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Vulnerability, plasticity, or vantage sensitivity: interpreting MAOA gene-environment interaction after childhood maltreatment

Kim N

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Abstract
Monoamine oxidase A (MAOA) has frequently been characterized as a vulnerability gene because certain MAOA-uVNTR variants are associated with increased antisocial behavior following childhood maltreatment. However, most studies supporting this classification have examined adverse environments without adequately assessing supportive conditions. Because the absence of maltreatment does not establish the presence of positive environmental experiences, these findings cannot conclusively distinguish vulnerability from differential susceptibility or vantage sensitivity. This review critically evaluates the MAOA–maltreatment literature, examining longitudinal evidence, meta-analytic findings, replication, environmental measurement, and statistical criteria for distinguishing gene–environment interaction models. Although the evidence supports increased vulnerability under adversity, the lack of direct assessments of supportive environments limits conclusions about the full range of environmental responsiveness. To address a broader explanatory gap, this review advances a biological network function hypothesis: genetic variants affecting homeostatic regulatory systems, such as MAOA and FKBP5, may preferentially produce vulnerability-dominant interactions, whereas variants affecting cognition, learning, and neural plasticity, such as DRD4 and BDNF, may more frequently produce differential susceptibility. Although homeostatic regulation is bidirectional, its behavioral consequences may be asymmetrical when regulatory functions are preferentially recruited by adversity. The resulting prediction is that the degree of adversity-related functional specialization of a biological network will predict the asymmetry of its gene–environment interaction. Three falsifiable predictions and a proposed comparative investigation provide a framework for evaluating this relationship using biological functions characterized independently of observed interaction patterns. The review thus challenges premature classification of MAOA as a vulnerability gene while proposing a testable biological explanation for differences in environmental sensitivity, without implying genetically determined behavioral outcomes.

Keywords
MAOA-uVNTR, Childhood maltreatment, Gene–environment interaction, Differential susceptibility, Diathesis–stress, Vantage sensitivity, Antisocial behavior, Environmental sensitivity, Gene–environment interplay, Developmental psychopathology

Nayun Kim, Newton Academy Seoul, 10, Nonhyeon-ro 135-gil, Gangnam-gu Seoul 06041, South Korea.
lsarang2@gmail.com

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1. Introduction

Comparing genotypes among maltreated males leaves the distinction between theories unresolved. Both diathesis-stress and differential susceptibility expect an environmentally sensitive group to fare worse under adversity; supportive conditions are where their predictions separate. Only differential susceptibility requires the same group to do better under the supportive scenario. Vantage sensitivity describes yet another possibility, in which support brings greater benefit without adversity bringing greater harm. Distinguishing these models therefore requires evidence from both adverse and supportive environments. Equally important is the reproducibility of the underlying association: findings for MAOA-L × maltreatment in males vary across cohorts, reflecting broader replication challenges in candidate-gene G×E research. Accordingly, the reported interaction is evaluated as a provisional, context-dependent association rather than a general predictor of developmental outcomes.

The World Health Organization defines childhood maltreatment as encompassing physical and emotional ill-treatment, sexual abuse, neglect, negligence, and exploitation within a relationship of responsibility, trust, or power (1). Estimates from WHO and UNICEF show how common these experiences are: physical punishment or psychological violence regularly affects six in ten children younger than five, and childhood sexual abuse is reported by approximately one in five women and one in seven men (1, 2). The consequences extend beyond antisocial behavior. Maltreatment is also associated with depression and substance use, poorer educational outcomes, and later violence, whether experienced as a victim or committed as a perpetrator (1).

Children exposed to maltreatment can nonetheless follow different developmental paths. Moffitt (3) and Rutter (4) placed that variation at the center of the G×E question: a genetic effect (G) may depend on the circumstances (E; environment) in which a child develops. Maltreatment research is one setting in which that possibility can be examined.

Located on the X chromosome, MAOA encodes monoamine oxidase A, an enzyme responsible for the oxidative breakdown of serotonin, norepinephrine, and dopamine (5). The common polymorphism discussed here is a variable-number tandem repeat in the promoter. In reporter assays, 3.5R and 4R usually have higher transcription than 2R and 3R (6-8). The higher- and lower-transcription groupings are termed MAOA-H and MAOA-L, respectively. Classification of the rare 5R allele differs across assays, so its repeat length should be reported instead of assuming one activity category. Caspi et al. (9) examined the common polymorphism in a longitudinal cohort. Among severely maltreated males, the lower-transcription group demonstrated higher rates of conduct disorder, violent convictions, and adult antisocial symptoms than the higher-transcription group. The later meta-analysis supported this interaction (10).

The male cohort findings provide the principal evidence evaluated in this review, although their interpretation remains provisional given inconsistent replication across populations and outcomes. Current evidence favors vulnerability over differential susceptibility, primarily

because supportive environments have been inadequately assessed. The absence of such measurements leaves the enhanced benefit predicted by differential susceptibility untested rather than disproven. Any classification must therefore remain specific to the sex, developmental stage, environmental conditions, and behavioral outcomes examined.

Nilsson et al. (11) highlighted the predominance of studies comparing adversity with its absence, rather than directly assessing supportive or enriched environments. Building on evidence published since 2018, this review evaluates the predictions of three competing models of environmental sensitivity and identifies the measurements and statistical tests needed to distinguish them. A Perspectives section additionally proposes the testable hypothesis that the biological network functions affected by genetic variation may influence the form of gene–environment interactions.

2. Review questions

1. To what extent has the MAOA-L × childhood maltreatment association in males been replicated across studies?
2. What evidence supports a vulnerability model, and what additional findings would establish differential susceptibility or vantage sensitivity?
3. Do studies directly assessing supportive environments demonstrate enhanced benefits among MAOA variant carriers?
4. Which environmental measurements and statistical approaches are needed to distinguish among these competing models?

3. Review methods

This structured narrative review was conducted without a preregistered systematic-review protocol. Literature searches through September 23, 2026, covered PubMed, Google Scholar, Crossref and DOI records, publisher websites, and WHO and UNICEF resources. Search terms included MAOA, MAOA-uVNTR, childhood maltreatment, antisocial behavior, conduct disorder, and gene–environment interaction. Additional terms addressed competing models of environmental sensitivity (differential susceptibility, vantage sensitivity, and plasticity allele) and potential mechanisms (knockout mouse, serotonin development, amygdala, prefrontal cortex, and neuroimaging). Foundational studies by Brunner et al. (12), Cases et al. (13), and Caspi et al. (9) served as starting points for backward and forward citation tracing.

Peer-reviewed prospective cohort studies and meta-analyses form the primary human evidence base, supplemented by animal experiments and neuroimaging studies to assess biological plausibility. Studies of supportive environments were selected for their direct assessment of positive caregiving or socioeconomic resources, or for explicit comparisons between vulnerability and differential susceptibility models. Importantly, the absence of maltreatment was not considered equivalent to an enriched environment. Popular accounts were included only to illustrate public misinterpretations of the evidence. No participants were recruited, and no new data were collected.

References were verified against publisher records or bibliographic databases for authorship, title, publication details, DOI, and relevance to the cited claims. Because

exhaustive dual screening and formal risk-of-bias assessment were not performed, the review does not assign systematic evidence grades. Byrd and Manuck (10) combined study-level P values, reporting P = .0044 across 20 male early-adversity cohorts (N = 11,064) and P = 8.2×10^{-7} for analyses restricted to maltreatment in males. These results indicate aggregate statistical evidence for an interaction but do not quantify its effect size or establish predictive accuracy for individual children.

4. MAOA and maltreatment in males

A model comparison first requires a reproducible interaction to explain. In the meta-analysis, statistical support was strongest for maltreatment in male samples: the combined P value was 8.2×10^{-7}, compared with .0044 for early adversity more broadly. These sample-size-weighted values do not quantify a pooled interaction effect. Several individual studies reported negative findings despite the support in the combined analysis. Any model assigned to this predominantly male pattern therefore remains provisional for the population and outcome studied.

Brunner et al. (12) identified a stop-gain MAOA mutation causing complete enzyme deficiency in five affected males from one Dutch kindred. All five exhibited a characteristic pattern of impulsive aggression. Cases et al. (13) subsequently examined MAOA-deficient mice, finding elevated developmental serotonin levels and increased adult aggression. The common promoter variant is distinct from either of these deficiency models. These early findings provided a rationale for investigating it but did not establish that the variant independently predicts antisocial behavior.

Caspi et al. (9) extended the hypothesis to the common MAOA promoter polymorphism. In their cohort, severely maltreated males with lower-transcription variants exhibited the highest rates of conduct disorder, violent convictions, and adult antisocial symptoms. Subsequent findings were mixed: Haberstick et al. and Young et al. did not replicate the interaction (14, 15), whereas several other cohorts and earlier syntheses reported supporting evidence (16–19).

Byrd et al meta-analysis (10) covered 27 independent investigations with more than 18,400 participants. It combined the evidence with the Liptak-Stouffer procedure. For the 20 male early-adversity cohorts (N = 11,064), the combined P value was .0044; restricting the male analyses to maltreatment yielded 8.2×10^{-7}. The combined evidence supports continued investigation even though some cohorts did not replicate the finding. Because the procedure combines statistical evidence rather than estimating a pooled interaction effect, it cannot establish how large the interaction is, whether it is consistent across outcomes, or whether it helps predict an individual's outcome.

MAOA breaks down monoamine neurotransmitters through oxidative deamination at the outer mitochondrial membrane (5, 20, 21). Removing the enzyme completely has large consequences for monoamine signaling. That condition differs from common promoter variation: MAOA-L and MAOA-H are reporter-assay categories based on transcription, and they do not measure enzyme activity in an adult brain (6-8, 22). Developmental changes introduce further complexity.

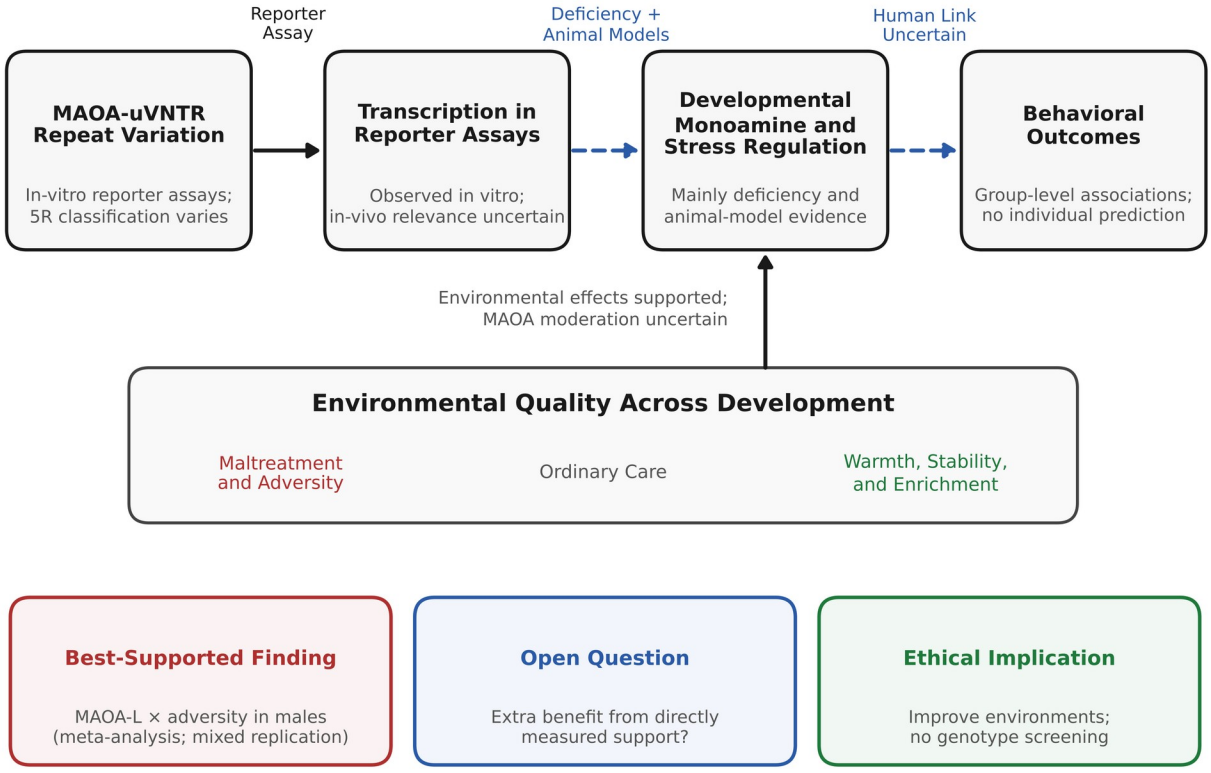


Figure 1. Evidence map for a proposed developmental pathway involving MAOA-uVNTR. The solid arrow from repeat variation to transcriptional activity represents differences observed in reporter assays; it does not establish corresponding differences in MAOA expression or monoamine signaling in the developing human brain. The first dashed arrow reflects evidence from severe MAOA deficiency and animal models, whose relevance to common human variants remains uncertain. The second dashed arrow shows a proposed, not demonstrated, pathway from stress-regulatory development to behavioral outcomes. The separate solid environmental arrow reflects evidence that early environments can shape stress-regulatory systems; whether MAOA-uVNTR moderates those effects across adverse and supportive conditions remains unknown. The best-supported human finding is an MAOA-L × adversity interaction in males with meta-analytic support, heterogeneous replication, and no basis for individual prediction.

Serotonin participates in developmental signaling as well as neurotransmission (23, 24). Cases et al. reported markedly elevated serotonin in the developing brains of MAOA-deficient mice and greater aggression in adult males (13). Early postnatal reduction of serotonin synthesis restored somatosensory barrel-field organization in a separate experiment (25). The behavioral findings differed from this anatomical rescue. When serotonin synthesis was inhibited postnatally in a later study, perseverative behavior improved, whereas aggression and social deficits did not (26).

Imaging evidence comes from small studies using emotional or inhibitory tasks. They reported differences in amygdala reactivity, amygdala-prefrontal structure or connectivity, and the recruitment of regulatory prefrontal

regions (22, 27, 28). Their results are task-specific group comparisons. In Sun et al.'s all-male study of acute stress, the larger cortisol response and right anterior hippocampal deactivation were found in MAOA-H rather than MAOA-L carriers (29). Neither a genotype-specific amygdala response nor a developmental causal pathway was established by that result. Imaging therefore adds possible neural correlates, while leaving the route from genotype through supportive care to behavior undemonstrated. It cannot currently predict an individual's outcome. Figure 1 brings these task-based findings within the wider evidence base.

Table 1. Evidence map for MAOA and the question of vulnerability versus plasticity.

Evidence source	What is best supported	What remains unresolved for model comparison
Molecular genetics	Reporter assays generally classify 3.5R/4R as higher-transcription and 2R/3R as lower-transcription; the rare 5R allele has been classified inconsistently (6-8).	Behavior under measured adversity and support remains unknown from a promoter assay alone.
Animal models	MAOA deficiency changes early monoamine levels and can increase aggression in adult males. Reducing serotonin early restored barrel-field anatomy in one experiment. A later behavioral study found no rescue of aggression (13, 25, 26).	Randomly assigning animals to enriched conditions would allow convergence and crossover to be compared.
Longitudinal cohorts	Several cohorts report elevated conduct and antisocial outcomes among maltreated MAOA-L males (9, 16, 18), while other cohorts did not replicate the interaction (14, 15).	These cohorts generally tell us more about maltreatment than about the support children received.
Meta-analysis	A synthesis of 27 investigations (more than 18,400 participants) supports aggregate evidence for a male interaction, especially under narrowly defined maltreatment (10).	The synthesis does not answer what happens under supportive care.
Neuroimaging	Small, task-specific studies have associated MAOA variation with differences in amygdala-prefrontal structure, reactivity, or connectivity (22, 27, 28).	Reactivity differences could fit vulnerability or plasticity. The response under measured environmental conditions is needed to distinguish them.
Positive-environment studies	Direct studies of parenting or socioeconomic resources have produced mixed findings that vary by sex and outcome (32-40).	The studies disagree, and some favorable associations are only nominal or weaken after adjustment.
Genome-wide evidence	Large GWAS/GWAMA studies support a highly polygenic architecture and have not identified MAOA as a large-effect main-effect locus (41, 42).	No direct test of the uVNTR or its interaction with measured exposure.

Comparisons between males and females are complicated by the X-linked inheritance of MAOA. Males carry a single copy, whereas females carry two copies, with X-inactivation potentially producing a mosaic of cells expressing different alleles. However, general evidence of variable X-linked expression does not establish how MAOA is expressed across

specific tissues (30). Findings in females are also inconsistent. In a study of 291 adult women, Ducci et al. reported higher rates of alcoholism and antisocial personality disorder among sexually abused women homozygous for low-transcription variants (31). Other studies have implicated higher-transcription or long-repeat variants, although they examined different environmental exposures and behavioral outcomes (11). Consequently, the evidence summarized in Table 1 must be interpreted in relation to each study's sex, allele classification, environmental measures, and outcomes.

5. Limitations of current evidence in distinguishing models of environmental sensitivity

Recording that a child was not maltreated leaves the quality of care unresolved. The absence of maltreatment does not necessarily imply the presence of a warm and emotionally and cognitively supportive environment. It also does not imply predictable care, a safe neighborhood, or a stable adult to turn to. A low adversity scale does not establish that these experiences did not occur. Thus, a low-adversity comparison group need not necessarily experience a positive environment (11). Both vulnerability and differential susceptibility predict the adverse outcome already observed. To test the latter's additional prediction, a study needs children whose supportive experiences were measured directly – not just inferred as absence of maltreatment.

This missing information also limits the interpretation of null findings. Failure to detect enhanced benefits is inconclusive when supportive conditions were not directly measured or highly supportive environments were underrepresented. Although the available evidence more closely supports vulnerability, it remains insufficient to test the key prediction distinguishing differential susceptibility. This limitation highlights the need for better environmental measurement rather than providing evidence that MAOA-L confers greater plasticity.

6. Competing models of environmental sensitivity

Vulnerability and differential susceptibility are the principal competing explanations evaluated here for MAOA-L. Vantage sensitivity provides a third model, characterized by enhanced benefits under supportive conditions without increased vulnerability to adversity, although current evidence offers limited support for its application to MAOA-L. Table 2 summarizes the observations needed to distinguish these models, while Figure 2 illustrates their predicted response patterns.

Under the diathesis–stress model, genotype differences emerge primarily under adverse conditions. MAOA-L carriers would exhibit poorer outcomes following maltreatment, with outcomes converging toward those of MAOA-H carriers as environmental conditions improve. Current findings in males are broadly consistent with this pattern, although classification remains provisional pending replication and sufficient observations across supportive environments to establish convergence.

The question for differential susceptibility is whether the group that fares worse with adversity also fares better when support is strong. Applied to MAOA-L, the model predicts both sides of that pattern (43, 44). Crossover

estimation and regions-of-significance tests, discussed below, can examine whether the evidence meets that prediction.

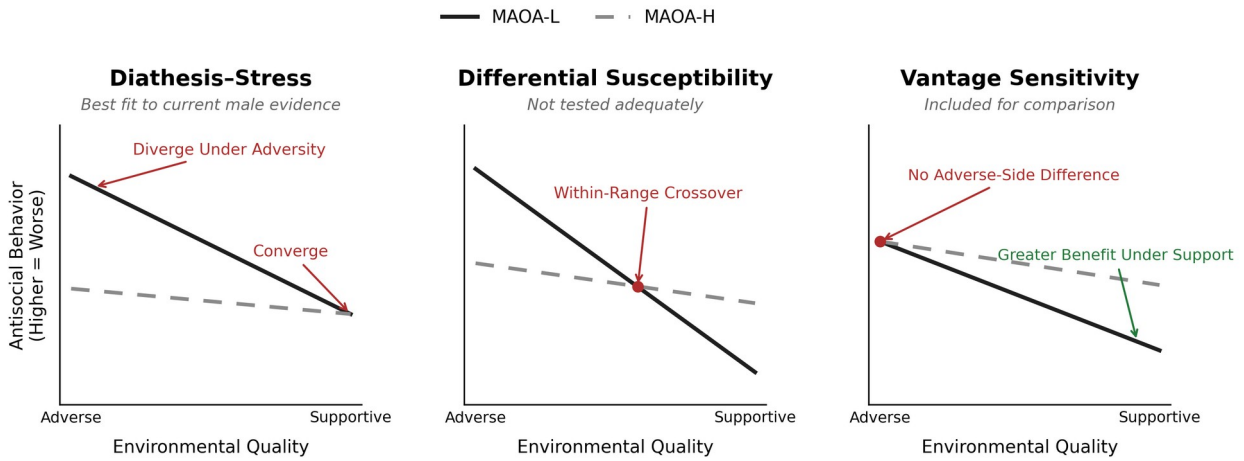


Figure 2. Stylized predictions for three MAOA-uVNTR × environment models in males. MAOA-L and MAOA-H denote the lower- and higher-transcription classifications generally applied to 2R/3R and 3.5R/4R alleles in reporter-assay studies; the rare 5R allele is not assigned because its classification has varied across assays. Under diathesis-stress, the groups differ under adversity and converge, without crossing, as conditions improve. Differential susceptibility predicts group differences at both ends of the environmental range and a crossover within the observed data. Vantage sensitivity predicts no group difference under adversity but greater benefit for the sensitive group under supportive conditions. The lines illustrate model predictions rather than measured MAOA effect sizes. Classification requires adequate sampling at both environmental extremes together with formal crossover, regions-of-significance, and competitive-model tests.

Table 2. Empirical predictions that distinguish the three models.

Question	Diathesis-stress prediction	Differential susceptibility prediction	Vantage sensitivity prediction
Where do genotypes differ?	At the adverse end only.	At both adverse and supportive ends.	At the supportive end only.
What happens under supportive conditions?	MAOA-L converges with MAOA-H.	MAOA-L does better than MAOA-H.	Sensitive genotype does better than the comparison genotype.
What is the graph shape?	Ordinal fan: lines separate under adversity but do not cross in observed data.	Disordinal crossover: lines cross inside the measured environmental range.	Lines separate only when environment is favorable.
Most informative statistical pattern	Region of significance limited to adversity; crossover at or beyond the supportive boundary.	Region of significance at both tails; crossover point and confidence interval inside observed range.	Region of significance limited to positive environments.
Main design requirement	Reliable adversity measurement.	Reliable adversity and enrichment measurement across the full range.	Strong positive-environment measurement plus enough adverse cases to rule out vulnerability.

Vantage sensitivity predicts a benefit from favorable environments without additional harm under adversity (45). Evidence for this account would require a genotype difference under support together with no difference under adverse conditions. That differs from the adverse-outcome association that is currently best supported for MAOA-L in males. A pure vantage pattern consequently appears unlikely, although it remains a useful comparator in formal model tests.

7. Statistical criteria for distinguishing environmental sensitivity models.

Fitted response lines may cross outside the environmental range observed in a sample. Such a crossover alone does not establish differential susceptibility, and a statistically significant interaction may still be consistent with diathesis–stress. Roisman et al. (46) proposed regions-of-significance analysis to identify where genotype differences are statistically significant, while Widaman et al. (47) developed competitive-confirmatory models to estimate and compare crossover patterns. Jolicoeur-Martineau et al. (48) found that both approaches performed accurately in large samples, although competitive-confirmatory analysis was more informative with smaller samples or weaker effects. To distinguish the models, studies should report the estimated crossover point and its confidence interval, determine whether both lie within the observed environmental range, and identify regions of significance. Model-fit comparisons using AIC or BIC can provide additional evidence. Statistical power should also be evaluated across the sampled environmental range, particularly at its adverse and supportive extremes.

For a study to favor differential susceptibility over diathesis-stress, its supportive observations must contribute to the result. A difference found only under adversity favors diathesis-stress. If the genotypes differ at both ends instead, differential susceptibility is favored provided that the crossover and its confidence interval lie within the sampled range. A supportive-only difference favors vantage sensitivity. The absence of a favorable-end difference is inconclusive when that end is missing or compressed. Under those conditions, a study has not made the comparison needed to separate vulnerability from plasticity.

8. Evidence from supportive environments

The results reported by Nilsson et al. (33) involved combinations of MAOA-uVNTR, BDNF, 5-HTTLPR, and environmental conditions in adolescent delinquency. The four-way findings are difficult to interpret as evidence for MAOA alone. The MAOA-by-relationship-quality term itself did not reach significance. Including positive as well as negative contexts therefore did not, in this analysis, yield a stable plasticity effect attributable to MAOA across sex, age, or outcome.

Pickles et al. observed maternal sensitivity at 29 weeks and examined its interaction with MAOA genotype in predicting anger proneness at 14 months (32). The descriptive estimates suggested greater sensitivity in lower-expression boys and in higher-expression homozygous girls. The sex contrast is easy to overread. The formal genotype-by-parenting-by-sex test gave P = .104, and the MAOA-LL female group contained only 17 infants. The study contributes a direct measure of positive

parenting, but the apparently opposite male and female patterns remain uncertain.

Bendre et al. (36) studied alcohol use in maltreated adolescent girls. In the analyses before adjustment, alcohol use was lower among SL/LL girls who reported a good parent-child relationship. SL/LL indicates carriage of at least one long-repeat allele: the study treated 2R/3R as short and 3.5R/4R/5R as long. Here L denotes repeat length, not the low-transcription MAOA-L grouping used for the male maltreatment finding. The findings also weakened under statistical checks. None of the pairwise contrasts survived Bonferroni correction, and full covariate adjustment removed significance from the three-way interactions.

Among the 290 Chinese children studied by Liu et al., the low-transcription boys showed poorer outcomes when maternal parenting stress was high or engagement was low. The favorable-end advantage needed for differential susceptibility was not demonstrated. Their regions-of-significance analyses favored vulnerability, and there were no interactions in girls (34). Wessels et al. reported a nominal interaction between MAOA-uVNTR and maternal education for boys' externalizing behavior in a Black South African cohort; the overall model fit was nonsignificant (35). Rehn et al.'s exploratory finding concerned a different outcome, performance on the Iowa Gambling Task. Male short-repeat carriers performed better with more positive parenting, but the sample was small and P values were not corrected for multiple testing (37). A decision-making association cannot by itself establish a comparable benefit for antisocial behavior.

Kinnally et al. provide a possible example of buffering in 159 adult women. In stress-exposed women, the association with less impulsivity and aggression was seen when perceived parental care was greater and the genotype was low-expression homozygous or heterozygous (38). With P = .048, the three-way result was borderline; this clinically enriched sample relied on retrospective reports and did not demonstrate a crossover. Li and Lee found no moderation of positive parenting in 150 boys with and without ADHD. Negative parenting predicted inattention only in MAOA-H carriers (39). Pueyo et al.'s preschool study included 368 children and found no interaction in boys. The result in girls rested on 15 MAOA-LL participants; in this group, greater positive parenting and greater punitive parenting were each associated with increased callous-unemotional traits (40). That direction does not represent the expected benefit under support.

Comparing these studies side by side reveals little agreement about which genotype responds to support. The outcomes and sexes differ, and some favorable associations appear only in exploratory or unadjusted analyses. The studies also assess different forms of support, from perceived parental care to observed maternal sensitivity and relationship quality. These findings warrant further study of positive environments, without establishing a general MAOA plasticity effect. They leave vulnerability as the better-supported reading and differential susceptibility incompletely tested.

A randomized parenting intervention involving DRD4 provides a useful comparison. Video-feedback training improved parental sensitivity, with reductions in toddlers' externalizing

behavior concentrated among carriers of the DRD4 7-repeat allele, while noncarriers showed little change (49). A related trial identified genotype-dependent differences in daily cortisol (50). These findings provide stronger experimental evidence of differential responsiveness to supportive intervention than is currently available for MAOA. Randomization permits clearer estimation of intervention effects within genotype groups, whereas averaging across groups may obscure differences in responsiveness (51). These studies therefore offer guidance for the design and statistical power of future MAOA intervention trials, but do not justify allocating services according to genotype.

9. Replication in candidate gene research

Positive findings from candidate-gene studies require independent replication before supporting broader theoretical conclusions. Small samples and the examination of numerous outcomes characterized early G×E studies, and many of their reported interactions were not replicated. Duncan and Keller (52) described the role of selective reporting and flexible analyses in false positives. In large samples, Border et al. tested and found no support for the historical candidate-gene or G×E hypotheses of major depression (53). For MAOA itself, the negative studies remain part of the evidence (14, 15), even though the meta-analysis offers a stronger basis for evaluation than a single positive cohort (10).

MAOA is not a strong individual predictor and should not be described as a violence gene. A genome-wide study of broad antisocial behavior found no significant association for the traditional candidate genes it examined. A genome-wide study of childhood aggression found no genome-wide significant variant for overall aggression (41, 42). Both are consistent with a highly polygenic account. Because neither study directly assessed MAOA-uVNTR or its interaction with measured environmental exposures, neither tested the specific G×E hypothesis examined here.

A gene–environment interaction can occur without a substantial genetic main effect. For MAOA, evidence from enzyme function, rare human deficiency, knockout experiments, neuroimaging, longitudinal cohorts, and meta-analysis collectively supports further investigation. However, these findings neither establish the generalizability of the reported interaction across populations and outcomes nor resolve the lack of direct measurements of supportive environments. The biological evidence therefore supports mechanistic plausibility but does not establish individual predictive accuracy or justify genotype-based policies.

10. MAOA and other candidate genes in gene-environment sensitivity

Classifying a genetic variant as a vulnerability or plasticity allele can obscure the context in which its effects were observed. An association with antisocial behavior among maltreated boys may not generalize to girls, other developmental stages, or different behavioral outcomes. The range of environmental conditions examined also influences the observed interaction pattern (54). Consequently, the same variant may receive different classifications across studies. Conclusions should therefore specify the population, environmental conditions, and

outcomes examined rather than assigning a universal label to all carriers.

Table 3. Proposed roles of candidate genes in the three models. The entries summarize published interpretations. None is an established biological classification, and all are contested.

Gene	Proposed vulnerability	Proposed plasticity	Proposed vantage sensitivity	Overall tenor of the literature
5-HTTLPR (SLC6A4)	Yes	Yes	Some evidence	Mixed; candidate-gene evidence contested (43-45, 53)
DRD4 (7-repeat)	Yes	Stronger, but contested	Some evidence	Frequently discussed as a plasticity candidate (43-45, 49-51, 55)
BDNF (Val66Met)	Yes	Some evidence	Limited	Mixed (33, 43, 44)
MAOA (uVNTR)	Yes	Preliminary and inconsistent	Limited current support	Vulnerability is better supported; plasticity has not been tested adequately (10, 11, 32-40).

Researchers have considered a similar change in interpretation for 5-HTTLPR in SLC6A4, the DRD4 variable-number tandem repeat, and BDNF Val66Met. The question in the plasticity reviews was whether variants described as risks might also confer greater responsiveness to support (43, 44); work on vantage sensitivity brought benefit under favorable conditions into the comparison (45). Table 3 records how these variants have been discussed. The categories summarize interpretations in a contested literature; none has been established as a biological classification.

Table 3 shows that the proposed classifications overlap. The DRD4 7-repeat allele and short 5-HTTLPR have each been proposed as plasticity candidates, with different and still contested bodies of evidence (43, 44, 55). The usual vulnerability description of lower-transcription MAOA may partly reflect how few studies measured favorable environments. Sampling can influence the apparent response pattern. It cannot, by itself, establish the supportive benefit required for plasticity.

The three models of gene–environment interaction—vulnerability, differential susceptibility, and vantage sensitivity—describe distinct patterns of responsiveness to adverse and supportive environments, but do not explain why particular genetic variants might produce one pattern rather than another. This raises a biological question: could the primary regulatory functions of a gene influence the form of its interaction with the environment? Variants affecting homeostatic systems, such as MAOA and FKBP5, might preferentially confer vulnerability to environmental adversity, whereas variants involved in adaptive and learning-related processes, such as DRD4 and BDNF, might be more likely to confer differential susceptibility, including enhanced benefits from supportive environments. Vantage sensitivity provides a third possible pattern that this framework must also accommodate. Although existing evidence does not establish

these proposed relationships (53, 56, 57), they offer a potential biological explanation for differences among the three statistical models. Section 12 therefore develops this hypothesis, derives testable predictions, and proposes a preregistered comparative investigation to determine whether biological network function predicts the observed form of gene–environment interaction.

11. Biological pathways linking MAOA, environmental exposure, and behavioral outcomes

Statistical analyses can establish whether a gene–environment interaction is more consistent with vulnerability, differential susceptibility, or vantage sensitivity, provided that adverse and supportive environments are adequately represented. However, identifying the interaction pattern does not explain the biological processes responsible for it. For MAOA, this requires investigating how genetic variation and environmental experiences jointly influence neurodevelopment, stress regulation, and ultimately behavioral outcomes. The available evidence suggests several possible pathways, but the complete biological mechanism linking common MAOA variants, environmental exposure, and behavior has not been demonstrated.

One possible connection between caregiving and behavior is the regulation of cortisol and stress responses by the hypothalamic-pituitary-adrenal (HPA) axis. In animals, maternal care changed the epigenetic regulation of hippocampal glucocorticoid receptors; cross-fostering could reverse the changes (58). Related receptor differences were reported by McGowan et al. in postmortem hippocampal tissue from suicide completers with documented childhood abuse (59). Caregiving can also buffer children's cortisol responses, as described in developmental reviews (60). The missing part for this review is a demonstrated MAOA moderator. Those studies show effects of environment on stress regulation, without showing that common MAOA genotype changes those effects.

Figure 1 assembles the evidence into a proposed pathway. MAOA variation is hypothesized to influence developmental sensitivity in monoamine systems, with environmental conditions shaping stress and neural regulation and, ultimately, behavior. Some of its links have evidence from separate lines of research. Reporter assays show transcription differences among uVNTR alleles, and deficiency models show developmental consequences of altered monoamine signaling. Animal and human caregiving studies show environmental effects on stress regulation. What is missing is the complete pathway in humans carrying the common MAOA-uVNTR variants. The solid and dashed connections indicate this difference in support.

A stress system that reacts strongly could contribute to poor outcomes in a harsh environment and to substantial benefit in a supportive one. Such a pathway is compatible with biological sensitivity to context (61) and evolutionary-neurodevelopmental accounts of differential susceptibility (62). Compatibility with a theory is still short of identifying a mechanism. Yet the estimated curve may depend on when the exposure occurs, the sex studied, the outcome chosen, the sampled environments, and the uncertainty around the

estimate (54, 63). Extending any label for vulnerability, plasticity, or vantage sensitivity to other populations or settings would therefore require further evidence.

12. Perspectives: Biological network function as a predictor of gene–environment interaction patterns

12.1 From statistical interaction patterns to biological function

The distinction between vulnerability, differential susceptibility, and vantage sensitivity has largely been developed through statistical descriptions of how genetic variants modify responses to environmental conditions. Vulnerability predicts greater impairment under adversity without corresponding advantages under support; differential susceptibility predicts heightened responsiveness to both adverse and favorable conditions; and vantage sensitivity predicts preferential benefit from favorable environments (43-48). These models describe different response patterns but do not, by themselves, explain why a particular genetic variant should produce one pattern rather than another.

A potentially important extension is that the form of gene-environment interaction may depend partly on the functional role of the biological network affected by the genetic variation. The original distinction proposed here is between systems primarily involved in maintaining physiological homeostasis and systems involved in adaptation, learning, and experience-dependent plasticity. Although these functions overlap substantially, they suggest different hypotheses about how genetic variation might influence responses across adverse and supportive environments.

The proposed hypothesis is that genetic variation affecting homeostatic regulatory functions may be more likely to produce vulnerability-dominant interaction patterns, whereas variation affecting experience-dependent learning and plasticity may be more likely to produce differential-susceptibility patterns. This is not an established biological classification, nor does it imply that individual genes belong exclusively to one functional category. Rather, it is a testable proposition concerning whether network function predicts the statistical form of environmental sensitivity.

12.2 Homeostatic regulation and vulnerability

Homeostatic systems maintain physiological variables within functional ranges through processes involving feedback, buffering, and compensatory regulation. Genetic variation affecting these systems could influence the ability to maintain stability when environmental demands become excessive.

MAOA provides a possible example because its enzyme regulates the degradation of serotonin, norepinephrine, and dopamine (5, 20, 21). Variations affecting monoamine metabolism could alter developmental responses to adverse environments, although the relationship between common MAOA promoter variants, enzyme activity *in vivo*, and behavioral outcomes remains incompletely established. FKBP5 offers another possible example through its involvement in glucocorticoid-receptor regulation and stress-response feedback, with reported associations between genetic variation,

childhood adversity, and later psychiatric symptoms (56).

The homeostatic hypothesis predicts that variants affecting regulatory stability may produce their largest observable differences when adverse conditions challenge the capacity of the system to maintain function. Under favorable conditions, compensatory processes may be sufficient to preserve relatively similar outcomes across genotypes. The resulting interaction would resemble vulnerability: genotype-associated differences would emerge primarily under adversity and diminish as environmental conditions improve.

Importantly, favorable environments could still benefit individuals carrying the more vulnerable variant. The predicted distinction is not between responsiveness and nonresponsiveness to support, but between restoration toward normal functioning and an additional advantage beyond the comparison genotype. Under the vulnerability model, supportive conditions would reduce or eliminate the disadvantage without necessarily reversing the genotype-associated ranking.

This proposed relationship is consistent with a homeostatic interpretation of MAOA-associated sensitivity, but the available evidence does not establish that MAOA's regulatory function causes the observed interaction pattern.

12.3 Adaptive and learning-related systems and differential susceptibility

Other biological systems are centrally involved in experience-dependent modification of neural function. Dopaminergic signaling, synaptic plasticity, and neurotrophic regulation contribute to learning and behavioral adaptation, although they also participate in homeostatic processes.

DRD4 and BDNF provide possible candidates for investigating this distinction. DRD4 is involved in dopaminergic signaling, while BDNF contributes to activity-dependent neuronal plasticity. Both have appeared in the differential-susceptibility literature, although the strength and reproducibility of candidate-gene associations remain contested (43, 44, 52, 53, 55).

Unlike the proposed homeostatic pattern, variation affecting adaptive responsiveness might alter the extent to which developmental experiences modify subsequent behavior in either direction. Under adversity, greater responsiveness could amplify maladaptive developmental outcomes. Under favorable conditions, the same heightened responsiveness could facilitate greater benefit from supportive caregiving, enrichment, or intervention.

The predicted statistical pattern would therefore be disordinal rather than merely ordinal: the genotype associated with poorer outcomes under adversity would be associated with better outcomes under sufficiently supportive conditions. The crossover would need to occur within the observed environmental range and be supported by appropriate uncertainty estimates and model comparisons (46-48).

Randomized parenting interventions involving DRD4 provide a methodological illustration of how genotype-dependent responses to environmental improvement can be investigated (49-51). They do not establish that adaptive

network function is responsible for differential susceptibility, nor do they validate the proposed functional classification. They demonstrate the kind of experimental design that could contribute to testing it.

The proposed relationship between biological network function and gene–environment interaction patterns may extend beyond the categorical distinction between homeostatic and adaptive systems. Although homeostatic regulation is inherently bidirectional, the behavioral consequences of genetic variation in particular homeostatic systems may be asymmetrical, especially when their regulatory functions are preferentially recruited by environmental adversity. Networks involved in threat detection, stress responses, and restoration of physiological stability may therefore exhibit greater sensitivity to adverse than supportive environments, producing vulnerability-dominant interactions. Conversely, networks involved in cognition, learning, and experience-dependent neural plasticity may respond more readily to both unfavorable and favorable experiences, making differential susceptibility more likely. This suggests a continuous, testable prediction: the degree of adversity-related functional specialization of a biological network should predict the asymmetry of its gene–environment interaction. The hypothesis could be evaluated by independently quantifying network functional specialization and examining its relationship to the relative magnitudes of genotype-associated responses under adverse and supportive conditions. Such an approach would avoid treating genes as exclusively homeostatic or adaptive while providing a mechanistic basis for predicting interaction patterns without implying deterministic behavioral outcomes.

12.4 Testable predictions of the biological network function hypothesis

The proposed functional hypothesis generates three predictions that extend beyond identifying individual gene-environment interactions.

12.4.1 *Prediction 1: Functional network characteristics will predict interaction form*

Across independently characterized genetic variants or polygenic profiles, variation affecting homeostatic regulatory functions will be associated more frequently with vulnerability-dominant response patterns, whereas variation affecting learning-related and adaptive functions will be associated more frequently with differential-susceptibility patterns. This prediction requires functional categories to be defined independently of the observed environmental interactions. Otherwise, the proposed association would be circular.

12.4.2 *Prediction 2: Environmental enrichment will distinguish restoration from enhanced adaptation*

When both adversity and genuine environmental support are measured, variants associated predominantly with homeostatic regulation will more often show convergence of outcomes as environmental quality improves. Variants associated with adaptive responsiveness will more often show a reversal in relative outcomes, with the genotype disadvantaged under adversity exhibiting greater benefit under support. These are predicted tendencies rather than universal properties of either class.

12.4.3 *Prediction 3: Biological function will explain variation in interaction form beyond measurement and study-design differences*

If the hypothesis is meaningful, functional network characteristics should contribute to predicting whether an interaction is ordinal or disordinal after accounting for environmental range, measurement reliability, statistical power, sex, developmental timing, and behavioral outcome. If the apparent functional distinction disappears after these factors are controlled, the proposed biological explanation would not be supported.

These predictions distinguish the hypothesis from the established observation that gene-environment interactions vary across studies. The hypothesis specifically proposes that some of this variation is systematically related to biological network function.

12.5 Proposed study design for testing the biological network function hypothesis

The hypothesis could be evaluated through a preregistered comparative study rather than through further narrative classification of candidate genes. Genes or genetic profiles would first be characterized according to independently established functional criteria, including their contributions to physiological regulation, feedback control, learning, and experience-dependent plasticity. Because these functions overlap, classification should allow continuous or multidimensional functional scores rather than require mutually exclusive categories.

Comparable environmental and developmental outcomes would then be examined across the genetic profiles. Adversity and positive environmental support must be measured separately, rather than treating the absence of maltreatment as enrichment. Analyses should also account for sex, developmental period, ancestry, polygenic background, and gene-environment correlation.

For each genetic profile, competing vulnerability, differential-susceptibility, and vantage-sensitivity models could be fitted using the methods discussed in Section 7. Crossover estimates, regions of significance, confidence intervals, and model fit would determine which interaction pattern is best supported. These results could then be compared with the independently assigned functional characteristics.

The critical analysis would test whether functional characteristics predict interaction form across genes or profiles, rather than simply determining whether particular candidate genes show statistically significant interactions. This distinction is essential because identifying a vulnerability pattern in MAOA and a plasticity pattern in DRD4 would not, by itself, demonstrate that their different biological functions caused those patterns.

An additional experimental approach could compare responses to adverse, standard, and enriched environments in genetically characterized animal models. Such studies would permit greater control over environmental exposure and developmental timing, although results from severe gene deficiencies would not automatically generalize to common human polymorphisms.

A failure to identify systematic differences between functional classes, particularly in adequately powered studies sampling the full environmental range, would count against the hypothesis. Likewise, substantial variation in interaction form within the same functional class, without a reproducible association with functional characteristics, would weaken its explanatory value.

12.6 Implications for interpreting MAOA

This perspective changes the central question from whether MAOA-L is intrinsically a vulnerability or plasticity allele to whether the biological functions influenced by MAOA variation help explain the observed form of its environmental interaction.

The current evidence favors vulnerability in the male maltreatment literature, but the limited measurement of genuinely supportive environments prevents a decisive exclusion of differential susceptibility. The proposed functional hypothesis offers a possible biological explanation for why vulnerability might predominate, without treating that explanation as established. It also accommodates the possibility that the same genetic variant may exhibit different interaction patterns depending on developmental timing, environmental domain, sex, or outcome. Homeostatic regulation and adaptive plasticity are interconnected biological processes, not mutually exclusive properties of genes. A network that buffers perturbations under one set of conditions may participate in experience-dependent reorganization under another.

The broader contribution of this hypothesis is therefore to connect three levels of investigation: the statistical form of gene-environment interaction, the environmental conditions required to identify that form, and the biological network functions that might generate it. If supported, this approach could help explain why different genetic variants appear to follow different environmental-sensitivity models. If unsupported, it would indicate that interaction form cannot be reliably predicted from the proposed functional distinction.

Either outcome would advance the investigation beyond assigning descriptive labels to individual candidate genes. The hypothesis provides a falsifiable framework for determining whether biological network function contributes to the organization of gene-environment sensitivity.

13. Limits of measurement and design

An interaction with a composite adversity score needs to be interpreted in terms of its components. Physical abuse, sexual abuse, emotional abuse, neglect, harsh discipline, and family dysfunction may contribute differently to development, even when they are included in the same score. An estimate based on that score can conceal the differences. Byrd and Manuck (10) found stronger combined statistical evidence when maltreatment was defined more narrowly. Since their synthesis combined P values, this should not be described as a larger pooled effect. It does suggest that the exposure definition affects the evidence obtained.

The method used to assess environmental exposure also influences the findings. Reuben et al. (64) found that retrospective reports and prospective assessments of childhood adversity

were correlated but identified only partially overlapping groups of individuals. When both measures are available, analyzing them separately would account for differences in exposure classification and allow their influence on gene–environment interaction estimates to be evaluated.

A measure of support should record experiences such as warmth, sensitive and consistent parenting, household chaos, school belonging, safety, cognitive stimulation, and access to a supportive adult. These experiences were not measured directly in many influential MAOA cohorts. Caregiving can be assessed in greater detail with instruments such as the HOME Inventory (65) and the Emotional Availability Scales (66). A non-maltreatment code cannot tell us how much support a child received.

Female MAOA findings need to be interpreted in light of X-linked inheritance and the cellular mosaicism caused by X-inactivation. Their interpretation also depends on repeat coding, environmental measurement, age, and outcome. A pooled estimate can conceal that variation. A claim that a result applies across sexes would require separate estimates for males and females, together with enough power to test the genotype-by-sex interaction directly.

A parent's genes can be related both to the genes transmitted to the child and to the rearing environment the parent provides. This gene-environment correlation (rGE) can complicate an apparent interaction. Maltreatment analyses by Kim-Cohen et al. (17) and Jaffee et al. (67) examined this problem. Analyses of supportive parenting likewise need controls drawn from family-based or other genetically informed designs.

14. Priorities for future MAOA studies

Future MAOA studies should specify the comparison between vulnerability and differential susceptibility before examining results. Vantage sensitivity can be included as a formal comparator. The measurements and analyses needed for this preregistered comparison are presented in Table 4.

Birth cohorts would need to recruit additional children from highly supportive homes to extend that part of the environmental range. In animal studies, deprivation, standard housing, and enrichment could be compared experimentally. Existing datasets may already allow other comparisons where genotype, environmental, and longitudinal measures are available. For those analyses, investigators can specify the competing models in advance and estimate the crossover and regions of significance within the recorded environmental range.

Dunedin produced the original finding (9). An Add Health subsample contains MAOA-uVNTR and longitudinal behavioral data (8, 72), although access to the relevant maltreatment and support measures, and their suitability for model comparison, still need to be verified. E-Risk is another possibility because it has already been used for MAOA G×E analyses (17). For E-Risk, maternal warmth was observed at ages 5 and 10, and children reported adult support at age 12 (70, 71, 73). Support at age 12 was measured at the same time as the age-12 outcome; the age-18 outcome provides a later observation. Any reanalysis would need to

retain that timing distinction. With suitable measures and permission under the relevant data governance, these cohorts could be used for preregistered comparisons of vulnerability and differential susceptibility, with vantage sensitivity included as a boundary comparator. Researchers without laboratory facilities could pursue these questions through secondary analysis. Even with cohort access, they would still need to preregister the competing models and account for genetic confounding. Sex and ancestry still need to be handled in the analysis.

Table 4. Measurements and analyses needed to compare the three models.

Design principle	Why it matters	Minimum requirement
Measure the full environmental range	A sample without enriched environments cannot test the benefit predicted by differential susceptibility.	Assess maltreatment using the Childhood Trauma Questionnaire (68), Maltreatment Classification System (69), or a comparable validated measure. Assess support separately with the HOME Inventory (65), Emotional Availability Scales (66), or adapted Five-Minute Speech Sample coding of maternal warmth (70, 71). Absence of maltreatment cannot substitute for a support measure.
Preregister competing models	Interpretations can change after researchers see a significant interaction.	Specify the tests for vulnerability, differential susceptibility, and vantage sensitivity in the preregistration.
Use regions of significance and crossover tests	An interaction term or a fan-shaped plot alone does not demonstrate plasticity.	Report where genotype estimates differ and whether the crossover falls within the environmental range sampled.
Stratify by sex	The X-linked gene requires attention to male and female genotype coding and response patterns.	Estimate the interaction separately in males and females. Test whether sex changes the interaction before combining estimates.
Control rGE and polygenic background	Parents' genes, family history, and broader genetic liability may confound an apparent single-gene interaction.	Use family comparisons when feasible and include ancestry and genome-wide controls when available.
Reanalyze interventions	Differential susceptibility predicts a greater response to parenting or enrichment in the environmentally sensitive genotype.	Check whether early-intervention trials have archived DNA suitable for reanalysis. Plan any new collection prospectively with ethical safeguards.
Test enrichment in animal models	Environmental quality can be randomly assigned in animal studies.	Compare MAOA-deficient and control animals under deprivation, standard housing, and enrichment.

15. Ethical and intervention implications

The reported associations lack the individual-level predictive accuracy required for clinical screening. Nevertheless, labeling a child according to MAOA genotype could bias adults' interpretations of otherwise ordinary behavior, potentially leading to stigmatization before any behavioral outcomes emerge. A particular

MAOA genotype does not establish that a child is predisposed to dangerous behavior and provides no justification for differential treatment.

If plasticity were demonstrated, a fixed risk label would overlook the benefit associated with the same genotype under support. Prevention of maltreatment, early recognition of abuse, and better caregiving remain public-health priorities regardless of that result. Genotype may have a place in research on mechanisms and variation in intervention response. Access to services should not depend on the result.

The animal findings on early serotonin signaling show that developmental timing can affect the organization of circuitry (13, 23, 25). They cannot specify a human MAOA age-of-exposure gradient. Prevention and support should begin early on ethical and public-health grounds, without waiting for a genotype-specific account of timing. The purpose is to reduce children's exposure to harm and improve their care.

16. Conclusion

MAOA has frequently been characterized as a vulnerability gene because carriers of certain variants exhibit greater adverse behavioral outcomes following childhood maltreatment. However, most studies supporting this classification have examined exposure to adversity without adequately measuring genuinely supportive environments. The absence of maltreatment is not equivalent to the presence of positive environmental experiences. Consequently, evidence of increased vulnerability under adversity does not establish the absence of enhanced responsiveness to support, and the existing literature cannot conclusively distinguish vulnerability from differential susceptibility. This represents a fundamental limitation in the interpretation of MAOA gene–environment interactions, rather than merely a shortage of replication studies.

Beyond this methodological limitation lies a more fundamental biological question: why should some genetic variants predominantly amplify the consequences of adversity, whereas others enhance responsiveness to both adverse and supportive environments? This review proposes a biological network function hypothesis in which variants affecting homeostatic regulatory systems, such as MAOA and FKBP5, may preferentially produce vulnerability-dominant interactions, whereas variants affecting cognition, learning, and neural plasticity, such as DRD4 and BDNF, may more frequently produce differential susceptibility. Although homeostatic regulation is inherently bidirectional, the behavioral consequences of variation in these systems may be asymmetrical when their regulatory functions are preferentially recruited by adversity. This leads to a novel, continuous prediction: the degree of adversity-related functional specialization of a biological network should predict the asymmetry of its gene–environment interaction.

The principal contribution of this review is therefore twofold: it challenges the classification of MAOA as a vulnerability gene in the absence of adequate evidence from supportive environments, and it advances a mechanistically motivated, falsifiable framework for predicting gene–environment interaction patterns from independently

characterized biological network functions. The proposed comparative investigation offers a means of testing whether functional specialization predicts vulnerability, differential susceptibility, or vantage sensitivity without assuming that these patterns are fixed properties of individual genes. Ultimately, the objective is to move beyond assigning retrospective statistical labels to genetic variants toward explaining and prospectively predicting the biological basis of environmental sensitivity, without conflating vulnerability with biological determinism.

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Abbreviations

BDNF: brain-derived neurotrophic factor, DRD4: dopamine receptor D4, FKBP5: FK506-binding protein 5, G×E: gene-environment interaction, GWAS: genome-wide association study, GWAMA: genome-wide association meta-analysis, HOME: Home Observation for Measurement of the Environment, HPA: hypothalamic-pituitary-adrenal, MAOA: monoamine oxidase A, MAOA-H: higher-transcription MAOA-uVNTR group, MAOA-L: lower-transcription MAOA-uVNTR group, MAOA-uVNTR: upstream variable-number tandem repeat in MAOA, rGE: gene-environment correlation, 5-HTTLPR: serotonin-transporter-linked polymorphic region.

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