

Human maternal behaviour is associated with arginine vasopressin receptor 1A gene

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Parenting is one of the main influences on children's early development, and yet its underlying genetic mechanisms have only recently begun to be explored, with many studies neglecting to control for possible child effects. This study focuses on maternal behaviour and on an allele at the RS3 promoter region of the arginine vasopressin receptor 1A (*AVPR1A*) gene, previously associated with autism and with higher amygdala activation in a face-matching task. Mothers were observed during a free-play session with each of their 3.5-year-old twins. Multilevel regression analyses revealed that mothers who are carriers of the *AVPR1A* RS3 allele tend to show less structuring and support throughout the interaction independent of the child's sex and RS3 genotype. This finding advances our understanding of the genetic influences on human maternal behaviour.

Keywords: arginine vasopressin receptor 1A; maternal behaviour; control; warmth; structuring

1. INTRODUCTION

Across a broad range of disciplines, there is a growing consensus on the importance of early childhood in influencing the trajectory of mental health later in life [1]. Of particular importance is parental behaviour that may contribute to future psychopathology, especially when combined with a child's predisposing genetic makeup. Intriguingly, despite individual differences in parenting styles and their demonstrated heritability [2], only recently have studies of specific genes underlying human parental behaviour been reported [3–6]. Furthermore, most of these studies focused on maternal sensitivity, and none has explored structuring (providing suggestions and expectations to the child) that has been shown to be an important aspect of parenting [7].

The oxytocin–vasopressin neural pathways play a crucial role in moulding the social brain in animals, and more recently, the effects of these social neurohormones have also been demonstrated in humans [8]. These two nonapeptides are also relevant to parental

behaviours across a variety of species [9]. The human arginine vasopressin receptor 1A (*AVPR1A*) gene region is characterized by four repeat polymorphisms, of which three are in the promoter region ((GT)₂₅, RS1 and RS3). Of special interest is RS3, and particularly its second most common allele ('target allele' in the current report) that has been associated with autism [10], lower generosity [11], marital problems [12] and amygdala activation in an emotional face-matching task [13]. Importantly, RS3 has been associated with mRNA expression levels in the hippocampus [14], and most recently with maternal sensitivity [6].

This research tests for an association between the 'target allele' and three maternal behaviours: positive parenting, negative control and a yet unexamined phenotype—focused support/structuring. Because children influence parental behaviour and share half of their genes with their parents, it is imperative to include both parent's and children's genotypes when examining genetic effects on parenting in order to establish causality (overrule a possible association with the parent's gene that actually represents an effect in which child's behaviour, associated with the child's gene, evokes parental behaviour, i.e. an evocative gene–environment correlation; rGE [15]). To this end, both mothers and their children were genotyped for *AVPR1A* RS3 and observed during free-play in a controlled, laboratory setting.

2. MATERIAL AND METHODS

Participants were mothers and their 3.5-year-old twins taking part in a longitudinal study [16] examining genetic and socialization influences on development. Phenotypic and genotypic data were available on 252 dyads that consisted of 135 mothers and their twins (in nine families, observational data on one of the twins were missing owing to technical problems. In nine other families, DNA data were available only for one twin owing to sample quality). Twins' mean age was 44.25 months, s.d. = 2.8, and mothers' mean age was 34.41 years, s.d. = 4.45.

Mothers were videotaped interacting with each of their twins individually during 10 min of free-play with a colourful set of play-dough and modelling tools. Trained research assistants rated maternal behaviours for each 2 min segment, and then scores were averaged across the 10 min session. Different observers rated mothers' behaviours towards each twin. Several aspects of maternal behaviour were rated on a zero (none) to four (frequent) scale: warmth; autonomy support (behaviours enhancing children's sense of value); negative affect; and structuring (preventing distractions, setting goals). Mothers' control (adapted from Kochanska & Aksan [17]) was indicated by computing the proportion of reactions towards the child that showed: (i) Social exchange: addressing the child in conversation, without making control attempts. (ii) Gentle guidance: using reasoning and suggestions. (iii) Assertive control: using demands with a hint of impatience, but without showing anger. (iv) Coercive control: controlling attempts that include a negative tone or aggression.

A factor analysis showed that warmth, negative affect and autonomy support loaded on a single factor (0.81, –0.73 and 0.84, respectively), accounting for 63 per cent of the variance. Therefore, a global composite of *positive parenting* was created by averaging the standardized scores of these measures (with negative affect reversed). 'Assertive control' and 'coercive control' were summed and standardized to create a measure of *controlling behaviour*. 'Structuring' and 'gentle guidance' substantially correlated ($r = 0.46$, $p < 0.001$), and were standardized and averaged in a composite of *focused support*. Two coders independently coded 63 random dyads and the inter-rater correlations for positive parenting, controlling behaviour and focused support were 0.88, 0.65 and 0.91 respectively (all $p < 0.001$).

(a) DNA extraction and genotyping

DNA extraction and genotyping were performed as detailed elsewhere [11]. The observed length of RS3 depends on the PCR primers employed, and the 327 bp allele in this study corresponds to the 334 allele in other studies [10,13]. In these studies and in

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the present investigation, this allele is the second most common RS3 variant (approx. 23%).

(b) *Statistical analysis*

Mendelian inheritance and Hardy–Weinberg equilibrium were verified with PEDSTATS v. 0.6.12 [18] (<http://www.sph.umich.edu/csg/abecasis/PedStats/>). SPSS v. 18 was used for descriptive and factor analyses. Multilevel analyses with families as clusters were carried out in MPLUS [19] v. 5.21, under the default option of maximum-likelihood estimation with robust standard errors, which is robust to non-normality, allowing for multilevel analyses based on unbalanced groups, taking care of non-independence of twin data. Mother's genotype was entered as a between variable and twins' genotypic data (0, non-carriers; 1, RS3 'target allele' carriers) and sex (0, boys; 1, girls) were entered as within variables to control for possible child effects. See electronic supplementary material for the dataset.

3. RESULTS

Thirty-five per cent of the mothers and 43 per cent of the twins were carriers of at least one 'target allele'. Mothers' parenting showed substantial inter-twin consistency (focused support, $r = 0.55$; positivity, $r = 0.59$; negative control, $r = 0.39$, all $p < 0.001$). The correlation between controlling behaviour and positive parenting was moderate and negative ($r = -0.43$, $p < 0.001$). Focused support correlated positively with positive parenting ($r = 0.21$, $p = 0.001$), and controlling behaviour ($r = 0.23$, $p < 0.001$), suggesting that focused support combines aspects of positive parenting and control.

(a) *Within-family (child-level) effects*

None of the parenting variables associated significantly with children's RS3 genotype, indicating that any effect of mothers' RS3 genotype on maternal behaviour is not confounded by an evocative rGE [15]. Maternal behaviour was sensitive to children's sex. Mothers exhibited more positive parenting ($\beta = 0.22$, $p = 0.02$) and less controlling behaviour ($\beta = -0.22$, $p = 0.007$) towards girls. Finally, mothers' focused support did not vary according to children's sex.

(b) *Between-family (mother-level) effects*

Positive parenting and controlling behaviour were not significantly related to mothers' RS3 genotype. Importantly, mothers' RS3 genotype was significantly associated with focused support ($\beta = -0.28$, $p = 0.003$), with carriers of the 'target allele' being less likely to support the child's functioning throughout the free-play session. This finding remained significant following the Holm–Bonferroni correction for multiple testing. The difference in R^2 between a model with mothers' RS3 genotype and without was 0.15, indicating the magnitude of the effect.

Follow-up analyses attested to the robustness of the findings. When randomly selecting one twin per pair, the RS3-focused support relationship remained significant ($p = 0.01$). Mother's age and socioeconomic status (1, below average income; 0, average/above) did not interact with RS3 in predicting focused support. Moreover, RS3 predicted focused support over and above these variables and their interactions with RS3 ($\beta = -0.39$, $p < 0.001$). Finally, both aspects of the focused support composite showed a significant association with mothers' genotype (gentle guidance, $\beta = -0.22$, $p = 0.009$; structuring, $\beta = -0.30$, $p = 0.014$).

4. DISCUSSION

We describe a novel negative association between mothers' supportive and guiding behaviour and the AVPR1A RS3 'target allele', independent of the child's sex and RS3 genotype. The allele previously associated with autism [10], higher marital problems [12], lower generosity [11] and higher amygdala activation in an emotional face-matching task [13] is shown here to be related to lower levels of maternal structuring and supportive behaviour.

Baumrind's three widely used parenting style characterizations (permissive, authoritative and authoritarian) [20] are combinations of different degrees of warmth and control, the two main dimensions of parenting that were examined in this study. Authoritative parenting, a balanced combination of warmth and control, is considered to be the most adequate in Western societies, as it is associated with children's self-reliance, self-control and contentment [20]. The RS3 'target allele' was found here to be associated with focused support but not with warmth or control. Interestingly, focused support, indexing the mother's involvement and gentle guidance during the free-play session, was found to be positively correlated with both dimensions. Indeed, focused support can be seen as the optimal parenting style during free-play, because it combines a non-controlling but not indifferent, level of parental involvement with autonomy support and requires the parent to organize and communicate with the child.

The underlying neurochemical mechanisms, whereby AVPR1A RS3 contributes to maternal-focused support remain to be elucidated. Possible mechanisms may be related to the role of this receptor in anxiety and stress [13,21] as well as in autism [10] whose core deficits are in the domain of social skills and communication. It is intriguing that a risk allele for autism and mild social deficits in non-clinical subjects contributes to a somewhat poorer maternal–child environment as it may have untoward consequences in future development. Our study sheds light on the genetic influences underpinning a previously unexplored maternal behaviour. During the writing of this report, our finding was strengthened by another group [6], who reported an association between RS3 and a composite of 'maternal sensitivity' that included positive control. We go one step further from this important first study in controlling for children's RS3 genotype, thereby showing that the observed effect is due to maternal genotype, rather than to an evocative rGE. Importantly, the particular RS3 allele shown here to contribute to mother–child interplay is the same allele implicated in autism, thus strengthening the notion that many psychopathologies represent the extreme in a continuum of liability to disease. Understanding how common variants contribute to behavioural phenotypes in normal subjects lends credence to the common-disease–common-variant hypothesis of many psychopathologies.

The protocol for the experiment was approved by the Ethics Committee of Sarah Herzog Hospital (Jerusalem), and informed consent was obtained from all participating mothers.

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