

CHS and Genetic Susceptibility

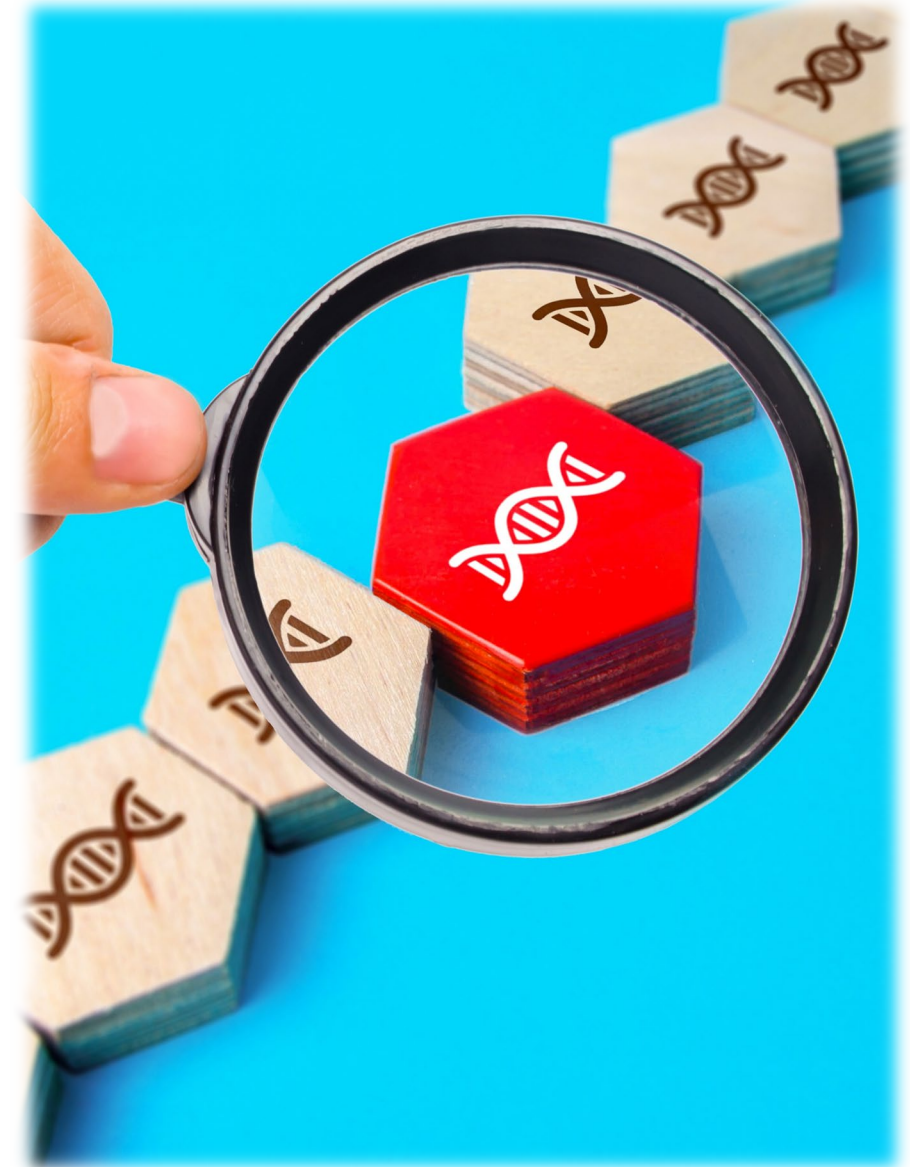


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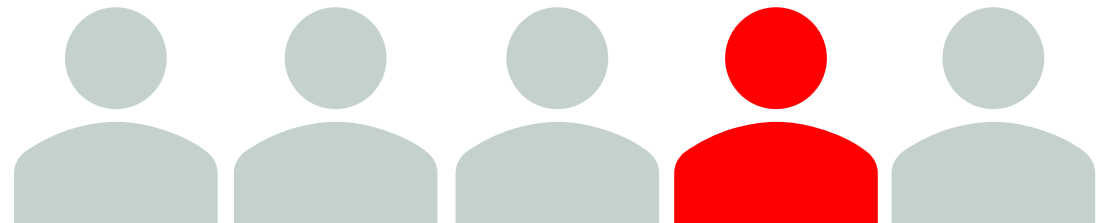
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No Conflicts of Interest



Who Becomes Susceptible to CHS?

- Cannabis exposure is necessary for CHS:
 - Dysregulated endocannabinoid system along the gut-brain axis
 - Stress response easier to switch on and harder to switch off
- But...**Not Sufficient!**
- So why this person, and not the person beside them?
 - Age?
 - Genetics?



First Study of CHS Genetics

- 2022, Cannabis and Cannabinoid Research
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Cannabinoid Hyperemesis Syndrome Survey and Genomic Investigation

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Abstract

Background: Cannabinoid hyperemesis syndrome (CHS) is a diagnosis of exclusion with intractable nausea, cyclic vomiting, abdominal pain, and hot bathing behavior associated with ongoing tetrahydrocannabinol (THC) exposure. Increasing cannabis use may elevate CHS prevalence, exacerbating a public health issue with attendant costs and morbidity.

Objective, Design, and Data Source: This study, the largest contemporaneous database, investigated genetic mutations underlying CHS. Patients with CHS diagnosis and ongoing symptoms were compared with current cannabis users lacking symptoms.

Target Population: A screening questionnaire was posted online. Of 585 respondents, 205 qualified as the CHS pool and 54 as controls; a reduced pool of 28 patients and 12 controls ultimately completed genomic testing.

Results: Patients and controls were high-frequency users of cannabis flower or concentrates (93%), using multiple grams/day of THC-predominant material. Among patients, 15.6% carried diagnoses of cannabis dependency or addiction, and 56.6% experienced withdrawal symptoms. About 87.7% of patients improved after cannabis cessation, most suffering recurrence rapidly after resumption. Findings in patients included mutations in genes *COMT* (odds ratio, 12 [95% confidence limit [CL], 1.3–88.1] $p=0.012$), transient receptor potential vanilloid receptor 1 (*TRPV1*) (odds ratio, 5.8 [95% CL, 1.2–28.4] $p=0.015$), *CYP2C9* (odds ratio, 7.8 [95% CL, 1.1–70.1] $p=0.043$), gene coding dopamine-2 receptor (*DRD2*) (odds ratio, 6.2 [95% CL, 1.1–34.7] $p=0.031$), and ATP-binding cassette transporter gene (*ABCA1*) (odds ratio, 8.4 [95% CL, 1.5–48.1] $p=0.012$).

Limitations: Some participants were reluctant to undergo genetic testing; only 28 of 99 CHS patients who agreed to testing ultimately returned a kit.

Conclusion: This is the largest patient cohort of CHS examined to date, and first to note associated mutations in genes affecting neurotransmitters, the endocannabinoid system, and the cytochrome P450 complex associated with cannabinoid metabolism. Although the sample size was smaller than desired, these preliminary findings may contribute to the growing body of knowledge, stimulate additional investigation, help elucidate the pathophysiology of CHS, and, ultimately, direct future treatment.

Keywords: cannabinoid hyperemesis syndrome; cannabinoids; tetrahydrocannabinol; cannabis; nausea; vomiting; abdominal pain; substance abuse; genomics

Table 3 Proposed pathophysiologic mechanisms for CHS

Mechanism	GRADE rating
The emetogenic and anti-emetic effects of $\Delta 9$ -THC and its analogs are mediated through CB-1 receptors (CB1r) and thus underlie the syndrome of CHS [106, 135]	Very low
Cannabinoids may bind to CB-1 receptors in the gastrointestinal tract and decrease GI motility and gastric emptying, which may override brainstem-mediated antiemetic effects and precipitate hyperemesis [9, 92, 95, 132]	Very low
Chronic cannabis use may lead to paradoxical and plastic changes in expression and downstream effects of cannabinoid receptors [133]	Very low
Chronic cannabis use leads to desensitization and downregulation of CB1 receptors that ordinarily have peripheral antiemetic effects, causing rebound vomiting and spasmodic pain that abates with abstinence and corresponding recovery of CB-1 receptor activity [98, 136, 185]	Very low
In chronic cannabis users, cannabinoid metabolites may accumulate in the brain and fatty tissues inducing a toxic effect [90, 94]	Very low
CHS may be caused by a non-THC, cannabinoid-like structure within <i>Cannabis sativa</i> , such as cannabidiol [96, 186]	Very low
Patients susceptible to developing CHS may have genetic variation in their metabolic enzymes resulting in toxic levels of cannabinoid metabolites [131]	Very low
$\Delta 9$ -THC may act as a partial agonist on CB1 receptors and thus relatively antagonize the effects of full endogenous agonists on these receptors, thus precipitating sudden withdrawal and hyperemesis in sensitive patients [97, 105]	Very low
THC causes dilation of splanchnic vasculature, resulting in CHS. Hot bathing leads to peripheral venodilation and shunts blood away from the splanchnic bed, resulting in symptom improvement [102, 137]	Very low



Sorensen CJ, et al. 2017. Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment-a Systematic Review. J Medical Toxicology

De Vuono MV, Parker LA. 2020. Cannabinoid Hyperemesis Syndrome: A Review of Potential Mechanisms. Cannabis Cannabinoid Res

- Biphasic nausea and vomiting response to THC
 - Endocannabinoid dysregulation
 - Activation of the stress axis (hypothalamic-pituitary-adrenal axis, autonomic nervous system)
 - Genetic predisposition - untested in 2020
- *Pesticides and neem are not substantiated causes

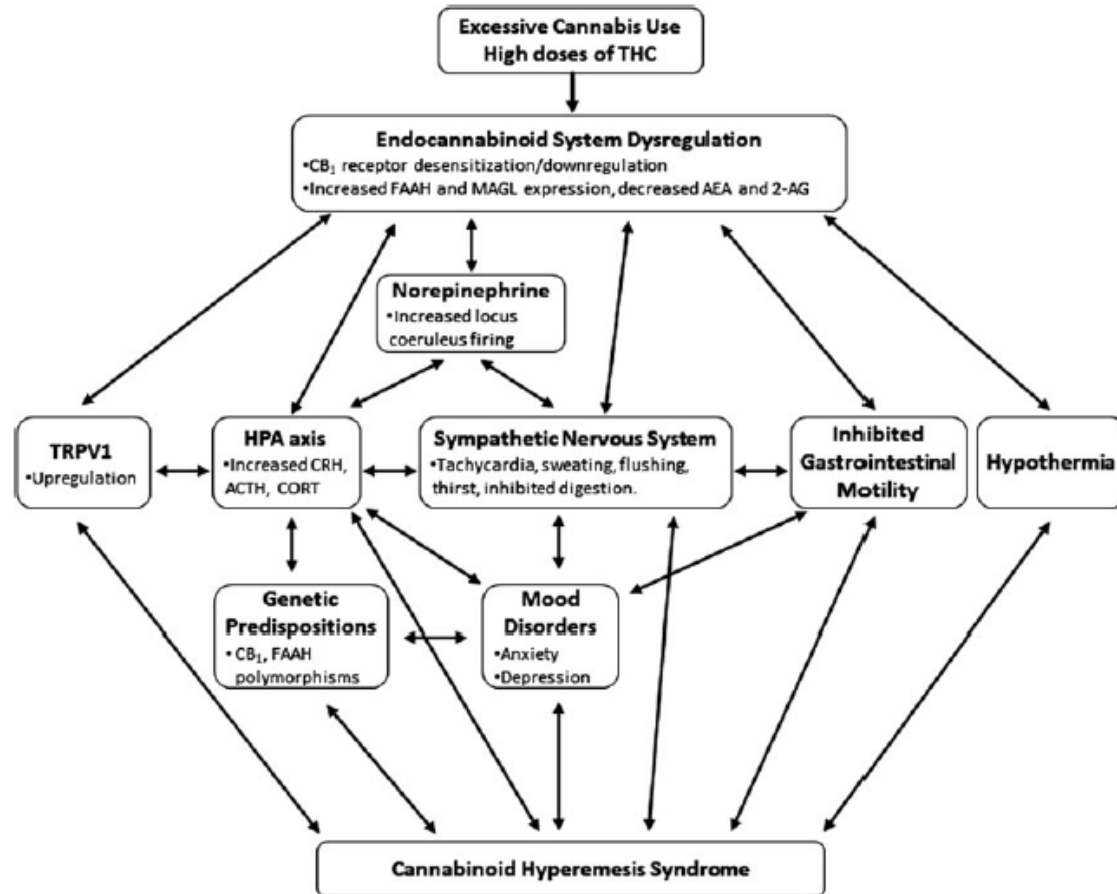
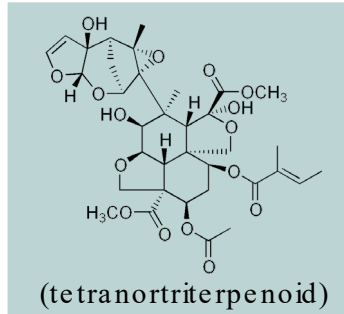


FIG. 1. Schematic representation of factors that may contribute to CHS. CHS, cannabinoid hyperemesis syndrome.

Myth Busting CHS: What Does Not Cause CHS

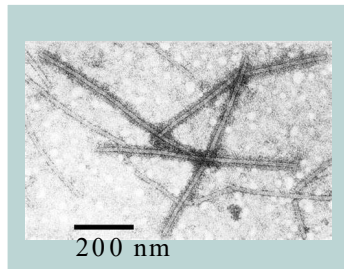


Pesticides



Neem Oil

Azadirachtin



Hop Latent Viroid

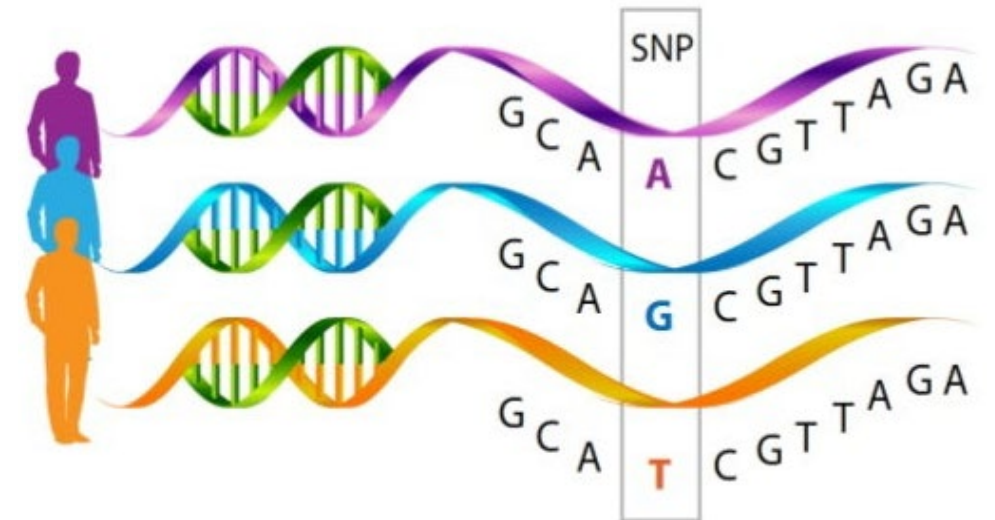
- **None** fit the symptomatology of CHS
- No compulsive hot bathing
- Neem oil B.P. 792°C, safe daily intake 17mg for an avg. adult
- No plant virus ever documented to infect a human
- Synthetic cannabinoids have no pesticides and cause CHS anyway

CHS and Genetic Susceptibility: Hypotheses

- Genetic predispositions are already described for:
 - Cyclic vomiting syndrome
 - Mood disorders
 - Substance use disorders
 - Individual differences in drug metabolism
- Single Nucleotide Polymorphism (SNP): one-letter difference in genetic code

Predicted Genes of Interest:

- CNR1, the gene for the CB1 receptor
- TRPV1, the heat and pain channel
- Enzymes that break down THC



Who Was Studied

585 Respondents completed the Screening Questionnaire



CHS patients

205 qualified: Physician diagnosis,
ongoing symptoms

99 agreed to genomic testing

28 kits returned



Controls

54 qualified: regular heavy use, never
diagnosed, no symptoms

12 kits returned

Who Was Studied

	CHS Patients (205)	Controls (54)
Age	mean 33.8	mean 43.8
Sex	54% female	60% female
Daily use or greater	91%	70%
Amount used per day	~4g/day	-
Diagnosis of cannabis dependency	15.6%	3.7%
Cannabis withdrawal	56.6%	24%
Diagnosis Cyclic Vomiting Syndrome	38.3%	0%*
Abdominal Pain	89.3%	0%*
Nausea and Vomiting	82.1%	0%*
Hospitalized for it	75%	0%*
Symptoms improve with cessation	87.7%	0%*

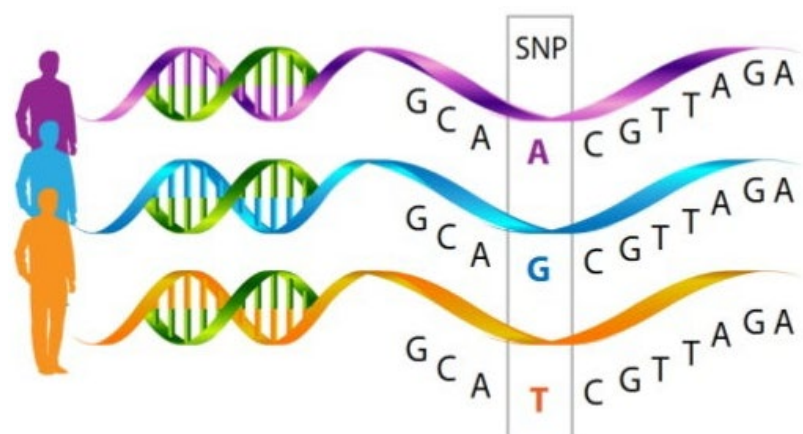
*Exclusion criteria for controls

Methods - Genotyping

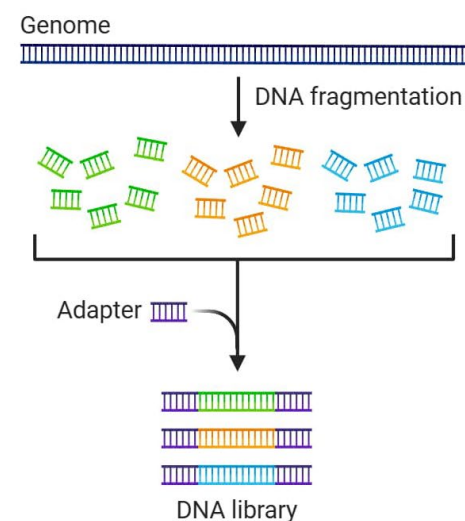
A SNP genotyping array

Illumina Infinium HTS, on BeadChips

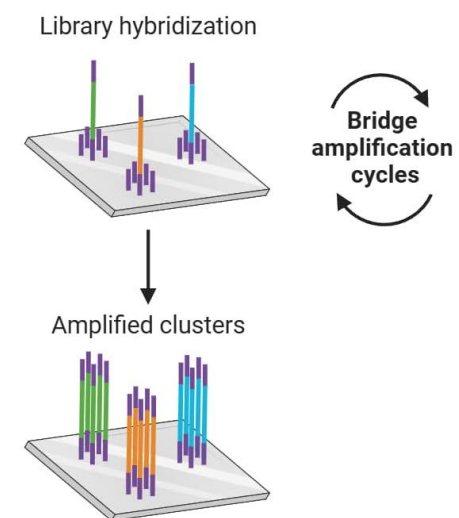
Variants judged likely to affect CHS were used as the base to find what the patients had in common



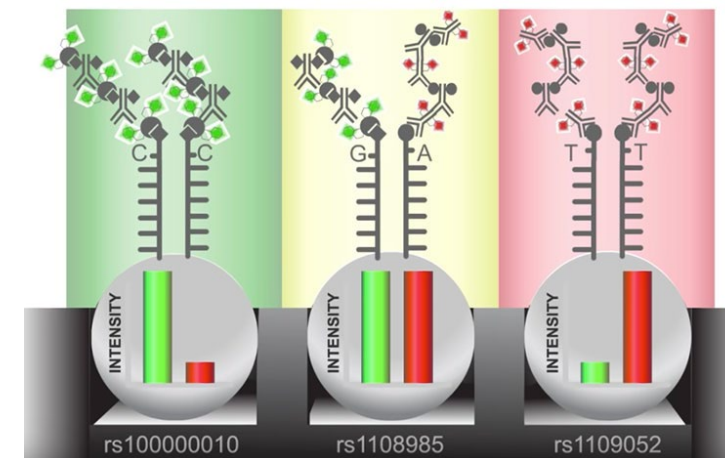
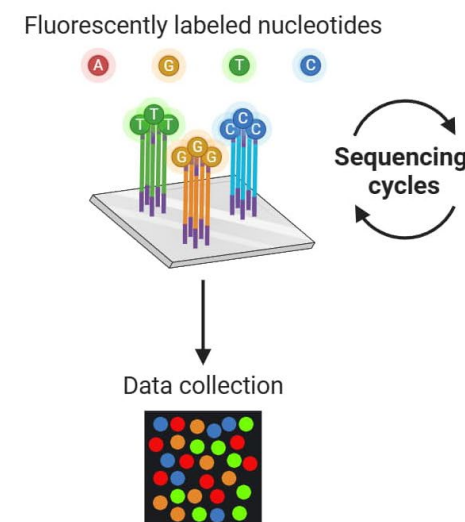
① Library preparation



② DNA library bridge amplification



③ DNA library sequencing



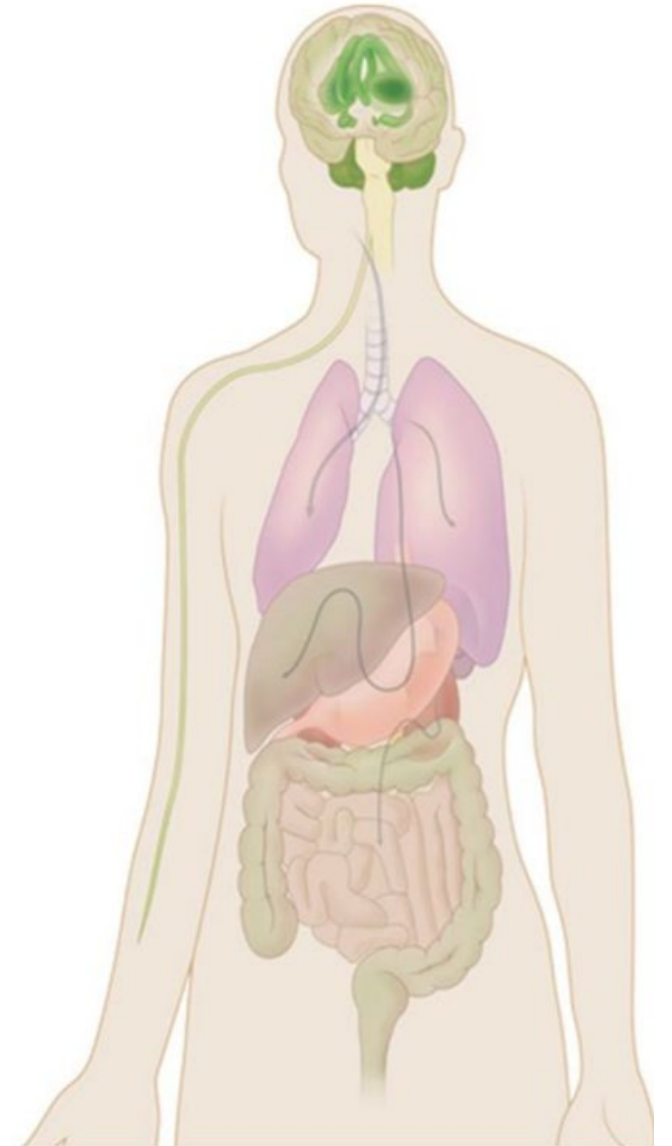
The SNP Variants

Gene	What it does	Controls	CHS	Odds ratio (95% CI)	p
COMT	Clears dopamine	10%	57%	12.0 (1.3-88.1)	0.012**
ABCA1	Moves cholesterol and lipids	20%	68%	8.4 (1.5-48.1)	0.012**
CYP2C9	Breaks down THC	10%	46%	7.8 (1.1-70.1)	0.043*(†0.011)
DRD2	Dopamine D2 receptor	20%	61%	6.2 (1.1-34.7)	0.031*
TRPV1	Heat and pain channel	30%	72%	5.8 (1.2-28.4)	0.015**
CYP2C19	Accessory THC breakdown	20%	54%	4.6 (0.8-25.7)	0.069(†0.007)

† CYP2C19 reaches $p = 0.007$, and CYP2C9 $p = 0.011$, when patients on proton pump inhibitors are excluded.

CNR1: The CB1 Receptor Gene

- Not significant in CHS
- Variants here have been linked to cannabis use patterns (Hryhorowicz, 2018)
- CNR1 variants are associated with cyclic vomiting syndrome (CVS)
 - rs806380 AG and GG: increased risk of CVS ($p < 0.01$)
 - rs806368 CC, and mu-opioid receptor OPRM1 rs1799971: decreased risk
- Wasilewski et al., 2017

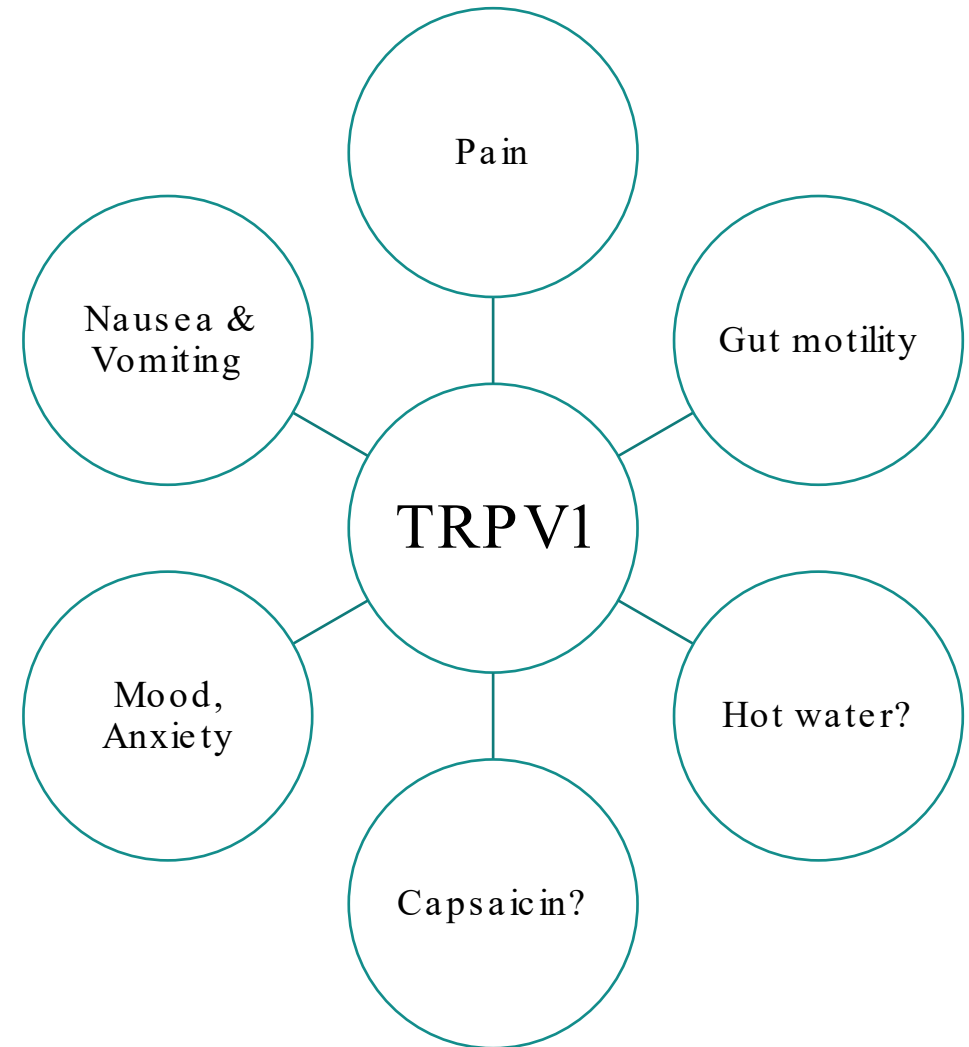


COMT: Catechol-o-methyl transferase

- COMT mutation rs4646316 on introns in 57% of CHS patients vs. 10% of controls ($p=0.012^{**}$)
- Odds ratio = 12 (95% CI, 1.3-88.1)
- COMT clears catecholamines, (i.e. Dopamine and Norepinephrine)
- Loss of function → dopamine build up
 - Associated with compulsive behaviours
- The same variant linked to:
 - Depression, and rumination (Nyman 2011; Pap 2021)
 - Heavy alcohol use starting younger, in women (Stadlin, 2014)
- Other variants linked to:
 - impulsivity, attention deficit hyperactivity disorder, anxiety, psychosis (Pap 2021)
 - susceptibility to cognitive effects of cannabis (Henquet, 2006)

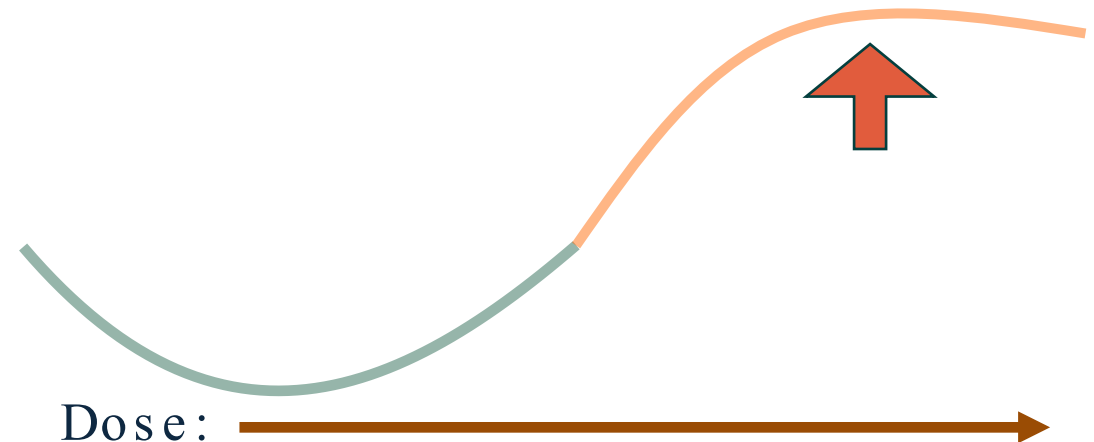
TRPV1: The Heat and Pain Channel

- A TRPV1 downstream mutation, rs879207, in 71.5% of CHS patients vs. 30% in controls (p=0.015**)
- Odds ratio = 5.8 (95% CI, 1.2-28.4)
- Specific mutation is not previously listed in NLM database



CYP2C9: A Drug Metabolizing Enzyme

- CYP2C9 homozygous intron mutation rs1934967 in 46.4% of CHS patients vs. 10% of controls ($p = 0.043^*$)
- Odds Ratio = 7.8 (95% CI, 1.1-70.1)
- CYP2C9 enzyme breaks down:
 - Various drugs
 - Arachidonic acid (endocannabinoid precursor)
 - THC, and 11-OH-THC
- Loss of function → Slower THC clearance, accumulation of THC and metabolites
- A dual mutation in CYP2C9 and CYP2C19 has been reported in a CHS patient case study (Kuzin, 2021)



DRD2: The Dopamine D2 Receptor

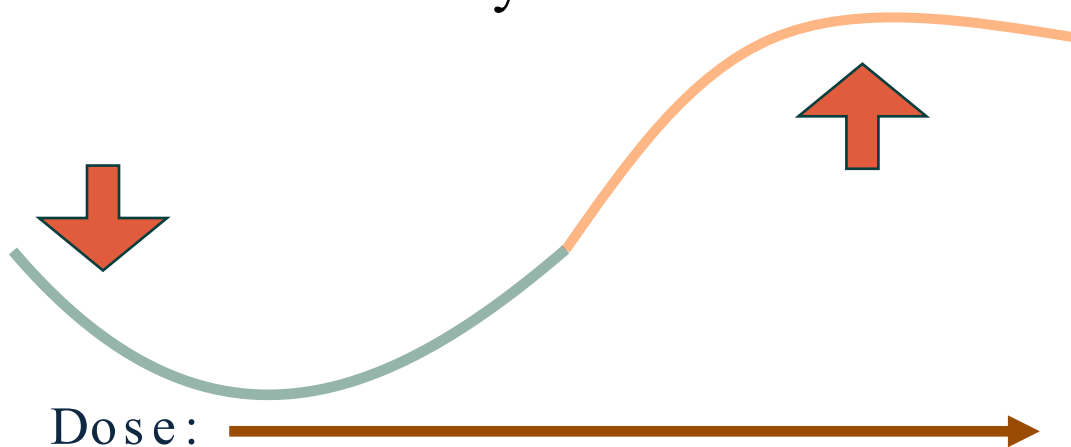
- DRD2 intron mutations, rs4648318 in 61% of CHS patients and 20% of controls (p=0.031*)
- Odds ratio: 6.2 (95% CI, 1.1-34.7)
- Target of many antipsychotic drugs (i.e. haloperidol)
- D2 stimulation is pro-emetic and slows gut motility (Belkacemi 2020)
- This mutation is linked to:
 - depression and anxiety (Nyman, 2011)
- Adolescent THC exposure leads to long term hyperdopaminergia (Renard et al 2017, De Vуono et al 2026)
- DRD2 + COMT mutation = double hit on dopamine

ABCA1: ATP-binding Cassette Transporter

- ABCA1 homozygous mutation, rs2230806, in synonymous areas in 68% of CHS patients vs. 20% of controls (p=0.012**)
- Odds Ratio= 8.4 (95% CI, 1.5-48.1)
- Controls cholesterol and phospholipid transport
- ABCA1 variants also linked to:
 - Dementia risk (ApoE and Amyloid β accumulation) (Feher, 2018)
 - Coronary disease
 - Type 2 diabetes

Conclusions

- Five variants with plausible biological links to CHS
- Potential screening test
 - Median cost before diagnosis ~\$95,000 per patient
Perrotta et al. 2012
- Genetic variants overlap with N&V, stress and endocannabinoid system



Cannabinoid Hyperemesis Syndrome can be thought of, not as a “functional” gastrointestinal disorder, but rather as a manifestation of gene-environment interaction unmasked by a toxic reaction to excessive THC exposure.

- Russo et al. 2022



Thank you!