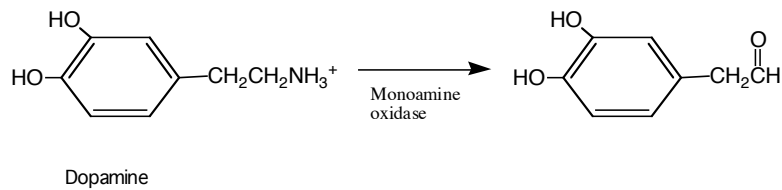
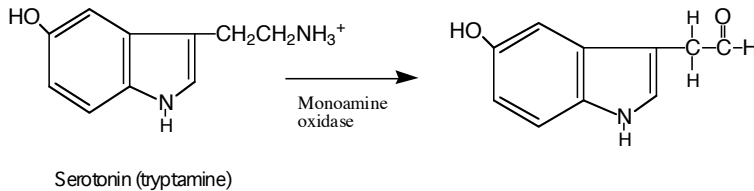


## Technical Background for the Science Paper on Monoamine Oxidase-A

### I. Background

Monoamine oxidase (MAO) is an enzyme that oxidizes a variety of amines, several of which have been identified as neurotransmitters (serotonin, norepinephrine, dopamine).



Serotonin falls in the category of indolamines, which seem to be involved in sleep, hunger and a variety of other processes. Dopamine and norepinephrine are members of the catecholamine family, compounds involved both as neurotransmitters in the central nervous system (CNS) and as agents that prepare the body for physical activity (flight or fight response)

Thus, MAO lowers the concentration of these compounds. Humans have two different forms of this enzyme, coded for by different genes. MAO-A works preferentially on serotonin and norepinephrine while MAO-B acts preferentially on dopamine and other benzylamines. The two enzymes are coded for by genes that lie close together on the X chromosome. You will recall that men have one X chromosome while women have two X chromosomes. Each male son gets one X from his mother and a Y chromosome from his father. If the mother has one X chromosome which carries a defective or altered gene, there is a 50% chance that she will pass that defect on to a son.

### II. MAO-A and Human Behavior

What is the evidence that the MAOs play a role in human behavior? Basically, three lines of evidence have been cited

1. Drugs that inhibit the action of monoamine oxidase are used to treat depression (and also high blood pressure!)
2. A nonsense mutation (destroys all enzyme activity) in MAO-A was reported in 1993 to be associated with mild mental retardation and with impulsive aggressive behavior in a single large family in the Netherlands (this is the only report of this association). Urine samples from affected males showed decreased levels of the degradation products of serotonin (5-HT) and dopamine (DA). However, Studies on prison inmates in Taiwan showed no evidence for altered monoamine metabolism.

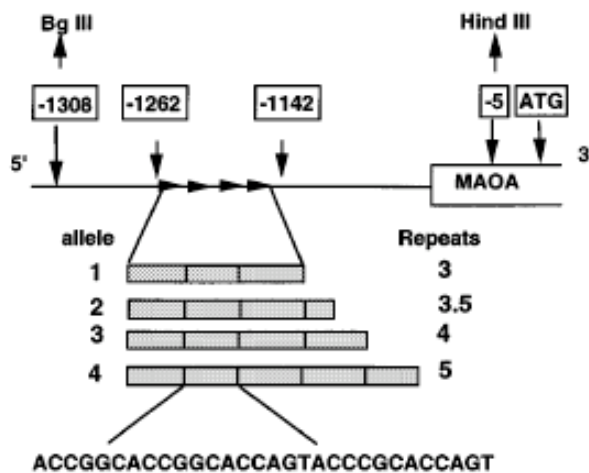
3. The strongest evidence for a link between monoamines and aggression come from studies on mice. Mice that have been genetically altered to have no MAO-A enzyme activity are reported to exhibit behavioral alterations as pups (trembling and difficulty in righting themselves) and increased aggression as adults (as assessed by observation of confrontations between resident and intruder mice). In addition, drugs that lower effective levels of monoamines (Ketanserine and TBZ) both diminish aggressive behavior of MAO-A deficient mice.

Many other studies have attempted to link alleles of the MAO-A gene in humans to various psychiatric disorders (bipolar disease, alcoholism, aggression, obsessive-compulsive disease). A review that I have read indicates that for every study that has shown a positive correlation there is another study that shows no correlation.

(my own critique of these studies: The Netherlands study is probably legitimate, but not all the affected males show similar behavior and it depends a lot of family reports which may not be accurate. Also, these individuals were totally MAO-A deficient, but normal humans show a wide range of MAO-A activity. It may be a stretch to conclude from the fact that MAO-A negative males show enhanced aggression that people with low levels of MAO-A would also show increased aggression. In addition, extensive use of MAO-A inhibitors (to treat people with depression) has never (as far as I know) been associated with an increase in impulsive aggression. Finally, the MAO-A “knock-out” mice show a variety of developmental changes in brain structure so that changes in adult behavior could be related to the drastic absence of this enzyme during development.

### III. Methodology

The Caspi paper focuses on males since males get only one copy of the MAO-A gene. Previous work has shown that the DNA just upstream (5') to the MAO-A gene contains a 30 base-pair repeat and that different individuals have different numbers of this 30 base pair sequence (this is called a “variable number tandem repeat polymorphism” or VNTR). The figure below is from the original Human Genetics paper that demonstrated this.



The key finding was that the number of repeats in this region differs from person to person and affects how active this gene is in coding for RNA and thus for the enzyme. In tissue culture cells, it was demonstrated that cells with 3.5 or 4 copies of the VNTR show a 2-10 fold higher transcription rate of the MAO-A gene than cells with either 3 or 5 (very rare) copies of the VNTR. When Caspi, et. al talk about MAO-A levels they are not actually measuring MAO-A enzyme activity in the brain, but they are determining the VNTR level in DNA and then assuming that the classification will apply (it is something of an extrapolation to assume that RNA levels in tissue culture will also predict protein levels in neurons – not a terrible assumption, but not an open-shut one either)

# Repeats in VNTR

- 3.5 high transcription rate of MAO-A gene
- 4.0 high transcription rate of MAO-A gene
- 3.0 low transcription rate
- 5.0 low transcription rate