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GENETIC EVIDENCE, *MAOA*, AND *STATE V. YEPEZ*

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On Monday, October 21, 2019, an amicus brief was filed in the case of *State v. Yepez*, a brief signed by scholars representing a variety of disciplines, including genetics, psychiatry, and law,[1] as well as by the law students in Duke Law's Amicus Lab, a course in which students participate in amicus briefing in cases raising law, science, and technology issues.[2] The *Yepez* case involved a novel issue regarding the admissibility of genetic evidence. The defense had sought to introduce evidence concerning the *MAOA* gene to argue that a murder was not committed intentionally, due to a genetic predisposition to violence.[3] The trial court denied leave to introduce such expert evidence and the appellate court affirmed, but finding error, and then finding the error to be harmless.[4] After all, the defendant was not convicted of an intentional first degree, but rather second-degree, murder. [5]

The New Mexico Supreme Court, in a rare if not unprecedented move, denied leave to file the amicus brief on November 5, 2019, in a summary order.[6] The motion seeking leave to file the brief had been made unopposed, with the consent of all parties to the case. [7] The brief was filed because the group of scholars shared an interest in the quality and improvement of psychiatric genetics in the courtroom. The brief described as its overriding goal that scientific evidence and courtroom testimony should be founded on scientific methods and knowledge. Further, the brief expressed a concerned that trial evidence grounded in unreliable or since-discredited psychiatric genetics can lead to unfairness in the administration of the criminal justice system.

We do not fully understand why the Supreme Court declined leave to file our brief; it would have been routine to at least consider it. The New Mexico

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1. Brief of Amicus Curiae, State v. Yepez, No. S-1-SC-37216 (N.M. Oct. 21, 2019) (on file with authors).

2. Duke Law, *Amicus Lab*, https://web.law.duke.edu/academics/course/section/2019/fall/472.01 [https://perma.cc/V38L-8FSZ].

3. *State v. Yepez*, 2018-NMCA-062, ¶ 32, 428 P.3d 301, 308.

4. *Id.* ¶ 1, 428 P.3d at 301.

5. *Id.* ¶ 36, 428 P.3d at 306.

6. Order Denying Motion for Leave to File Amicus Brief, State v. Yepez, No. S-1-SC-37216 (N.M. Nov. 5, 2019).

7. Unopposed Motion for Leave to File Brief of Amicus Curiae, State v. Yepez, No. S-1-SC-37216 (N.M. Oct. 21, 2019) (on file with authors).

Appellate rules call for amicus briefs to be conditionally filed, with a motion seeking leave to file.[8] Prominent amicus briefs, such as by the American Bar Association have been filed in the New Mexico Supreme Court in the past.[9] In this case, we were made aware of a notation from the Clerk of the Court, querying whether it was timely filed if it was a brief aligned with one of the sides.[10] However, no such reasons appeared in the summary order denying leave to file. The New Mexico Supreme Court has not yet decided the case. Thus, we do not yet know whether our filing could have played a role in the reasoning that the Court adopts. However, we emphasize that the amicus brief did not take a side; we simply addressed the limitations of such genetic evidence and the concerns with the expert evidence proffered, to be sure by the defense in this case, in the trial court. To take sides, however, in admitting amicus briefs raising issues of scientific evidence, raises deep concerns. Such amicus briefs are routinely admitted and we hope that the denial of leave in this case is an aberration and not a precedent-setting move.

The amicus brief offers two main contributions. First, we describe how *MAOA* studies based on the prior "candidate-gene approach" are unreliable due to inherent flaws in the methodology, leading to inconsistencies in replication. Second, the general scientific consensus has emerged that the earlier *MAOA* studies (upon which the defense experts relied) are now an outdated method of studying psychiatric genetics. Third, to the extent that recent studies adopting the more rigorous genome-wide association studies (GWAS) have attempted to replicate the earlier findings of *MAOA* candidate-gene studies, they have found no reliable correlation between *MAOA* and violence. Below, we provide the text of our brief. We hope that it will inform appraisals of the New Mexico Supreme Court's ruling, should it rule on the merits in this matter, but also inform future courts to consider the admissibility of such genetic predisposition evidence.

INTEREST OF THE *AMICUS CURIAE*

This brief is signed by scholars representing a variety of disciplines, including genetics, psychiatry, and law, as well as by the law students in Duke Law's Amicus Lab, a course in which students participate in amicus briefing in cases raising law, science, and technology issues. The scholars have an interest in the quality and improvement of psychiatric genetics in the courtroom. *Amici* believe that scientific evidence and courtroom testimony should be founded on scientific methods and knowledge. *Amici* are interested in improving the administration of justice in general, and in maintaining the accuracy of evidence in particular. *Amici* are concerned that trial evidence grounded in unreliable or since-discredited psychiatric genetics can lead to unfairness in the administration of the criminal justice system. A list of *Amici* is appended to the signature page. On September 11, 2019, counsel for all parties were notified of the intent of *Amici* to file this brief. Counsel for all parties have responded that they do not oppose the filing of this brief.

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8. Rule 12-320 NMRA.

9. Brief of Amicus Curiae American Bar Association in Support of Petitioners, State ex rel. Baur v. Shoobridge, No. S-1-SC-36375 (N.M. June 5, 2017).

10. *See also* email from Roderick Kennedy to authors, Nov. 5, 2019 (on file with authors).

SUMMARY OF ARGUMENT

After a pre-trial hearing, the District Court "denie[d] Defendant's request for admission of expert testimony regarding scientific studies finding a gene with environment interaction such that persons with a low functioning maoa gene and a history of child abuse, are predisposed or included toward antisocial and aggressive behaviors, which includes violent acts."[11] The Court of Appeals found this denial to be erroneous, but the error harmless.

In so doing, the Court of Appeals did not independently evaluate the reliability of the scientific evidence at issue. Had it done so, it would have found that the candidate-gene methodology for studying psychiatric genetics, upon which the Defendant's claim relies, does not meet the scientific standard of admissibility adopted by New Mexico.

As discussed below, the District Court's decision to exclude testimony regarding the interaction between low *MAOA*, childhood maltreatment, and violence was not an abuse of discretion because the science at issue has been found unreliable by the scientific community. Established science now reveals several crucial concerns about the candidate-gene-based *MAOA* theory in the form it was presented to the District Court.

First, *MAOA* studies based on the prior "candidate-gene approach" are unreliable due to inherent flaws in the methodology, leading to inconsistencies in replication. Candidate-gene studies were underpowered, the effect sizes of any particular genes was quite small, and there were significant challenges in defining the genetic, environmental, and behavioral variants of interest. Consequently, the science sought to be admitted in the District Court is unable to reliably prove what it purports to prove as is required under the New Mexico evidentiary standards.

Second, the general scientific consensus has emerged that the earlier *MAOA* studies (upon which the defense experts relied) are now an outdated method of studying psychiatric genetics. For scientific testimony to be admissible the scientific expert opinion testimony offered must be generally accepted in the particular scientific field.[12] The candidate-gene environment (cGxE) approach, the scientific basis of the expert testimony, has been replaced by the scientific community in favor of more robust genetic techniques. Leading scientists and scientific organizations have recommended abandoning the cGxE approach in favor of well-powered and unbiased genome-wide association studies (GWAS).[13]

Third, to the extent that recent studies adopting the more rigorous genome-wide association studies (GWAS) have attempted to replicate the earlier findings of *MAOA* candidate-gene studies, they have found no reliable correlation between *MAOA* and violence.

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11. R. at 669.

12. State v. Anderson, 1994-NMSC-089, ¶ 15, 118 N.M. 284, 881 P.2d 29 (quotation marks and quoted authority omitted).

13. *See infra* Part III.

BACKGROUND

As the criminal justice system becomes more reliant on scientific evidence, courts play an increasingly fundamental role in ensuring that only valid, reliable expert testimony is admitted as evidence. In light of recent developments in behavioral genetics, this gatekeeping function is especially crucial. We write to inform the New Mexico Supreme Court of issues concerning the admissibility of the *MAOA* genetic evidence relied on by the defense.

In this case, defendant Anthony Yepez was convicted of, among other charges, the second-degree murder of George Ortiz in Santa Fe in 2012.[14] At trial, Mr. Yepez sought to present evidence of his inability to form the specific intent necessary for a jury to find him guilty of first-degree murder.[15] The defense hoped to call two M.D.'s and a Ph.D. to allege that Mr. Yepez's possession of a low activity *MAOA* gene variant, coupled with Mr. Yepez's experience of childhood maltreatment made it significantly more likely that he would engage in antisocial or violent behavior if triggered.[16] Mr. Yepez filed a pretrial motion *in limine* seeking to admit this evidence and also filed a notice of incapacity to form specific intent.[17] The State filed its own motion *in limine* requesting the exclusion of this expert testimony contending that the science is not trustworthy and reliable, that the would not assist the trier of fact, and that the testimony would be extremely complicated, confusing, and misleading.[18]

The District Court excluded the expert testimony after several briefs from the parties and an evidentiary hearing.[19] Specifically, the trial judge ruled that *Daubert* factors as stated in *Daubert v. Merrel Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), had been met regarding these studies, but that the proposed lines of expert testimony should not be admitted under *State v. Alberico*, 861 P.2d 192 (N.M. 1993).[20] The District Court also concluded that Dr. James Walker's testimony did not satisfy the *Daubert* test, was not "material to the issues in this case" and would not "assist the trier of fact."[21] The District Court subsequently denied Mr. Yepez's motion for reconsideration.[22] Despite not hearing this evidence at trial, the jury found Mr. Yepez guilty of second-degree murder instead of first-degree murder.[23] The Court of Appeals concluded that the District Court's exclusion of the expert testimony was erroneous and an abuse of discretion,[24] but that the error was harmless because Mr. Yepez was acquitted of first-degree murder and the excluded evidence

14. R. at 857.

15. R. at 58–59.

16. R. at 66–70, 132–34.

17. R. at 66, 131.

18. R. at 138–49.

19. R. at 669–81.

20. R. at 680.

21. R. at 675, 679.

22. R. at 680.

23. R. at 857.

24. An abuse of discretion occurs if "the trial judge's action was obviously erroneous, arbitrary, or unwarranted" or the action is "clearly against the logic and effect of the facts and circumstances before the court." State v. Alberico, 1993-NMSC-047, ¶ 63, 116 N.M. 156, 861 P.2d 192 (quoted authority omitted).

was irrelevant to his second-degree murder conviction.[25] The Court of Appeals did not independently evaluate the reliability of the evidence.[26] However, the specific scientific theory asserted by Mr. Yepez's experts is currently neither generally accepted nor reliable. Rather, it relies on an outdated and limited candidate-gene approach to studying complex traits which renders the conclusions unreliable.

ARGUMENT

I. THE DISTRICT COURT'S DECISION TO EXCLUDE TESTIMONY REGARDING THE INTERACTION BETWEEN LOW *MAOA*, MALTREATMENT AND VIOLENCE WAS NOT AN ABUSE OF DISCRETION BECAUSE THE SCIENCE AT ISSUE IS UNRELIABLE

In 2002, Caspi and colleagues published the seminal paper on the central issue in this case, examining the role of the monoamine oxidase A gene (*MAOA*) in the development of antisocial behaviors.[27] They discovered that of the 442 males in their study, those with a genetic variant called *MAOA*–L (the low activity form of the *MAOA* gene) were more likely to exhibit violent behavior if they had been maltreated as children compared to those with the genetic variant *MAOA*-H (the high activity form of the *MAOA* gene).[28] From this, Caspi and collegues concluded genes influence our behavior, and our environment influences the way genes are expressed.[29]

This study was heralded as the first successful candidate-gene-environment (cGxE) study of a complex psychiatric trait.[30] This led to a series of follow-up candidate-gene-environment (cGxE) studies dedicated to understanding the connection between *MAOA*, the environment, and aggression.[31] As discussed more fully below,[32] the results of these studies varied; some supporting, some not supporting the 'candidate-gene hypothesis" for *MAOA* and aggression.[33]

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25. State v. Yepez, 2018-NMCA-062, ¶ 34, 428 P.3d 301, 308.

26. *Id*.

27. *See* Avshalom Caspi et al., *Role of Genotype in the Cycle of Violence in Maltreated Children*, 297 SCI. 851 (2002).

28. *Id*. at 853.

29. *Id*.

30. Candidate gene studies are studies that test for an association between one or a small number of variations in a gene ("polymorphisms"), the environment, and a phenotype of interest (e.g. violence, maladaptive behavior), without examining genome-wide data. Laramie E. Duncan et. al., *How Genome-Wide Association Studies (GWAS) Made Traditional Candidate Gene Studies Obsolete*, 44 NEUROPSYCHOPHARMACOLOGY 1518, 1518 n.2 (2019).

31. *See, e.g.*, J Kim-Cohen et al., *MAOA, Maltreatment, and Gene–Environment Interaction Predicting Children's Mental Health: New Evidence and a Meta-Analysis*, 11 MOLECULAR PSYCHIATRY 903 (2006).

32. *See infra* Section I.A.

33. *See, e.g.*, Amy L. Byrd et al., *MAOA, Childhood Maltreatment, and Antisocial Behavior: Meta-Analysis of a Gene-Environment Interaction*, 75 BIOLOGICAL PSYCHIATRY 9, 15–16 (2014). *See generally* Richard Border & Matthew C. Keller, *Commentary: Fundamental Problems with Candidate Gene-by-Environment Interaction Studies—Reflections on Moore and Thoemmes* (2016), 58 J. CHILD PSYCHOL. & PSYCHIATRY 328 (2017); Danielle M. Dick et al., *Candidate Gene–Environment Interaction Research: Reflections and Recommendations*, 10(1) PERSP. ON PSYCHOL. SCI. 37 (2015).

Despite early enthusiasm for the candidate-gene findings, multiple replication failures coupled with newer and better-powered techniques in applied genetics led to a growing skepticism and concern about the quality of this rapidly expanding literature.[34] Although the Court of Appeals did not independently evaluate the reliability of the scientific evidence to reach its conclusions, this court must now do so.

To make this determination, this court must consider:

> (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) the known potential rate of error in using a particular scientific technique and the existence and maintenance of standards controlling the technique's operation; and (4) whether the theory or technique has been generally accepted in the particular scientific field.[35]

Measured against these established scientific principles, the expert testimony of Dr. Walker and evidence regarding the defendant's low *MAOA* and its correlation with impulsivity and violence lacked sufficient indicia of reliability to be offered to the jury as expert testimony. As such, it was not an abuse of discretion for the District Court to have excluded the evidence.[36]

A. MAOA Candidate-Gene Studies Were Inconsistently Replicated

Part of the reason for earlier enthusiasm in the scientific community about the *MAOA* theory was some successful early replications of the Caspi et al. results. For example, Julia Kim-Cohen and her colleagues developed a meta-analysis that evaluated cGxE studies on the impact of *MAOA*, childhood maltreatment, and violence.[37]

In their meta-analysis, the researchers analyzed five studies and presented new data using a sample size of nine hundred and seventy-five seven-year-old boys, finding support for the contention that there is a link between *MAOA*-L and

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34. *See generally* Laramie E. Duncan & Matthew C. Keller, *A Critical Review of the First 10 Years of Candidate Gene-by-Environment Interaction Research in Psychiatry*, 168 AM. J. PSYCHIATRY, 1041 (2011); Matthew C. Keller, *Gene x Environment Interaction Studies Have Not Properly Controlled for Potential Confounders: The Problem and the (Simple) Solution*, 75 BIOLOGICAL PSYCHIATRY 18 (2014); Border & Keller, *supra* note 23; Dick et al., *supra* note 33.

35. State v. Anderson*,* 1994-NMSC-089, ¶ 15, 118 N.M. 284, 881 P.2d 29 (quotation marks and quoted authority omitted).

36. In 1993, in *State v. Alberico*, 1993-NMSC-047, 116 N.M. 156, 861 P.2d 192, the New Mexico Supreme Court adopted *Daubert v. Merrel Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 592 (1993), to guide its determination of when expert scientific testimony should be admissible. In reviewing a trial court's determination of whether to admit expert scientific testimony, New Mexico follows the federal abuse of discretion standard, which holds that "[o]nce the [trial] court has made a determination on [the admissibility of expert opinions], such a decision is accorded great weight by a reviewing court and this decision will be upheld absent an abuse of discretion." *State v. Vigil*, 1985-NMCA-110, ¶ 10, 103 N.M. 643, 711 P.2d 920. Under this standard, "[t]he trial court has wide discretion in determining whether a witness is qualified to testify as an expert." *Id.*

37. *See* Kim-Cohen et al., *supra* note 31.

aggression.[38] Other studies were also successful in replicating Caspi's findings.[39] In a large meta-analysis conducted by Professors Amy L. Byrd and Stephen Manuck, they similarly found an "association between cG×E and *MAOA*, and a higher probability of antisocial behavior among male carriers of *MAOA*-L who were exposed to childhood maltreatment."[40]

But many other studies failed to replicate the Caspi et al. findings.[41] Brett Haberstick and his colleagues, using a cohort of seven hundred and seventy-four, examined *MAOA* in relation to childhood maltreatment and victimization.[42] They were "unable to confirm the hypothesis that differences in the *MAOA* promoter region plays a moderating role in the relationship between maltreatment as a child and conduct problems in adolescence and young adulthood."[43]

Similarly, Young et al. found "no genetic-environmental interaction with genotype for maltreatment."[44] The largest study with a sample size of one thousand and two-men also did not replicate the Caspi findings, leading the authors to conclude that the "failure to replicate the interaction in a large, representative sample must raise some doubts about the robustness of this finding, given that it does not appear to generalize across samples."[45]

B. Significant Challenges in Defining the Genetic Variants of Interest, Maltreatment, and Violence Confounded Replication Across MAOA Studies

As can be readily appreciated, there are significant challenges in consistently defining the genetic, environmental, and psychiatric behaviors of interest when evaluating the influence of *MAOA* and the environment. The variation between researchers in characterizing these traits led to differing and inconsistent results between studies.[46]

These characterization failures significantly limited the reliability and replicability of *MAOA* candidate-gene studies. As such, while *MAOA* studies have been widely referenced over time, the underlying principles and methodologies

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38. *Id*.

39. *See, e.g.*, Alexis C. Edwards et al., *MAOA uVNTR and Early Physical Discipline Interact to Influence Delinquent Behavior*, 51(6) J. CHILD PSYCHOL. & PSYCHIATRY 679 (2010); David M. Fergusson et al., *Moderating Role of the MAOA Genotype in Antisocial Behavior*, 200(2) BRIT. J. OF PSYCHIATRY 116 (2012).

40. Kent W. Nilsson et al., *Gene-Environment Interaction of Monoamine Oxidase A in Relation to Antisocial Behaviour: Current and Future Directions*, 125 J. NEURAL TRANSMISSION 1601, 1603 (2018) (discussing Amy L. Byrd & Stephen Manuck., *MAOA, Childhood Maltreatment, and Antisocial Behavior: Meta-Analysis of a Gene-Environment Interaction*, 75 BIOLOGICAL PSYCHIATRY 9 (2014)).

41. *See, e.g.*, Brett C. Haberstick et al., *Monoamine Oxidase A (MAOA) and Antisocial Behaviors in the Presence of Childhood and Adolescent Maltreatment*, 135(1) AM. J. MED. GENETICS 59, 63 (2005).

42. *Id*. at 60.

43. *Id*. at 62.

44. Susan E. Young et al., *Interaction Between MAO-A Genotype and Maltreatment in the Risk for Conduct Disorder: Failure to Confirm in Adolescent Patients*, 163:6 AM. J. PSYCHIATRY 1019, 1019 (2006).

45. Zoë Prichard et al., *No Evidence for Interaction Between MAOA and Childhood Adversity for Antisocial Behavior*, 147 AM. J. MED. GENETICS PART B 228, 232 (2008).

46. *See generally id*.

grounding them have been successfully challenged over time, such that today they do not meet the "maintenance of standards" and "potential rate of error" prongs in *State v. Anderson*.[47]

There are several genetic variations (alleles) in *MAOA* that have been studied over time. The specific alleles studies have varied between researchers.[48] As such it's difficult to relate any specific genetic variant identified in a particular criminal defendant to a specific effect on violent behavior.

The definition of maltreatment has proven even more difficult for researchers to consistently characterize. Even with hospital records, childhood maltreatment is not a well specified behavior or phenotype (the physical expression, or characteristics, of that trait), which makes it subjective and inherently unreliable to measure.[49] Moreover, there are many overlapping phenotypes that could result in similar outcomes.[50]

Childhood maltreatment broadly correlates with other forms of conduct disorders ranging "from anxiety and depression to rule-breaking and aggression."[51] For instance, nearly all individuals who have been physically or sexually abused have also experienced childhood neglect or emotional abuse.[52] While this fact alone is uncontroversial, it makes determining the specific relationship between childhood trauma and adult outcomes problematic because the cumulative effects of these issues correlate to other forms of abuse "and those other forms of abuse are thereby implicitly considered in statistical models."[53] Thus, assessments of experiences of trauma will often include the effects of previously experienced trauma making "it can be difficult to draw conclusions about the effects of the timing and severity of different forms of life stressors in relation to childhood maltreatment."[54]

Moreover, the effect of childhood maltreatment on *MAOA* gene expression may change based on other factors. For instance, maltreatment may also be accompanied by many other factors such as low parental income or unemployment.[55] Consequently, it can be very difficult to characterize the gene-environment interaction with maltreatment since other highly stressful life events could have a disproportionate impact on the predictors of maltreatment being studied.[56]

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47. 1994-NMSC-089, ¶ 15, 118 N.M. 284, 881 P.2d 29 (quotation marks and quoted authority omitted).

48. Individuals may have different points in their copy of *MAOA* gene that vary, and each different variation could contribute to low expression of *MAOA*. *See* Kent W. Nilsson et al., *supra* note 40, at 1616–17.

49. *See id*. at 1615 (citing David D. Vachon et al., *Assessment of the Harmful Psychiatric and Behavioral Effects of Different Forms of Child Maltreatment*, 72 JAMA PSYCHIATRY 1135, 1140–41 (2015)).

50. *See id.* at 1602, 1613.

51. *Id*. at 1615.

52. *Id*. at 1614.

53. *Id*. at 1615.

54. *Id*.

55. *Id.* (citing Irina Patwardhan et al., *Child Maltreatment as a Function of Cumulative Family Risk: Findings from the Intensive Family Preservation Program*, 70 CHILD ABUSE & NEGLECT, 92, 92–99 (2017)).

56. *Id*.

Finally, the outcome measure in these studies – complex behavioral traits like violence and maladaptive behavior – have been characterized differently by different researchers across cGxE *MAOA* studies. In some studies violence has been defined as "lying or cheating, and destroy[ing] things,"[57] while other studies have defined it as "extreme criminal violent behavior[.]"[58] The measures of violence itself may vary considerably based on the research context and cohort being studied. Studies from low violence locales like Sweden have stronger correlations between *MAOA* and behaviors like vandalism, rather than correlations with murder.[59] Similarly, the researchers have found that maladaptive behaviors could be defined as "early-onset," "life-course persistent," or even psychopathic depending on disciplinary origin of the study.[60]

As a result of the failures to replicate, together with concerns about the validity of the candidate-gene approach itself (as discussed *infra*), cGxE studies linking *MAOA* to maladaptive or violent behavior have by now been largely superseded by more robust and better-powered approaches to studying the genetic contributions to complex psychiatric traits.

II. THE CANDIDATE-GENE-ENVIRONMENT (cGxE) APPROACH, FOR STUDYING COMPLEX TRAITS, WHICH WAS THE SCIENTIFIC BASIS OF THE EXPERT TESTIMONY, HAS SINCE BEEN DISCREDITED BY THE SCIENTIFIC COMMUNITY

A. A General Scientific Consensus Has Emerged Against Studies Focusing on Single Gene Explanation for Complex Behaviors

When researchers in 2011 conducted a thorough review of the first ten years of candidate-gene studies using candidate genes in psychiatry, they found that while 96% of initial novel findings were significant, they were only replicated 27% of the time.[61] The biggest reason for the high replication failure rate was the underlying assumption to studying psychiatric genetics that only a few genetic variants were implicated in complex behaviors and traits.[62] As a result of the fundamental difficulties with in the candidate-gene approach itself, earlier research studies such as the Caspi et al. one linking *MAOA* to maladaptive or violent behavior have been superseded by modern genetic techniques.

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57. *See, e.g.*, Kim-Cohen et al., *supra* note 31, at 906 (other categories included "very restless," "cannot concentrate," and "unhappy, sad, or depressed").

58. *See*, *e.g.*, J. Tilhonen et al., *Genetic Background of Extreme Violent Behavior*, 20 MOLECULAR PSYCHIATRY 786 (2015).

59. *See* Kent W. Nilsson et al., *Role of Monoamine Oxidase: A Genotype and Psychosocial Factors in Male Adolescent Criminal Activity*, 59(2) BIOLOGICAL PSYCHIATRY 121, 121–127 (2006); Rickard L. Sjöberg et al., *Adolescent Girls and Criminal Activity: Role of MAOA-LPR Genotype and Psychosocial Factors*, 144B(2) AM. J. MED. GENETICS 159, 159–164 (2007).

60. *See* Nilsson et al., *supra* note 40, at 1612.

61. *See* Peter T. Tanksley et al., *The Genome-Wide Study of Human Social Behavior and Its Application in Sociology*, 4 FRONTIERS IN SOC. 1, 2 (2019).

62. *Id*.

For scientific testimony to be admissible the scientific expert opinion testimony offered must also be generally accepted in the particular scientific field.[63] The current scientific consensus is that candidate-gene association studies upon which the *MAOA* conclusion was made are obsolete.[64] This includes the focus on "low activity *MAOA*" as being "statistically associated with the occurrence of maladaptive or violent, behavior in individuals who have experienced maltreatment in childhood."[65]

To understand why, it is necessary to understand how genotypic[66] variance (variance in genes such as *MAOA*) could ultimately produce phenotypic[67] variance (e.g. variance in expressed behaviors like maladaptive behavior, violence, impulsivity, aggression, or antisocial behavior).[68]

1. Complex Traits are Polygenic

The scientific consensus is that complex behaviors, such as maladaptive or violent behavior, are the result of action and interaction of many genes and are additive to environmental effects.[69]

Genes can contribute to variations in human behavior in different ways, such as through monogenic (single gene) effects or polygenic (multiple or many gene) effects. Under a monogenic effect model, a variation in a single gene could be the sole cause of a phenotype (a physical or behavioral expression). If a person possesses that variation in the gene, then he or she will develop the phenotype, and by contrast if they do not, then they will not. Although thousands of diseases and disorders are produced by this monogenic (one gene: one behavior) model,[70]complex behavioral phenotypes such as antisocial, maladaptive, and violent behavior, are *not* produced by such a simple genetic model.[71]

When a phenotype (the physical expression of a trait) is produced through polygenic effects, that means that instead there are many genes that each have a small influence on the phenotype. When aggregated, however, these small effects can collectively account for a large proportion of the phenotypic variance seen between individuals. But importantly, under a polygenic model, common variants in single genes such as *MAOA* are neither necessary nor sufficient for the phenotype to surface; rather, they work in a probabilistic manner whereby the possession of a

63. *See* State v. Anderson, 1994-NMSC-089, ¶ 15, 118 N.M. 284, 881 P.2d 29 (quotation marks and quoted authority omitted).

64. *See* Duncan et. al., *supra* note 30, at 1518.

65. R. at 6.

66. The genotype is the set of alleles in our DNA which are being tested for association to a particular trait.

67. The phenotype is the physical expression, or characteristics, of that trait.

68. *See* KEVIN M. BEAVER ET AL., *On the Genetic and Genomic Basis of Aggression, Violence, and Antisocial Behavior*, in THE OXFORD HANDBOOK OF EVOLUTION, BIOLOGY AND SOCIETY (Rosemary L. Hopcroft ed., Oxford Univ. Press 2018).

69. Duncan et al., *supra* note 30, at 1518 (2019).

70. This includes sickle cell disease, cystic fibrosis, polycystic kidney disease, osteogenesis imperfecta, Tay-Sachs disease, hemophilia, inborn errors of metabolism, and other diseases.

71. *See* BEAVER ET AL., *supra* note 68.

common single variant increases (or decreases) the probability that the phenotype will emerge but only slightly.

The scientific consensus is that complex behavioral phenotypes, such as maladaptive or violent behavior, are the result of polygenic patterns of transmission such that the contribution of any single gene is likely quite small.[72] Consequently, studies that begin with a hypothesis about a single gene and study its effects, without the much broader background of the many other genes involved, ignore the pattern by which such behaviors are transmitted. The result is a biased study that overstates the relationship of any particular gene to a complex behavior.

2. Effect Sizes of Common Variants in Single Genes in Complex Traits are Quite Small

More modern techniques in psychiatric genetics, such as genome-wide association studies,[73] made possible by better technology and much larger sample sizes, have revealed that the effect sizes associated with common individual common genetic variants such as those studied in *MAOA* are actually very small. In other words, an individual harboring a common variant in *MAOA* would have only a very small change in their expected behavior and could be modified by other genes that were not examined.[74]

The small sample sizes in earlier candidate-gene studies further confounded this issue, since the studies were underpowered for detecting genetic influences with such small effect sizes.[75] These underpowered studies in turn may lead to *overestimates* of effect size and low reproducibility of results. The Caspi study had a sample size of 1,037 children.[76] By comparison, a recent GWAS study on schizophrenia had a sample size of >13,800 cases and >18,000 controls.[77]

In short, under a polygenic model, common variants in any single gene like *MAOA* are likely to have only have a very small – if any—influence on complex maladaptive behaviors such as violence, and that influence is modified by many other genes.[78]

3. Complex Behaviors Are Likely Moderated by Other Unspecified Variables

Moreover, there are often confounding variables that are not accounted for in candidate-gene association studies. Put simply, the effects seen in the studies of *MAOA* on complex behaviors could in fact be attributable to other genetic and non-genetic factors that are not accounted for in the study.[79]

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72. *See* Duncan et. al., *supra* note 30, at 1518.

73. *See infra* Part III.

74. *See* Dick et al., *supra* note 33.

75. *See id.* at 41; Katherine S. Button et al., *Power Failure: Why Small Sample Size Undermines the Reliability of Neuroscience*, 14 NATURE REV. NEUROSCIENCE 365, 365 (2013).

76. Caspi et al., *supra* note 27, at 852.

77. Dick et al., *supra* note 33, at 41.

78. *See* BEAVER ET AL., *supra* note 68.

79. *See* Border & Keller, *supra* note 23.

As a result of these fundamental limitations in the candidate-gene approach to studying complex behavioral traits, the scientific community began to appreciate the role of *MAOA*/maltreatment as a predictor of violent was far more nuanced, and ultimately dependent on understanding the complex interaction between many other genetic and environmental factors that had not yet been accounted for in research.

B. Leading Scientists and Scientific Organizations Now Recommend Abandoning the Candidate-Gene Approach in Favor of Well-Powered and Unbiased Genome-Wide Association Studies (GWAS)

Concerns about the Caspi et al. study itself, and the candidate-gene-environment (cGxE) approach more generally, led to a series of recommendations by leading scientific organizations for reform in the approach to studying complex behavioral traits.

For example, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) sponsored a workshop in January 2013 that brought together a group of researchers to discuss challenges in psychiatric genetics and cGxE studies, and to provide recommendations for how to move the field forward. Those discussions resulted in a statement discrediting the historic cGxE model, and issuing a set of robust research recommendations to improve future psychiatric genetic studies, including the importance of genome-wide association studies.[80]

Similarly, a working group of leading scientists was convened in 2016 by the National Institute of Mental Health (NIMH) to address challenges in psychiatric genetics.[81] This Working Group stated:

> 'Candidate gene' is a term with no consensus definition, but can be taken to refer to genes selected for study by means other than an unbiased, genome-wide approach, most often based on prior biological hypotheses. Candidate gene studies attempting to find associations with neuroimaging or other biological phenotypes have historically been vastly underpowered partly because of the high cost of the phenotypic readouts and partly on serious misunderstandings of the influence of sample size on the robustness and significance of results (Button et al., 2013). Candidate Gene-by- Environment (GxE) studies, which might be better described as candidate gene-by- candidate environment studies, have similarly suffered from inadequate power and poor design, including vague definitions of the effective environment. The spawn of candidate gene and candidate GxE studies have been many costly and futile follow-on studies, publication bias, and the propagation of false, if superficially plausible explanations of psychopathology (Duncan & Keller, 2011).[82]

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80. *See* Dick et al., *supra* note 23.

81. This Working Group was formed to advise the NIMH director on how best to proceed in recognition of the importance of genetics to the NIMH mission, the significant place of genetics in the NIMH research portfolio, and the challenges that earlier studies posed to robust scientific knowledge about the intersection of genes and behavior.

82. Nat'l Advisory Mental Health Council, *Report of the National Advisory Mental Health Council Workgroup on Genomics: Opportunities and Challenges of Psychiatric Genetics*, NAT'L INST. OF

Behavioral Genetics, the leading journal concerned with the genetic analysis of complex traits, published in cooperation with the Behavior Genetics Association, in 2012 issued an editorial critical of the candidate-gene method.[83] In that editorial, they noted that

> "[t]he literature on candidate gene associations is full of reports that have not stood up to rigorous replication. This is the case both for straightforward main effects and for candidate gene-by-environment interactions. As a result, the psychiatric and behavioral genetics literature has become confusing and it now seems likely that many of the published findings of the last decade are wrong or misleading and have not contributed to real advances in knowledge."[84]

The editorial went on to make recommendations a minimum requirement of direct replication of findings before any candidate-gene studies would again be published in the journal.[85]

This general scientific consensus has given way to more robust approaches to studying complex behavioral traits like violence, and those scientific approaches have not replicated the earlier *MAOA* findings.

III. THE CANDIDATE-GENE APPROACH FOR STUDYING PSYCHIATRIC TRAITS HAS GIVEN WAY TO BETTER POWERED GENOME-WIDE ASSOCAITION (GWAS) STUDIES, WHICH HAVE NO REPLICATED EARLIER *MAOA* FINDINGS

Candidate-gene studies have been superseded by more robust genome-wide association studies (GWAS) in psychiatric genetics.[86] GWAS are hypothesis-free studies, meaning they do not start with the belief that any particular gene is implicated in a behavior. Instead, hundreds of thousands to millions of genetic markers known as single nucleotide polymorphisms (SNPs) are genotyped across the genome in an attempt to identify common variants that are associated with a particular outcome (disorder, behavior, etc.).[87] These GWAS studies are consistently and reliably reproducible (the same genetic variants identified by GWAS in one sample are identified by GWAS in another sample), unlike the cGxE studies of the past.[88] By summing up identified risk alleles (variations in genes), researchers can calculate polygenic risk scores, which have demonstrated some reliable, although

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MENTAL HEALTH, https://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/report-of-the-national-advisory-mental-health-council-workgroup-on-genomics.shtml [https://perma.cc/53Y4-52P8] [hereinafter NIMH Report].

83. *See* John K. Hewitt, *Editorial Policy on Candidate Gene Association and Candidate Gene-by-Environment Interaction Studies of Complex Traits*, 42 BEHAV. GENETICS 1 (2012).

84. *Id.* at 1 (citations omitted).

85. *Id*.

86. *See* Dick et al., *supra* note 33.

87. *Id.* at 39.

88. *See* Duncan et. al., *supra* note 30, at 1519.

modest, predictions for complex genetic phenotypes. Analysis of polygenic risk score usage and performance in diverse human populations.[89]

Robust and repeatedly replicated results from GWAS studies cast serious doubt on earlier candidate-gene studies, particularly where widely studied genes like *MAOA* did not emerge as significantly correlated to aggression when studied genome wide.[90] Thus far, genome-wide association studies do not find a statistically significant interaction between males with low-activity *MAOA* and maltreatment, nor do they find any interaction between *MAOA* and stressful life events in relation to conduct problems in males or females.[91]

Genome-wide association studies (GWAS) have made it possible to assess the whole genome for associations with psychiatric disorders by assaying upwards of 500,000 variants simultaneously. This increased coverage means that, in contrast to candidate gene studies of the past, GWAS are able to take a hypothesis-free approach which does not require any a priori assumptions regarding the role of specific genes in a disorder. While initial GWAS were limited by inadequate sample sizes to detect variants of small effect at genome-wide significance, the formation of consortia and the pooling of data have made mega-analyses and meta-analyses possible, resulting in substantial progress in identifying replicable disorder-associated variants.[92]

Thus far, only a few genes have been identified in GWAS studies that may be of potential interest to the criminal justice system and none of those genes include *MAOA*. But there remains significant research to be done before that research may even be considered relevant for introduction in criminal justice cases.

CONCLUSION

MAOA candidate-gene studies purport to predict violent propensities in individuals. The *MAOA* studies cited by Mr. Yepez's experts are unreliable and the general scientific consensus has largely evolved beyond their underlying candidate-gene approach for studying complex behavioral traits like violence. Violence is a complex and difficult to characterize phenotype. Even if it could be consistently characterized, as a complex trait it would arise from many different interacting genetic and environmental factors that are not yet well understood in science. Newer studies that use genome-wide association techniques that overcome some of the

89. *See* L. Duncan et al., *Analysis of Polygenic Risk Score Usage and Performance in Diverse Human Populations*, 10 NATURE COMM. 3328 (2019).

90. *See id.*; *see also* Veronika V. Odintsova et al., *Genomics of Human Aggression: Current State of Genome-Wide Studies and an Automated Systematic Review Tool*, 29 PSYCHIATRIC GENETICS 170 (2019).

91. *See* I. Hyun Ruisch et. al., *Interplay Between Genome-Wide Implicated Genetic Variants and Environmental Factors Related to Childhood Antisocial Behavior in the UK ALSPAC Cohort*, 269 EUR. ARCHIVES OF PSYCHIATRY AND CLINICAL NEUROSCIENCE 741, 749 (2018); *see also* M-R Rautiainen et al., *Genome-Wide Association Study of Antisocial Personality Disorder*, 6 TRANSLATIONAL PSYCHIATRY e883 (2016); JE Salvatore et al., *Genome-Wide Association Data Suggest ABCB1 and Immune-Related Gene Sets May be Involved in Adult Antisocial Behavior*, 5 TRANSLATIONAL PSYCHIATRY e558 (2015); Jorim J. Tielbeek et al., *Unraveling the Genetic Etiology of Adult Antisocial Behavior: A Genome-Wide Association Study*, 7 PLOS ONE e45068 (2012).

92. Elham Assary et al., *Gene-Environment Interaction and Psychiatric Disorders: Review and Future Directions*, 77 SEMINARS IN CELL & DEV. BIOLOGY 133, 137 (2018).

identified flaws in earlier research techniques have not found a correlation between *MAOA* and violence. For the reasons set forth herein, *amici curiae* suggest that holding of the Court of Appeals was correct, but that its reasoning was erroneous, because the District Court's exclusion of expert testimony seeking to introduce a connection between Mr. Yepez's low *MAOA*, childhood maltreatment, and violence was not an abuse of its discretion and was a correct finding. The science relied upon by Mr. Yepez's experts is neither generally accepted nor reliable and therefore its exclusion at trial was not erroneous but required by *Alberico* and *Daubert*.

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