individuals had higher externalizing symptom scores on average as hypothesized, this difference did not reach significance, nor were there significant differences by genotype on any of the other variables.

Zero-order correlation analyses revealed no significant associations between externalizing behavior score and any of the decision making parameters (Uncertainty tolerance—$r = -0.03$, $p = 0.63$. Risk sensitivity—$r = -0.03$, $p = 0.56$. Reward sensitivity—$r = -0.03$, $p = 0.53$).

Results of the Poisson regression predicting externalizing behavior are presented in Table 2. Significant main effects emerged for sex ($\beta = 0.53$, $p < 0.001$) and maternal IQ ($\beta = -0.01$, $p < 0.001$) at step 1 (pseudo $R^2 = 0.07$). Main effects for genotype and hypoxia exposure that emerged at step 2 (which demonstrated a significant improvement from step 1, Δpseudo $R^2 = 0.014$, $\chi^2(4, 328) = 56.5$, $p < 0.001$) were qualified by an interaction term ($\beta = 0.13$, $p < 0.001$) at step 3 (a significant improvement from step 2, Δpseudo $R^2 = 0.003$, $\chi^2(5, 327) = 13.12$, $p < 0.001$). In order to examine the nature of the interaction, a simple slope analysis was conducted, and results are illustrated in Figure 2. Analyses indicated a significant increase in incidents of externalizing behavior as a function of hypoxia exposure among A1+ individuals (estimate = 0.14, $p < 0.001$). However, no significant association between externalizing behavior and hypoxia was observed among A1− individuals.

Results of the stepwise multiple linear regression models predicting uncertainty tolerance, reward sensitivity, and risk sensitivity are presented in Table 3. Standardized beta values are reported.

TABLE 1 Externalizing behavior, hypoxia exposure, and decision parameter means (*SD*) by genotype group

	A1+	A1−	*F*(1, 331)
Externalizing behaviors	10.22 (11.81)	8.24 (9.90)	2.63
Hypoxia exposure	0.92 (1.01)	0.84 (0.86)	0.53
Uncertainty tolerance	3.71 (5.61)	4.58 (5.51)	1.82
Reward sensitivity	1.29 (0.76)	1.45 (0.92)	2.70
Risk sensitivity	−2.81 (1.64)	−2.97 (1.61)	0.75

Note. One-way ANOVA comparisons between genotypes did not reach significance.

3.1 | Uncertainty tolerance

Step 1 was significant ($R^2 = 0.04$, $F(3, 329) = 4.10$, $p = 0.007$), with only task order emerging as a significant predictor of tolerance ($\beta = -0.40$, $p = 0.001$). No significant improvement in the model was observed at step 2 ($\Delta R^2 = 0.005$, $F(5, 327) = 1.82$, $p = 0.16$). However, a significant increase in model prediction was observed at step 3 ($\Delta R^2 = 0.009$, $F(6, 326) = 3.91$, $p = 0.04$) with the inclusion of the hypoxia × genotype interaction ($\beta = 0.24$, $p = 0.04$).

In order to examine the nature of the interaction, a simple slope analysis was conducted and results are illustrated in Figure 3. Analyses indicated a significant decrease in uncertainty tolerance (more conservative decision making) as a function of hypoxia exposure among A1− individuals (estimate = −0.18, $p = 0.02$). No significant association between uncertainty tolerance and hypoxia was observed among A1+ individuals.

3.2 | Sensitivity to risk

Unlike the model for uncertainty tolerance, none of the steps in the regression model significantly predicted risk sensitivity (Step 1: $R^2 = 0$, $F(3, 329) = 0.43$, $p = 0.73$; Step 2: $R^2 = 0$, $F(5, 327) = 0.52$, $p = 0.76$; and Step 3: $R^2 = 0$, $F(6, 326) = 0.49$, $p = 0.82$).

TABLE 2 Poisson regression model predicting externalizing behavior count score

	Estimate	Odds ratio
Step 1		
Intercept	2.57***	
Sex	0.53***	1.70
Maternal IQ	−0.01***	0.99
Step 2		
A1 status	0.24***	1.27
Hypoxia	0.07***	1.07
Step 3		
A1 status × Hypoxia	0.13***	1.39
Final model pseudo-R^2	0.09	

Note. AIC = 6,248.9.
***indicates $p < 0.001$.

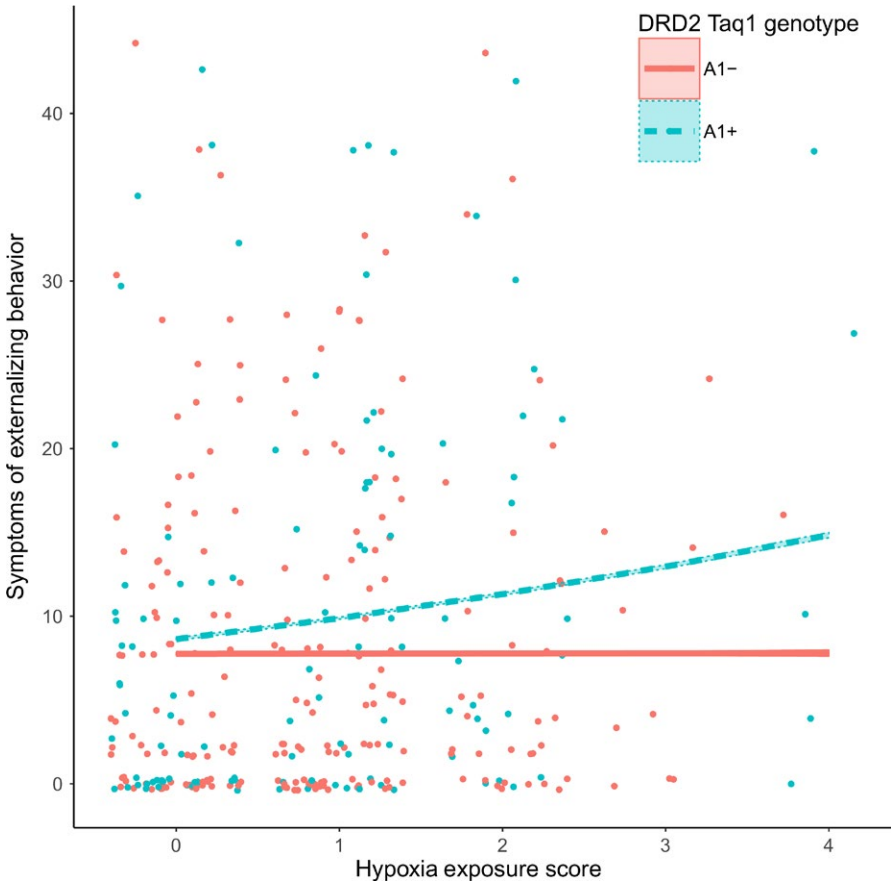

FIGURE 2 Plot of the interaction between DRD2 Taq1A genotype status and hypoxia exposure score predicting externalizing behavior. Results showed a significant increase in externalizing behavior scores at higher levels of hypoxia exposure among A1+ individuals, but no significant relationship between externalizing behavior and hypoxia exposure among A1− individuals

TABLE 3 Stepwise linear multiple regression models for uncertainty tolerance, reward, and risk sensitivity

	Tolerance	Reward	Risk
Step 1			
Intercept	0.06	−0.02	0.10
Block order	−0.40**	−0.10	0.04
Sex	0.12	0.03	0.10
Maternal IQ	−0.001	−0.001	−0.003
Step 2			
A1 status	−0.14	−0.18	0.10
Hypoxia	−0.09	−0.07	0.04
Step 3			
A1 status × Hypoxia	0.24*	−0.01	0.07
Final model adjusted R^2	0.041**	−0.004	−0.009

Note. Standardized betas reported.
*and ** indicate $p < 0.05$ and $p < 0.01$, respectively.

3.3 | Sensitivity to reward

As with sensitivity to risk, none of the steps in the regression models significantly predicted reward sensitivity (Step 1: $R^2 = 0$, $F(3, 329) = 0.25$, $p = 0.86$; Step 2: $R^2 = 0$, $F(5, 327) = 0.92$, $p = 0.47$; and Step 3: $R^2 = 0$, $F(6, 326) = 0.77$, $p = 0.59$).

Results indicate associations between biological risk and behavioral outcomes with regard to both externalizing symptoms and decision making. However, due to the lack of correlation between externalizing and decision making behavior, the mediation hypothesis was not supported.

4 | DISCUSSION

The present study sought to examine whether Taq1A genotype and/or perinatal exposure to hypoxia predicted children's teacher-reported externalizing behavior across the early elementary school years, and whether this association was mediated through changes in sensitivity to risk or tolerance of uncertainty. Results indicated that genotype significantly moderated the association between hypoxia and externalizing behaviors as well as uncertainty tolerance, although the nature of these interactions differed as a function of genotype. Greater exposure to hypoxic events was associated with more externalizing symptom severity only for children with A1+ status. However, the association between greater hypoxia exposure and more tolerance of uncertainty among A1+ individuals did not reach significance, suggesting that the mechanism by which early developmental adversity interacts with genotype to increase externalizing outcomes is not

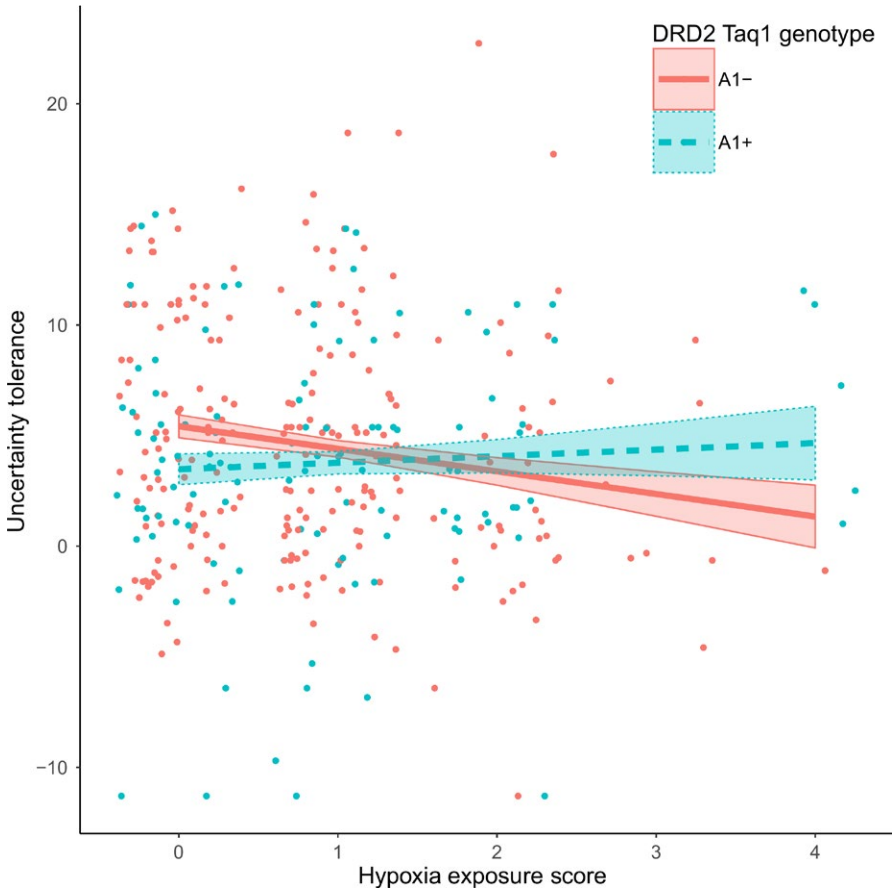

FIGURE 3 Plot of the interaction between DRD2 Taq1A genotype status and hypoxia exposure score predicting uncertainty tolerance. Results showed a significant decline in uncertainty tolerance at higher levels of hypoxia exposure among A1− individuals, but no significant relationship between uncertainty tolerance and hypoxia exposure among A1+ individuals

explained by probabilistic decision making. Interestingly, hypoxia exposure was significantly associated with a decrease in uncertainty tolerance (i.e., more conservative decision making) among A1− individuals. The differences in behavioral outcomes associated with hypoxia exposure are consistent with the possibility that hypoxia influences neural development through different biological pathways depending on individual differences in D2 receptor function, as indicated by Taq1A genotype.

Evidence from pharmacological manipulations indicates that D2 receptor activity is associated with reductions in risk-taking behavior (Simon et al., 2011), which may explain why individuals who possess the less efficient A1 allele are more prone to developing externalizing behavior. The present results did not observe a main effect of A1 allele status on externalizing behavior, although this could be a function of the relatively young age of the sample. It is possible that this susceptibility, particularly for behaviors such as substance abuse, remains latent in these children and could manifest later in life. Whether genotype alone is sufficient to confer vulnerability, the present findings suggest that perinatal exposure to hypoxic stress significantly exacerbates this vulnerability and is associated with externalizing behavior in childhood. This finding is consistent with animal research demonstrating that hypoxia results in a significant and sustained reduction in D2 receptors (Kostic et al., 1991). A1+ individuals who already have lower D2 receptor function may be especially vulnerable to the behavioral consequences of additional cell loss.

Although there was a significant dose–response relationship between the number of hypoxic events and the severity and chronicity of teacher-rated externalizing behaviors across childhood among A1+ individuals, the hypothesized effect of hypoxia on decision making did not reach significance. Because D2 receptor activation has been shown to enhance the saliency of loss experiences, the present task may not have been optimal for detecting differences as a function of genotype. In the present task, there was no condition in which previously accumulated points could be lost. Future research is needed to examine whether the increase in externalizing symptoms observed among A1+ individuals exposed to hypoxia is a function of reduced ability to respond appropriately to punishment (i.e., loss of points). Specifically, associations may be more evident in a task incorporating a learning component, in which sensitivity to loss could be measured as the extent to which individuals learned to adjust future decision making as a function of past experience (Zalocusky et al., 2016).

Although there was no direct correlation between uncertainty tolerance and externalizing symptoms, the increased tendency for A1− individuals to be more conservative in the face of uncertainty may indirectly contribute to what appears to be a protective buffer against developing externalizing problems. This heightened sensitivity of the A1− individuals to physiological indicators of adversity (hypoxia) may even serve an adaptive function. This association also suggests that hypoxia may influence the developing dopaminergic system differently in the context of the A1− genotype. The

observed increase in conservative decision making is consistent with the neuronal effects of cortisol release in response to hypoxic stress. Prenatal cortisol exposure has been shown to contribute to a decrease in tolerance for uncertainty, driving individuals toward more cautious and conservative behavior (Weinstock, 2017), likely through an increase in D2 receptor expression (Rodrigues et al., 2012). The possibility that hypoxia has differential effects on brain development as a function of genotype is consistent with research indicating that D2 receptors contribute to the cellular response to acute hypoxic events. D2 receptor activation mediates a neuroprotective response, reducing reactive cell death (Bozzi & Borrelli, 2006). Thus, A1+ status may influence the extent of D2 receptor availability that, when exposed to hypoxic stress, could moderate the nature or extent of the biological response. A1+ individuals may be less able to invoke a protective response, resulting in greater D2 receptor loss and a reduced sensitivity to the effects of punishment on decision making. In contrast, A1− individuals may be able to engage protective processes including cortisol release that mitigates the extent of cell loss, but activates compensatory processes that result in an increase in conservative behavior.

Although the associations between hypoxia and behavior suggested a cumulative dosage effect, it is important to note that this study was not able to quantify actual degree of hypoxia or to examine the effects of timing, duration, and chronicity of hypoxic exposure. It is possible, for instance, that effects are strongest for acute events of a greater severity, such as obstructed breathing during delivery, than more extended but mild events such as maternal smoking. Because smoking and high blood pressure were more common events in the present sample, it is not clear whether the stronger effects on uncertainty tolerance evident among those with more hypoxic events represent a cumulative effect of all events, or the likelihood that those with a higher count were more likely to have had severe events. Future studies that are able to document medical events throughout pregnancy are needed to further examine these issues. The current results do, however, suggest that even low-grade hypoxia associated with blood pressure or smoking appear to affect behavior in genetically moderated ways.

While it can be adaptive to discount for low probability, particularly in contexts where resources are limited, an inability to tolerate uncertainty could be maladaptive. Because there was no condition in which points could be lost in the current decision task, it is not clear that avoiding uncertain decisions is inherently adaptive. For example, the decision to accept an offer worth 5 points at 50% probability has an expected value of 2.5 points, whereas the decision to reject the offer has an expected value of 0 points. From a purely probabilistic perspective, the choice is between a 50% chance of getting no points and a 100% chance of getting no points. A growing body of research has linked the construct of uncertainty intolerance to pathological worry and internalizing disorders such as anxiety (Carleton et al., 2012; Ladouceur et al., 2000). As the Family Life Project continues to collect data as the participants move into adolescence, future work with this sample will examine whether higher levels of uncertainty intolerance are associated with the emergence of anxiety behaviors over time, as well as whether the potential protective effects of uncertainty intolerance with regard to childhood externalizing behavior are also evident with regard to potentially harmful behaviors during adolescence, including the initiation of substance use.

4.1 | Limitations and future directions

The Family Life Project provides an optimal opportunity to examine gene × environment interactions due to its prospective longitudinal design (Johnston, Lahey, & Matthys, 2013), and the independent measurements of the environment (maternal-reported hypoxic events) and behavior (teacher-rated externalizing; child tested decision making) (Moffitt, Caspi, & Rutter, 2005). Furthermore, this study fulfills the recommended practices for examining gene × environment interaction in psychological research by examining hypotheses informed by specific proposed neurobiological mechanisms of action by which environmental inputs affect behavioral profiles, as well as examining more proximal intermediary behavioral profiles that may or may not confer vulnerability for psychological disorders later in life (MacKillop & Munafò, 2013). However, the preliminary nature of these findings warrants caution and requires further examination and replication (Dick et al., 2015). Furthermore, although the relative racial and socioeconomic homogeneity of the present sample may enhance the ability to detect genetic associations, it is important to note that it cannot be assumed such findings generalize to other racial subgroups or under different environmental conditions (Gatzke-Kopp, 2016).

Although sex was included as a covariate in all models, future research should examine whether sex moderates any of the observed associations. In addition to the greater incidence of externalizing behavior among males, research indicates that males are more susceptible to the neuronal effects of early hypoxia (Kheirandish, Gozal, Pequignot, Pequignot, & Row, 2005; Simon & Volicer, 1976). Although no evidence was found for two-way interactions between sex and hypoxia risk or Taq1A genotype, the present sample lacked the power to examine a 3-way interaction. Finally, although the interaction of Taq1A genotype with early hypoxic exposure predicting uncertainty tolerance was statistically significant, it accounts for a relatively small proportion of the variance. The Taq1A allele is but one marker of a complex genetic phenomenon, and as more is learned about the functional implications of additional genetic variants related to the D2 receptor, research could explore more comprehensive genetic susceptibility profiles which may account for larger explanatory variance. Of particular, interest would be an assessment including the multiple genetic variants in linkage disequilibrium with the Taq1A polymorphism, such as rs2283265 and rs6277 and other SNPs associated with DRD2 gene expression and receptor function (Markett et al., 2010; Zhang et al., 2007).

In summary, our findings lend support to the hypothesis that genetic factors moderate the effect of the environment by determining an individual's sensitivity to different environmental inputs. Although it is likely that a complete understanding of this phenomenon will ultimately require a more complex assessment of how

multiple genes contribute in an additive or interactive process to vulnerability, the examination of these scores remains exploratory, with no specific biological model guiding which genes are likely to contribute under which conditions. As such, studies such as this, which examine a single candidate gene in the context of theoretically selected environmental factors, contribute to the literature base needed to better inform more complex approaches to defining genetic susceptibility.

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ORCID

Roisin White http://orcid.org/0000-0002-5851-7905

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