



Molecular genetics of shyness and aggression in preschoolers

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Abstract

Associations between three candidate gene polymorphisms [dopamine D4 receptor (DRD4), serotonin transporter (5-HTT), and serotonin 2C receptor (5-HT2C)] with shy and aggression-related behaviors derived from maternal report and peer play at age four were examined. We noted a significant association of the DRD4 receptor gene with maternal report of problems with aggression at age four. Children with long versus short repeat alleles of the DRD4 gene were reported by their mothers to have significantly more problems with aggression at age four. There were no significant associations of the DRD4 gene with observed behavioral measures of aggression at age four. There were, in addition, no significant associations of either of the serotonin genes with any of the maternal report and observed behavioral measures. The present study extends earlier findings of adults to the preschool years and appears to be the first large scale investigation to examine the molecular genetics of preschoolers' temperament using behavioral and maternal report measures in normal childhood development. © 2002 Elsevier Science Ltd. All rights reserved.

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The notion that there may be a genetic basis to individual differences in temperament is an idea that dates from the time of the early Greeks and extends to contemporary personality research. Much of the scientific support for this concept is derived from three disparate literatures (Eley & Plomin, 1997), two of which have been reliable and convincing sources for years and a third which has emerged only within the last decade. The first literature involves studies of domesticated and laboratory animals in which there is strong evidence in support of a genetic basis to

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temperament. For example, it has long been noted that inbred strains of animals can be produced that are highly fearful, defensive, aggressive, or subdued (see Plomin, DeFries, McClearn, & Rutter, 1997 for a review). A second body of work concerns findings derived from behavioral genetics studies of human twins. Such studies often find that monozygotic twins, raised either apart or together, appear temperamentally more similar than dizygotic twins and adopted children (see Plomin, 1989 for a review). A third source concerns recent findings from the rapidly emerging field of the molecular genetics of human personality (see Cloninger, Adolfsson, & Svrakic, 1996; Hamer & Copeland, 1998; Plomin & Rutter, 1998 for reviews). These studies, mostly involving human adults, have found associations between complex human behavioral traits and genes that regulate specific neurochemical systems. Overall, these three sources are beginning to converge to provide the strongest evidence to date that there may be a genetic etiology underlying some complex human personality traits.

The purpose of the present study was to explore whether there may be a molecular genetic basis to individual differences in childhood temperament as manifested through shy and aggressive social behaviors. We have been following four separate cohorts of children who have been participating in a larger longitudinal study on socio-emotional development. To date, we have found a number of reliable findings. Individual differences in certain patterns of infant temperament, which appear early in life, are modestly predictive of social interactive behaviors in the preschool years. For example, Fox and his colleagues (Calkins, Fox, & Marshall, 1996; Fox, Henderson, Rubin, Calkins, & Schmidt, 2001) have described two groups of infants who appear to reflect distinct temperamental types. One group of infants are highly reactive and exhibit a high degree of distress to the presentation of novel auditory and visual stimuli at 4 months of age. These infants are likely to display behavioral inhibition at 14 (Calkins et al., 1996) and 24 months (Fox, Calkins, & Bell, 1994) and social reticence to unfamiliar peers at 48 months (Fox et al., 2001), and are reported by their mother as contemporaneously shy at age four (Schmidt et al., 1997). A similar set of findings has been reported by Kagan and his colleagues (Kagan & Snidman, 1991). These infants also exhibit a distinct pattern of psychophysiological activity, including heightened fear-potentiated startle responses at age 9 months (Schmidt & Fox, 1998) and greater right frontal EEG asymmetry at 9 (Calkins et al., 1996), 14, and 48 months of age (Fox et al., 2001) and may be at risk for anxiety-related problems during the early school age years (e.g. Fox, Schmidt, Calkins, Rubin, & Coplan, 1996; Hirshfeld, et al., 1992; Schmidt, Fox, Schulkin, & Gold, 1999).

A second group of infants exhibit a high degree of motor arousal and positive affect to novel auditory and visual stimuli at 4 months. These infants display low levels of uncertainty, fear in response to novelty or discrepancy at 14 and 24 months of age, and are socially interactive and engaging as preschool children. Interestingly, they display, as a group, a good deal of continuity across the early childhood years. No children in this group were identified as fearful or inhibited or socially reticent at 4 years of age and few children were in the average range. Most remained high in novelty seeking and low in fear across the 4 years of the longitudinal study. This group, Fox (Fox et al., 2001) calls *exuberant*, also displayed consistent patterns of left frontal EEG asymmetry at 9, 14, and 48 months of age.

Our study of the molecular genetics of child temperament and social behavior focuses on candidate genes involved in signaling by dopamine and serotonin, two key neurotransmitters that have previously been implicated in individual differences in personality in adults. The dopamine D4 receptor gene (D4DR), which contains a functional repeated sequence polymorphism within

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