CPIC Guideline Proposal: *BCHE* and Succinylcholine

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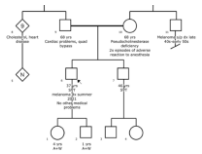
Clinical Cases

- **Genetics e-Consult:** 35-year-old pregnant woman with recent **reproductive carrier screening results** in need of interpretation by the Pharmacogenomics Clinic team:

Disease	Summary	Result	Interpretation
PSEUDOCHOLINESTERASE DEFICIENCY	POSITIVE	BCHE: c.435delinsAG (p.F146Vfs*12)	This individual is a heterozygous carrier for the pathogenic c.435delinsAG (p.F146Vfs*12) variant in the BCHE gene, which is associated with Pseudocholinesterase deficiency. Reproductive risk for Pseudocholinesterase deficiency is dependent on the partner's genetic status, therefore testing of the partner is recommended. Genetic counseling is recommended.

- **Pharmacogenomics Clinic Referral:** 37-year-old male whose **mother woke up from anesthesia with full body paralysis following succinylcholine administration**. Patient advised to do genetic testing to assess his risk to prevent a similar reaction from happening to him in the future.



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REVIEW

Hereditary Pseudocholinesterase Deficiency and Succinylcholine: Historical Perspective, Therapeutic Implications, and Future Considerations

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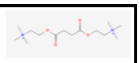
Pseudocholinesterase

- Pseudocholinesterase = plasma cholinesterase = serum cholinesterase = **butyrylcholinesterase**
  - Encoded by the ***BCHE*** gene
  - Physiological functions and biological significance not fully elucidated
- **Pseudocholinesterase deficiency** – not associated with disease, but has PGx implications

ACQUIRED	Caused by non-genetic factors (phenoconversion) – e.g., malnutrition, advanced age, malignancy, liver or kidney disease, pregnancy, burns, organophosphate poisoning, certain medications
INHERITED	Caused by genetic variation – *quantitative variants* (low enzyme levels) vs. *qualitative variants* (dysfunctional enzyme)

Succinylcholine (SUX)



- **Drug class:** Depolarizing **neuromuscular blocking agent**
- **Duration of action:** Normal muscle function restored about 10 min. after discontinuation (in patients with normal pseudocholinesterase enzyme activity)
- **Indications:** Adjunct to general anesthesia to facilitate endotracheal intubation or electroconvulsive therapy, provide skeletal muscle relaxation during surgery or mechanical ventilation
- **Adequate patient sedation is critical** before and during use to prevent patient distress

Historical Perspective

Werner Kalow, MD (1917-2008)

- Dr. Kalow is considered a "founding father" of pharmacogenomics
- One of the first to attribute differences in pseudocholinesterase enzyme activity between individuals to inherited variation (1950s)
- Developed a biochemical assay to distinguish variant forms of the enzyme, which is still in use today: **Dibucaine Inhibition Test**
  - >70% inhibition: predicted normal activity
  - 30-70% inhibition: predicted heterozygote
  - 0-30% inhibition: predicted homozygote

Pharmacogenetics and Genomics. 2008;18(10):835-836.

The Danish Cholinesterase Research Unit

- **Established in 1973** in Copenhagen, Denmark
- Primary aims (as described in their first paper in 1977):
  1. "To provide a central service for determining genotypes and activity of serum cholinesterase;
  2. To offer relatives of patients with abnormal serum cholinesterase the possibility of being investigated;
  3. To issue warning cards to all patients 'at risk' of showing prolonged apnoea after suxamethonium;
  4. To demonstrate a possible correlation between serum cholinesterase activity and genotype and the duration of apnoea after suxamethonium;
  5. To investigate the type of neuromuscular block after suxamethonium in patients with abnormal serum cholinesterase;
  6. To evaluate methods of treatment once apnoea occurs."
- Still active – most recent publication in 2024
- >4000 patients have been referred to the DCRU since inception

Acta Anaesthesiol Scand. 1977;21(5):405-12.

>75 *BCHE* variants identified to date

NORMAL

QUALITATIVE VARIANTS — Cause impaired enzyme *function*

QUANTITATIVE VARIANTS — Cause lower enzyme *levels*

BCHE nomenclature

TABLE 1 | Characteristics of commonly described *BCHE* variants.

Variant name	rsID[a]	Nucleotide change[a]	Amino acid change[a]	Impact on pseudocholinesterase
U	n/a	No change	No change	Normal enzyme activity and plasma concentration
A	rs1799807	c.293A>G	p.Asp98Gly	Reduced enzyme function; dibucaine resistant
F-1	rs28933389	c.812C>T	p.Thr271Met	Reduced enzyme function; fluoride resistant
F-2	rs28933390	c.1253G>T	p.Gly418Val	Reduced enzyme function; fluoride resistant
H	rs527843566	c.508G>A	p.Val170Met	~90% reduced plasma concentration of enzyme
J	rs121918556	c.1574A>T	p.Glu525Val	~66% reduced plasma concentration of enzyme
K	rs1803274	c.1699G>A	p.Ala567Thr	~33% reduced plasma concentration of enzyme
S[b]	rs104893684	c.1004T>C	p.Leu335Pro	No, or very little, detectable enzyme activity

[a]Variant information from ClinVar [31].
[b]There have been numerous silent variants described to date. The one presented in the table is an example found in the Vysya population of India.

Testing for Pseudocholinesterase Deficiency: Biochemical vs. Genetic Testing

Biochemical Testing

+ Current standard of practice (DN, enzyme level)
+ Captures acquired factors/phenoconversion

- Difficult to differentiate inherited vs. acquired
- Normal enzyme level ≠ Normal enzyme activity
  - Qualitative variants
- Normal dibucaine number ≠ Normal enzyme activity
  - Quantitative variants
- Lack of assay standardization
- Sensitive to methodology, such as sample storage, timing of sample, etc.

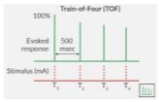
Genetic Testing

+ Evaluate inheritance risk, cascade testing
+ Differentiate inherited vs. acquired
+ Sequencing can identify novel variants

- Genotyping may miss clinically relevant variants
- Sequencing may identify variants of unknown significance (VUS)
- Requires interpretation in a clinical context due to potential acquired factors (phenoconversion)

Clinical Measurements and Outcomes

- Prolonged neuromuscular blockade (minutes → hours)
  - Apnea
  - Paralysis
  - Psychological consequences
- Train of Four (TOF)
  - Monitoring for nerve block
    - T4/T1 Ratio > 90% goal



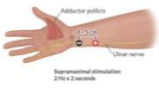


Image obtained from: https://www.apoanesthesia.com

Literature Review Methodology

PubMed Search (1966 to November 2024) for the keywords([pseudocholinesterase OR butyrylcholinesterase OR cholinesterase OR BCHE] AND **[succinylcholine OR suxamethonium]**) and limited to the English language (n=820)

↓

Publications with ***BCHE* genetic testing** and associated specific variants with prolonged neuromuscular blockade after **succinylcholine** administration (n=28)

↓

Of these included 28 papers:
- 9 (32%) were from The Danish Cholinesterase Research Unit
- 15 (54%) were case reports and case series

Literature Common Themes

- *BCHE* genetic variants were consistently associated with prolonged duration of neuromuscular blockade with succinylcholine
- Crucial role of genotyping with or without additional genetic sequencing to complement biochemical testing
- Confounding factors influenced biochemical results (e.g., sample collection, storage conditions)
- "A" and "K" variants were the most common and could occur as individuals or in LD as "AK"

BCHE Variants Identified

- **Heterozygous**
  - K/WT (n=96)
  - AK/WT (n=74)
  - A/WT (n=7)
  - S/WT (n=2)
- **Compound heterozygous**
  - AK/K (n=19)
  - AK/A (n=18)
  - S/AK (n=7)
  - K/F (n=5)
  - S/A (n=3)
  - S/K (n=2)
  - S+K/K (n=2)
  - A/K (n=1)
  - F/A (n=1)
  - S+K/S (n=1)
  - S/F (n=1)
  - S/H (n=1)
- **Homozygous**
  - AK/AK (n=73)
  - K/K (n=17)
  - A/A (n=13)
  - S/S (n=6)
  - F/F2 (n=1)

Literature limitations

- Many studies had **limited genotyping panels** that only tested for the most common variants ("A" and "K")
- **Phasing** was not well described in many studies, making it difficult to differentiate cis vs trans (e.g., A/K or WT/AK)
- Some studies included **both succinylcholine and mivacurium**, but did not differentiate succinylcholine-only clinical outcomes
- Reported **clinical outcomes were variable and limited** to chart review due to majority being retrospective studies

Suggested Genotype to Phenotype Table by Zhu et al (2020)

Predicted Phenotype	Criteria	Genotypes	Clinical Interpretation Provided on the Laboratory Test Report
Normal BChE activity	No variants detected	No variants detected	Patient is expected to have normal pseudocholinesterase activity and normal response to succinylcholine.
Mild BChE deficiency	1) Not meeting criteria for moderate or severe BChE deficiency, and 2) one copy of K	K	Patient's genotype is associated with slightly reduced pseudocholinesterase activity and slightly increased duration of action of succinylcholine, but the differences are expected to be small unless the patient also has other factors leading to reduced pseudocholinesterase activity
Moderate BChE deficiency	1) Not meeting criteria for severe BChE deficiency, and 2) one copy of A, F_1, F_2 or S_1, or two copies of K	KK, AK, F_2, AKK, A, F_2K, F_1, S_1, F_1K, KS_1	Patient's genotype is associated with reduced pseudocholinesterase activity. In patients with similar pseudocholinesterase activities, clinically significant prolongation of neuromuscular blockade after succinylcholine use has been reported but is expected to be rare.+Prescribing information recommends: Succinylcholine should be used carefully in patients with reduced pseudocholinesterase activity.
Severe BChE deficiency	Homozygotes of A, F_1, F_2 or S_1, or positive for two or more of the four variants	AAKK, AF1K, AF1K, F1F2	Patient is expected to have low pseudocholinesterase activity and experience prolonged neuromuscular blockade when succinylcholine is administered. Prescribing information recommends: Succinylcholine should be used with caution, if at all, in patients known to be or suspected of being homozygous for the atypical pseudocholinesterase gene. Prescribing information also recommends specific test doses for these patients

Zhu GD, et al. *Pharmgenomics Pers Med*. 2020;13:405-414. Published 2020 Sep 30.

Available Clinical Guidance

- **FDA drug label:** "Succinylcholine is metabolized by plasma cholinesterase and should be used with caution, if at all, in patients known to be or suspected of being homozygous for the atypical plasma cholinesterase gene…Patients **homozygous for atypical plasma cholinesterase gene** (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of succinylcholine. In these patients, a 5- to 10-mg test dose of succinylcholine may be administered to evaluate sensitivity to succinylcholine, or neuromuscular blockade may be produced by the cautious administration of a 1-mg/mL solution of succinylcholine by slow IV infusion. Apnea or prolonged muscle paralysis should be treated with controlled respiration."
- **FDA Table of Pharmacogenetic Associations:**

Succinylcholine	BCHE	intermediate or poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk (prolonged neuromuscular blockade). Avoid use in poor metabolizers. May administer test dose to assess sensitivity and administer cautiously via slow infusion.

Mivacurium (not available in US)

- Another neuromuscular blocker – same PGx association as succinylcholine

Rationale for CPIC Guideline

- One of the oldest known PGx associations with data dating back to the 1950s
- Prescribing actionability
- Serious physical (i.e., apnea) and psychological (e.g., post-traumatic stress) consequences if pseudocholinesterase deficiency undetected
- *BCHE* included on some commercially-available PGx *and* reproductive carrier screening panels
- Succinylcholine and mivacurium are commonly used medications
- FDA labeling information available (limited)

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