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LETTER TO THE EDITOR

Age-dependent effect of the *MAOA* gene on childhood physical aggression

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Quantitative genetic studies suggest that genetic contributions account for a substantive part of a range of disruptive behaviors.[1] At a molecular level, Caspi *et al.*[2] reported no main effect of the monoamine oxidase A (*MAOA*) gene but an interactive effect with early maltreatment in the prediction of aggressive behavior. Later studies using different research designs as well as various measures of disruptive behavior and early adversity have yielded mixed results. These studies mainly relied on one or two time point assessments in adolescence or adulthood; few studies focused on childhood.[3,4] As such, no study has yet modeled explicitly an age-dependent contribution of MAOA. Suggestions have been made as to why the effect of genotype may decrease or increase with age.[5] Accordingly, we examined the age-dependent contribution of MAOA alone or in interaction with family socioeconomic adversity to the frequency of physical aggression during the elementary school years.

We selected 436 boys from a longitudinal study of kindergarten children in Quebec (Canada). The study sample has been described elsewhere.[6] The boys' frequency of physical aggression was rated annually from age 6 to 12 years by teachers with the Social Behavior Questionnaire[7] (each item rated on a three-point scale (0–2, from 'never applies' to 'frequently applies'). Three items were used: (1) fights, (2) bullies and (3) kicks, bites, or hits (alphas ranging from 0.79 to 0.86). We used an index of family socioeconomic adversity based on information collected at the start of the study[6] about: (1) family structure, (2) parents' levels of education, (3) parents' occupational status and 4) parents' age at the birth of the first child. We imputed the values for 20 participants from the constituent variables of the index and from behavioral characteristics of the boys at 6 years. We assessed common tag single-nucleotide polymorphisms (SNPs; minor allele frequency $>5\%$) and SNPs located up to 5-kbp upstream of the transcription site. Tag SNPs were obtained using HapMap and Tagger's multimarker-tagging procedure ($r^2 > 0.8$).[6] To reduce the number of statistical comparisons, only the most informative SNPs were selected from our genetic database using an algorithm based on r^2 linkage disequilibrium.[8] Table 1 presents the selected SNPs and their frequencies. Details on genetic assessments for this sample are provided elsewhere.[6]

We utilized a Latent Growth Modeling framework to model age-dependent effects (Full Information Maximum Likelihood and Maximum Likelihood Robust estimator). The baseline model without predictors indicated a linear decline of physical aggression ($P<0.001$), with a slope estimated to -0.06 each year, corresponding to a decline from a mean score of 1.04 at 6 years to 0.68 at 12 years (coherent with the well-documented decline of physical aggression from 3 to 4 years onwards).[9] Then, we estimated one model for each SNP by entering a given SNP and the adversity index as predictors. Adversity made a significant positive contribution to the initial level (but not the slope) of physical aggression in every model (β between 0.15 and 0.16; all $P<0.01$). The SNP rs5906957 had a significant main effect on the slope of physical aggression, meaning that levels of aggression for T carriers decreased less (linear decline of -0.01 each year) than for C carriers (-0.08 each year). T carriers also had a trend toward lower initial levels of physical aggression than C carriers ($P=0.05$). Therefore, T carriers tended to have lower initial level of physical aggression but this initial level remained relatively stable, whereas it decreased for C carriers. Table 1 shows similar results for rs5953385 and rs2283725. All models fitted well: standardized root mean square residual <0.10; root mean square error of approximation <0.05; comparative fit index >0.95. No interaction was detected between adversity and any SNP for initial level or slope.

The results suggest that the *MAOA* gene may have a role in the development of physical aggression prior to adolescence. For example, the stable physical aggression levels of T carriers for rs5906957, compared with the declining levels of C carriers, suggest that T carriers do not take advantage of the socialization forces exerted on physical aggression during the elementary school years. A previous study[4] assessed children at one point

Table 1. Contributions of family adversity and MAOA SNP's to the initial level and slope of childhood physical aggression

SNPs[1]	N	*Genetic contribution*					
		On the initial level			*On the slope*		
		B	β	P-*values*	B	β	P-*values*
rs5906957	C = 344; T = 92	−0.28	−0.10[†]	0.05	0.06	0.16*	0.04
rs5953385	G = 325; A = 111	−0.24	−0.09[†]	0.09	0.06	0.16*	0.047
rs2283725	G = 299; A = 137	−0.19	−0.08	0.15	0.05	0.16*	0.03
rs3027400	G = 322; T = 114	−0.09	−0.03	0.52	0.03	0.09	0.25
rs2072744	G = 294; A = 142	−0.06	−0.03	0.63	0.04	0.11	0.16

Abbreviations: MAOA, monoamine oxidase A; SNP, single-nucleotide polymorphism.
Note: As only boys were included in the analyses and that *MAOA* gene is linked to the X-chromosome, there were no heterozygous genotypes. [1]Six SNPs were selected through linkage disequilibrium analysis. However, the minor allele (T) for rs3027405 was too infrequent ($n=28$) to conduct the statistical analyses. *$P<0.05$; [†]$P<0.10$.

(7 years) and reported a significant genetic main effect (but no significant interaction) for antisocial behavior. Unexpectedly, children with the *high* activity MAOA allele had higher levels of antisocial behavior. Our study shows that a developmental approach may shed light on these findings: an initial genetic trend in one direction may be progressively overridden by a developmental genetic effect (as exemplified by C carriers above). We did not detect any significant interaction for either the initial level or the slope of physical aggression. Previous investigations conducted in adolescence and adulthood suggest that interactions may emerge during adolescence.[3]

Our measure of family socioeconomic adversity did not include maltreatment: the present study should not be directly compared with findings using maltreatment, and was not designed to replicate earlier findings.[2] Although not all SNPs reached the significance threshold, all effects were in the same direction. However, caution is required until the present findings are replicated. Overall, these results call for a more systematic consideration of developmental issues when examining genetic contributions to behaviors. Our findings suggest that the *MAOA* gene may not affect physical aggression in a constant fashion but rather exerts an influence that emerges over time, such as enhancing or preventing the ability to learn a specific behavior expected in a given social environment. Such developmental effects are easily overlooked when targeted outcomes are measured at one point in time or averaged across time.[10]

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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