#ret #incomplete

---

1 | SNP. Project. Write-up.

Resources: [[KBxSNPPCR]] Instructions

1.0.1 | Init Planning

Outline

- basics
- function and regulation
- SNP effect

Writing!

1.0.2 | Part One!

The *COMT* gene, or catechol-O-methyltransferase, encodes the *COMT* enzyme which is responsible for breaking down neurotransmitters the brain's prefrontal cortex. More specifically, it acts as a catalyst for the transfer of a methyl group from S-adenosylmethionine to dopamine, epinephrine, and norepinephrine. This process, called O-methylation, leads to the degradation of the aforementioned neurotransmitters. The *COMT* enzyme also effects the metabolism of exogenous substances, but that is irrelevant for the mutation at hand citation. The *COMT* gene itself is 27.22kb long and located on chromosome 22q11.2 citation. It has ubiquitous expression in 27 tissues, including the placenta, the adrenal, and the lung citation. Val158Met, also known as rs4680, is a common missense mutation swapping a guanine for an adenine. It has the frequency G=0.510915, and thus, A=0.489085. Val158Met causes the *COMT* enzyme to be roughly 25% as effective compared to the wild type. Expression levels in mRNA, despite its reduced protein abundance, are not effected by Val158Met citation & citation. Thus, Val158Met must be located in a protein-coding region causing the *COMT* enzyme to have lower protein integrity, explaining the discrepancy between mRNA expression and protein expression. This lower protein integrity is most likely manifested as diminished thermostability of the enzyme citation. The higher level effect of this reduced enzyme efficacy is greatly debated, and linked to many different phenotypes. At a broad level, lower *COMT* activity leads to higher levels of catecholamines in the prefrontal cortex. The actual effect of these increased levels are not well understood. One proposed theory is the Warrior versus Worrier hypothesis, which outlines two groups of personality traits based upon the Val158Met mutation citation. The "Warrior" group, defined as the wild type group with lower levels of catecholamines like dopamine, are said to have an advantage in processing aversive stimuli. They are also said to have higher pain tolerance, be less prone to stress, less exploratory, and ect. However, many of these claims are not well defined and bordering on pseudoscience citation. The "Worrier" group, those with the mutation, are said to have an advantage in memory and attention tasks citation. The Val158Met mutation has also been linked to schizophrenia, but this claim is debated citation.

Citations: *(order of appearance)*

- NCBI COMT catechol-O-methyltransferase *Homo sapiens* (human)
- Chromosomal mapping of the human catechol-O-methyltransferase gene to 22q11.1——-q11.2
- Gene Expression – NCBI COMT catechol-O-methyltransferase *Homo sapiens* (human)
- Lack of Association between rs4680 Polymorphism in Catechol-O-Methyltransferase Gene and Alcohol Use Disorder: A Meta-Analysis
- Functional Analysis of Genetic Variation in Catechol-O-Methyltransferase (COMT): Effects on mRNA, Protein, and Enzyme Activity in Postmortem Human Brain
- Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme
- Warriors versus worriers: the role of COMT gene variants
- Self Decode rs4680
- The effect of rs1076560 (DRD2) and rs4680 (COMT) on tardive dyskinesia and cognition in schizophrenia subjects

1.0.3 | Feedback and revisions

This is looking good so far. It is based in solid research and you're clear about what's still unknown

The *COMT* gene, or catechol-O-methyltransferase, encodes the *COMT* enzyme which is responsible for breaking down neurotransmitters the brain's prefrontal cortex. More specifically, it acts as a catalyst for the transfer of a methyl group from S-adenosylmethionine to dopamine, epinephrine, and norepinephrine. This process, called O-methylation, leads to the degradation of the aforementioned neurotransmitters. The *COMT* enzyme also effects the metabolism of exogenous substances, but that is irrelevant for the mutation at hand citation. The *COMT* gene itself is 27.22kb long and located on chromosome 22q11.2 citation. It has ubiquitous expression in 27 tissues, including the placenta, the adrenal, and the lung citation. This expression is dynamically regulated during brain development and due to environmental stimuli. Despite much research into COMT regulation, the actual processes are still mostly unknown citation. COMT has two promoters —— P2 functions constitutively, whereas P1 has tissue dependent regulation. This tissue specific regulation is most likely done by C/EBPalpha. citation. Val158Met, also known as rs4680, is a common missense mutation swapping a guanine for an adenine. It has the frequency G=0.510915, and thus, A=0.489085. Val158Met causes the *COMT* enzyme to be roughly 25% as effective compared to the wild type. Expression levels in mRNA, despite its reduced protein abundance, are not effected by Val158Met citation & citation. Thus, Val158Met must be located in a protein-coding region causing the *COMT* enzyme to have lower protein integrity, explaining the discrepancy between mRNA expression and protein expression. This lower protein integrity is most likely manifested as diminished thermostability of the enzyme, in turn leading to its reduced effectiveness citation. The higher level effect of this reduced enzyme efficacy is greatly debated, and linked to many different phenotypes. At a broad level, lower *COMT* activity leads to higher levels of catecholamines in the prefrontal cortex. The actual effect of these increased levels are not well understood. One proposed theory is the Warrior versus Worrier hypothesis, which outlines two groups of personality traits based upon the Val158Met mutation citation. The "Warrior" group, defined as the wild type group with lower levels of catecholamines like dopamine, are said to have an advantage in processing aversive stimuli. They are also said to have higher pain tolerance, be less prone to stress, less exploratory, and ect. However, many of these claims are not well defined and bordering on pseudoscience citation. The "Worrier" group, those with the mutation, are said to have an advantage in memory and attention tasks citation. The Val158Met mutation has also been linked to schizophrenia, but this claim is debated citation.

Citations: *(order of appearance)*

- NCBI COMT catechol-O-methyltransferase *Homo sapiens* (human)
- Chromosomal mapping of the human catechol-O-methyltransferase gene to 22q11.1——-q11.2
- Gene Expression – NCBI COMT catechol-O-methyltransferase *Homo sapiens* (human)
- The Catechol-*O*-Methyltransferase Gene: Its Regulation and Polymorphisms
- Characterization of the rat catechol-O-methyltransferase gene proximal promoter: identification of a nuclear protein-DNA interaction that contributes to the tissue-specific regulation
- Lack of Association between rs4680 Polymorphism in Catechol-O-Methyltransferase Gene and Alcohol Use Disorder: A Meta-Analysis
- Functional Analysis of Genetic Variation in Catechol-O-Methyltransferase (COMT): Effects on mRNA, Protein, and Enzyme Activity in Postmortem Human Brain
- Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme
- Warriors versus worriers: the role of COMT gene variants
- Self Decode rs4680
- The effect of rs1076560 (DRD2) and rs4680 (COMT) on tardive dyskinesia and cognition in schizophrenia subjects

1.0.4 | Part Two!

infographic time.

- **Create an infographic that diagrams the various connections between the gene/SNP genotypic variants and the known phenotypic associations. This graphic should visually show the biological effects of the gene/protein and studied genotypes on human traits/phenotypes. It is also important to highlight the ways in which the environment affects gene expression, protein function and/or phenotype (see the example infographic for APOE below, which makes connections to diet and traumatic brain injury). You can choose to visually organize and/or lay out your graphic in a variety of formats, but make sure that the following information is included:**
- info to include
  - **gene basics**
    - Gene info (gene size, location of SNP, SNP variants, SNP frequency)
    - Protein info (protein size, protein variants if known)
    - reg
      - estrogen?
      - brain develpoment
      - eviromental
      - P2:
        - constitutively
      - P1:
        - tissue dependent, C/EBPalpha, ect.
  - **SNP variants to human phenotype relationships**
    - reduced COMT enzyme activity
    - warrior worrier stuff
  - **Gene-environment Interactions**
    - above → situations that better suite?
    - gene / enviroment stuff? https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3447184/

1.0.5 | **Part *Three*.**

outlinin: prompt: In this section, you should try to provide some evolutionary insight on the SNP alleles that we see for your gene in the human population. You may focus on one particular allele if you see that it is better-researched. Using actual research into the evolution of the allele(s) and/or research about gene and gene variant functions, explain why/how the SNP allele(s) you studied were maintained in the human population (in over 1% of people studied). At some point the allele first appeared as a mutation but it subsequently spread into a relatively large proportion of people; why might that have been? - Although this section should be based on gene/SNP research and your understanding of evolution, your explanations may be somewhat speculative due to the difficulty in obtaining evidence for certain evolutionary predictions/hypotheses (because environmental pressures, migrations, and random events that influenced evolution likely happened long ago). That is okay; just show us that you're using research-backed reasoning about your allele(s) and that you have an understanding of evolutionary mechanisms. - In terms of evolutionary mechanisms, you should be thinking about possible selective pressures that may have maintained certain alleles in the human population (and disfavored others). Note that evolution typically operates over long timescales, so the selective pressures that are most likely to have played a role were operating before civilizations, agriculture, etc (with some exceptions that may have evolved more "recently", like lactase persistence, high-altitude adaptation, and disease resistances). - It's also important to remember the possible contributions of mechanisms like gene flow and genetic drift in getting to the allele frequencies that we see today. It would be harder to detect whether/when these happened without complex analyses of sequences, but you can still acknowledge their possible impact and explain how these mechanisms operate.

allele: g → a

selection factors:

population makes it's own selection factors need for warrior / worrier

organism, gene, population

greedy epsilon, worrier as epsilon

evolution on multiple levels like genetic, epigenetic, symbolic, cultural, ect

fitness landscapes of organisms but also of tech

worriers are better for jumping out of local minima warriors are better for carrying out the best strategy

perhaps a collection of personality-ish traits that are all being balanced

research:

> A comparison of human and mouse COMT confirms that the amino acid at the Val/Met locus is important for COMT activity and suggests that COMT activity has decreased during the course of evolution. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1182110/

derived allele uniqe to humans

https://www.jstage.jst.go.jp/article/ase/121/3/121_130731/_html/-char/en

We write. Not much is known about the evolution of the COMT*L allele. In the sea of speculation, only two facts emerged: COMT activity has decreased during the course of recent evolution, and COMT*L is a derived allele unique to humans citation & citation. For the following speculation, the phenotypes said to arise from different variations of the COMT gene will be assumed true. Speculating about evolution on the organism level

is relatively straightforward: this organism evolved a patch of photosensitive skin so it could tell which way was up. This level of analysis breaks down when trying to explain altruism, and thus comes speculation on the gene level: