



Novel Genetic Mutation Causing Clinical Bleeding in English Springer Spaniels

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Bugsy's Story

- 7 month-old, ESS
- Veterinary visit: lethargy x10 days
 - Routine spay 6 weeks prior





Bugsy's General Practice Veterinary Visit

- Physical examination: pale gums, elevated heart rate, abdomen distended
- Initial diagnostics:
 - Complete blood count: low numbers of red blood cells = anemia
 - Chemistry profile: normal



Bugsy's Primary Care Veterinary Visit

- Physical examination: pale gums, elevated heart rate, abdomen distended
- Initial diagnostics:
 - Complete blood count: low numbers of red blood cells = anemia
 - Chemistry profile: normal

Referred to Specialty ER for blood transfusion



Bugsy's Specialty ER Veterinary Visit

- Additional diagnostics
 - Quick abdominal ultrasound: internal bleeding = hemoabdomen





Causes of Hemoabdomen

1. Physical Source

Trauma
Surgery
Masses

2. Clotting Abnormality

Platelets
Clotting Factors



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Medical Workup of Hemoabdomen

2. Clotting Abnormality

Platelets

Normal number - CBC
Normal function - BMBT

Clotting Factors



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Medical Workup of Hemoabdomen

2. Clotting Abnormality

Platelets

Normal number

Normal function

Clotting Factors

Normal function - PT/PTT



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Medical Workup of Hemoabdomen

1. Physical Source

Trauma
Surgery
Masses

CT scan = concern for
bleeding from surgery site

2. Clotting Abnormality

Platelets

Normal number
Normal function

Clotting Factors

Normal function



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Causes of Hemoabdomen

1. Physical Source

Trauma
Surgery
Masses

2. Clotting Abnormality

Platelets: normal
Clotting Factors: normal





Why is Bugsy Bleeding?

- No physical source
- Initial tests of clotting system normal
 - CBC
 - BMBT
 - PT/PTT
- Discharged after 3 days hospitalization





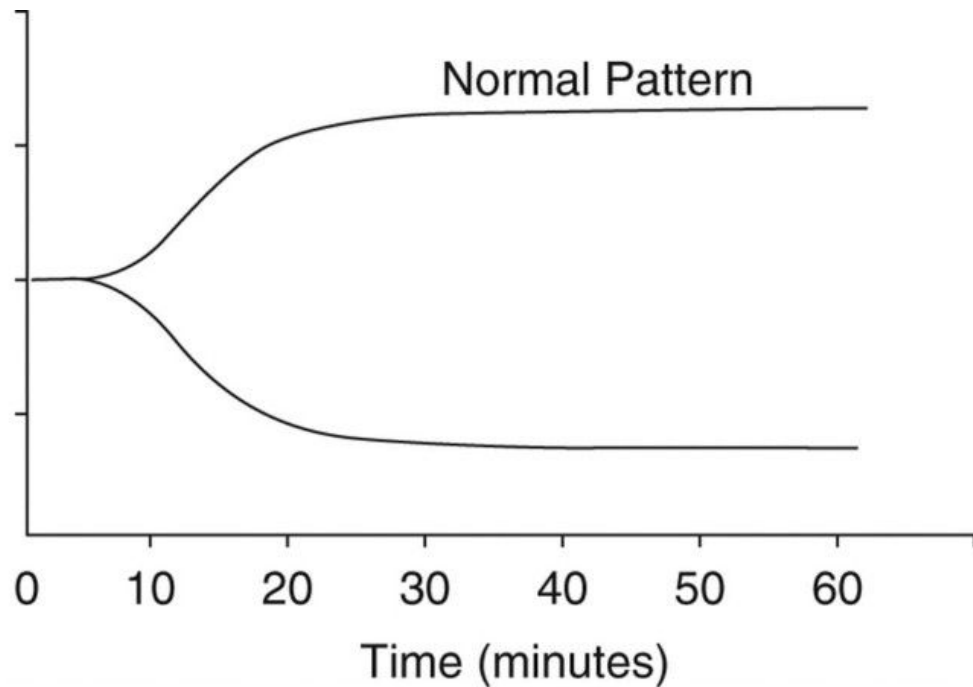
Bugsy's UW Madison Veterinary Visit

- Physical examination: painful/slight bleeding at incision site, bruising on legs
- Additional tests of clotting system
 - Cornell Hemophilia panel: von Willebrand, specific clotting factor deficiencies (8, 9)
 - Normal
 - Thromboelastography



Thromboelastography

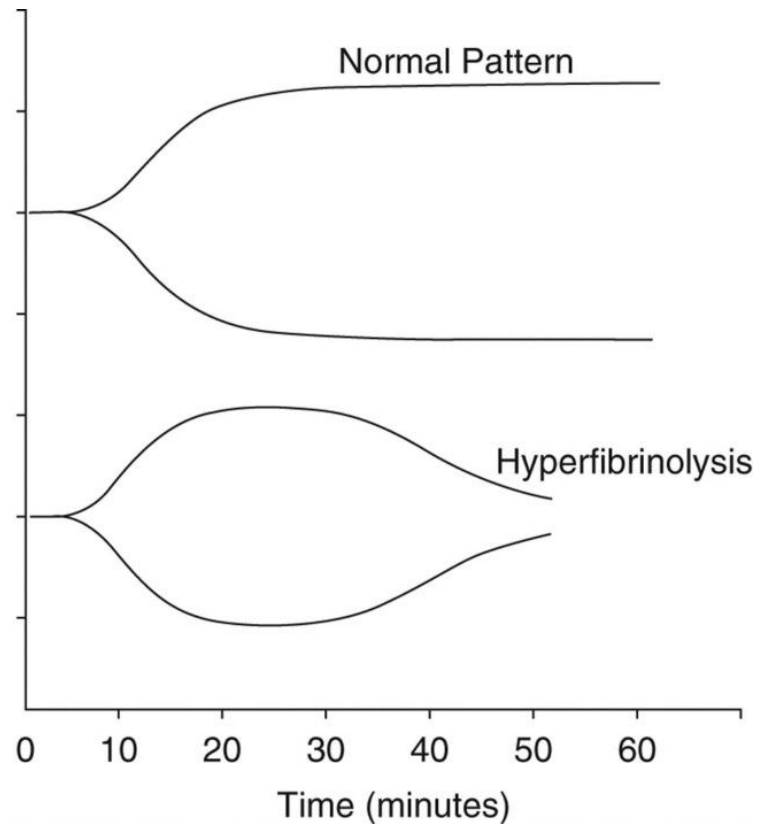
- Graphs the entire clotting process over time
- Clotting factors
- Platelet function
- Other aspects of clotting
 - Fibrinogen
 - Clot breakdown





Thromboelastography

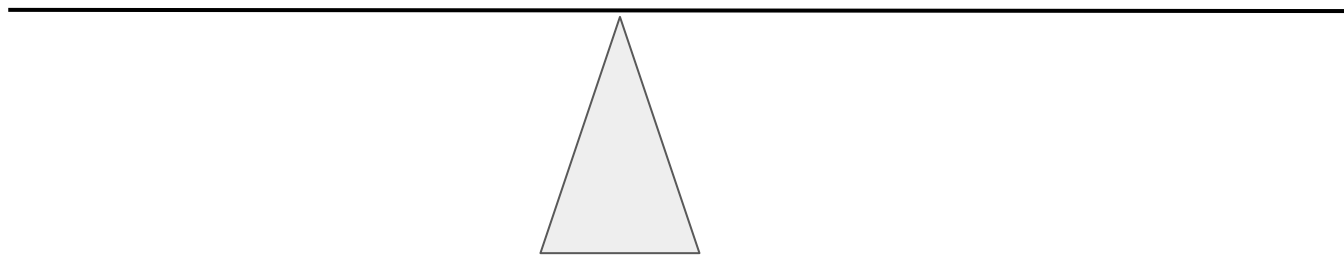
- Abnormal clot breakdown = hyperfibrinolysis





Normal Clotting System

Platelets + clotting
factors form clots



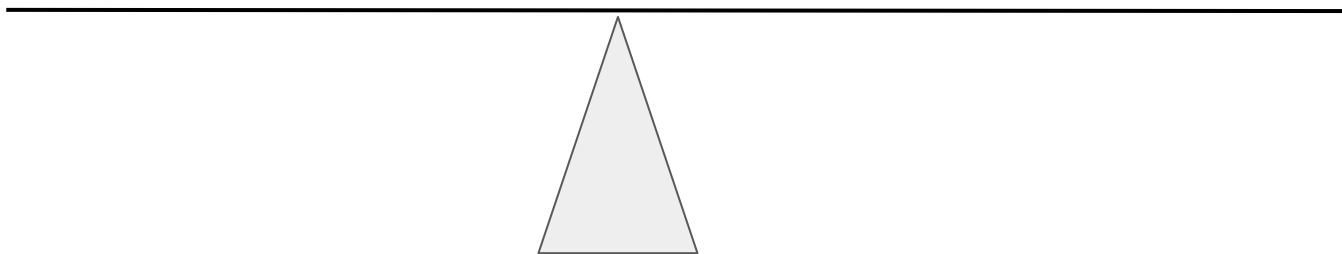
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Normal Clotting System

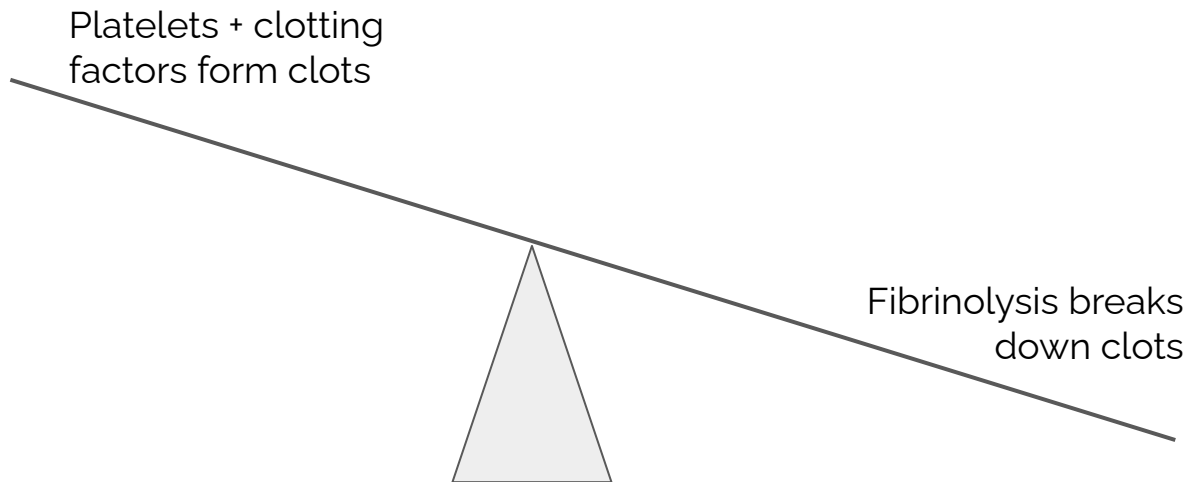
Platelets + clotting
factors form clots

Fibrinolysis breaks
down clots





Normal Clotting System



Clots don't last long enough to control bleeding → hemorrhage



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Hyperfibrinolysis

- Reported in sighthounds
 - Suspected inherited basis
- Congenital hyperfibrinolysis reported in humans

- Dr. Friedenberg at U of M to evaluate for genetic basis





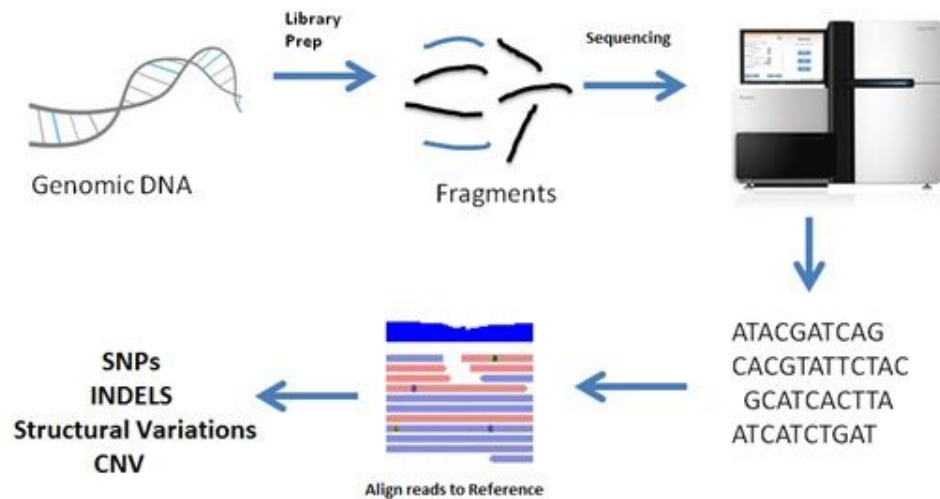
Bugsy's Story

- Treatment for hyperfibrinolysis = drugs to stabilize clots
 - Aminocaproic acid
 - Tranexamic acid
- No further bleeding with treatment
 - Discontinued clot medications after 1 month





Whole genome sequencing



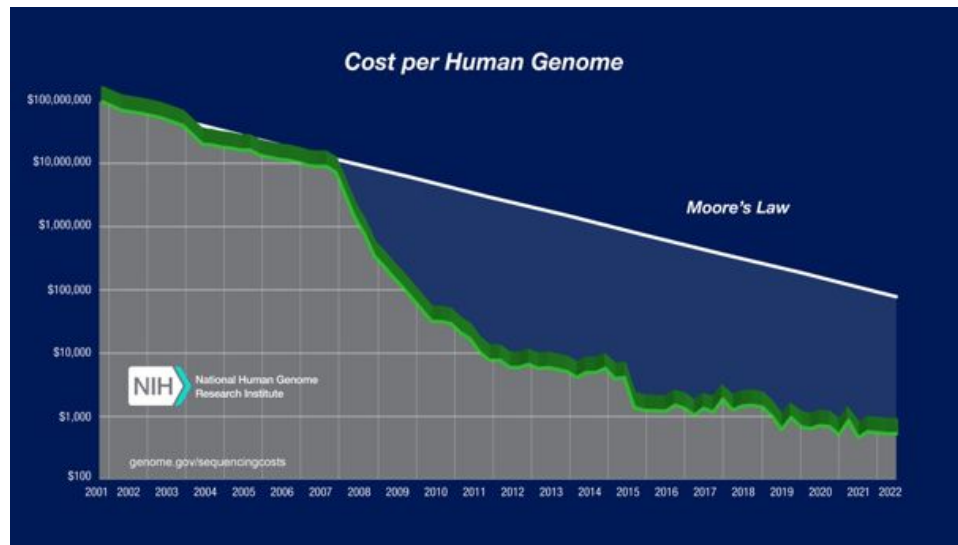
Source: 1010genome.com



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Whole genome sequencing costs



Source: National Human Genome Research Institute, November 2022



Sequencing Buggy's genome

Initial discussions 8/10

↳ Sample received @ UMN 9/29

↳ Sample received @ sequencing core 10/11

↳ Data received from sequencing core 10/24

↳ Analysis complete 10/26

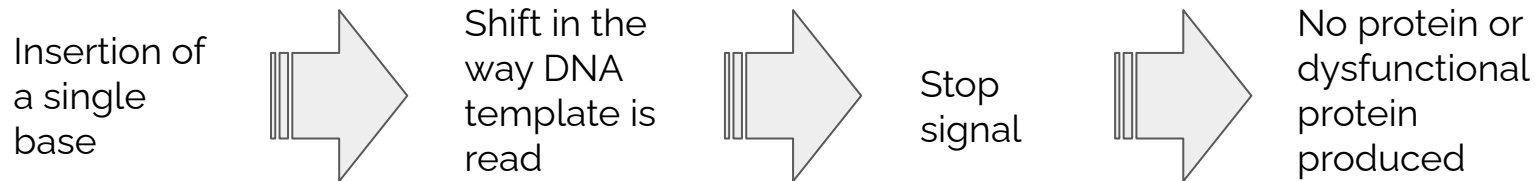


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Effect of the mutation

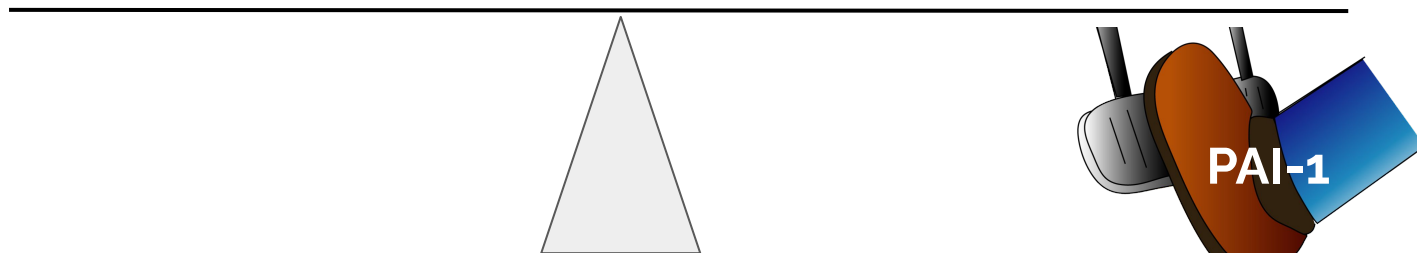




SERPINE1 creates a protein called PAI-1

Platelets + clotting
factors form clots

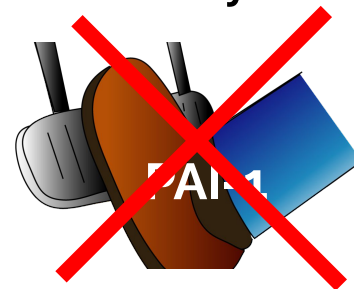
Fibrinolysis breaks
down clots





Without PAI-1, bleeding can occur more easily

Platelets + clotting factors form clots



Fibrinolysis breaks down clots

Clots don't last long enough to control bleeding → hemorrhage



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Beyond Bugsy

- Cornell BioBank
 - 4 ESSP collected over the past 15 years with similar bleeding disorders
- ESSP breeding community
- Bugsy's family
 - Littermate
 - Mom and dad?



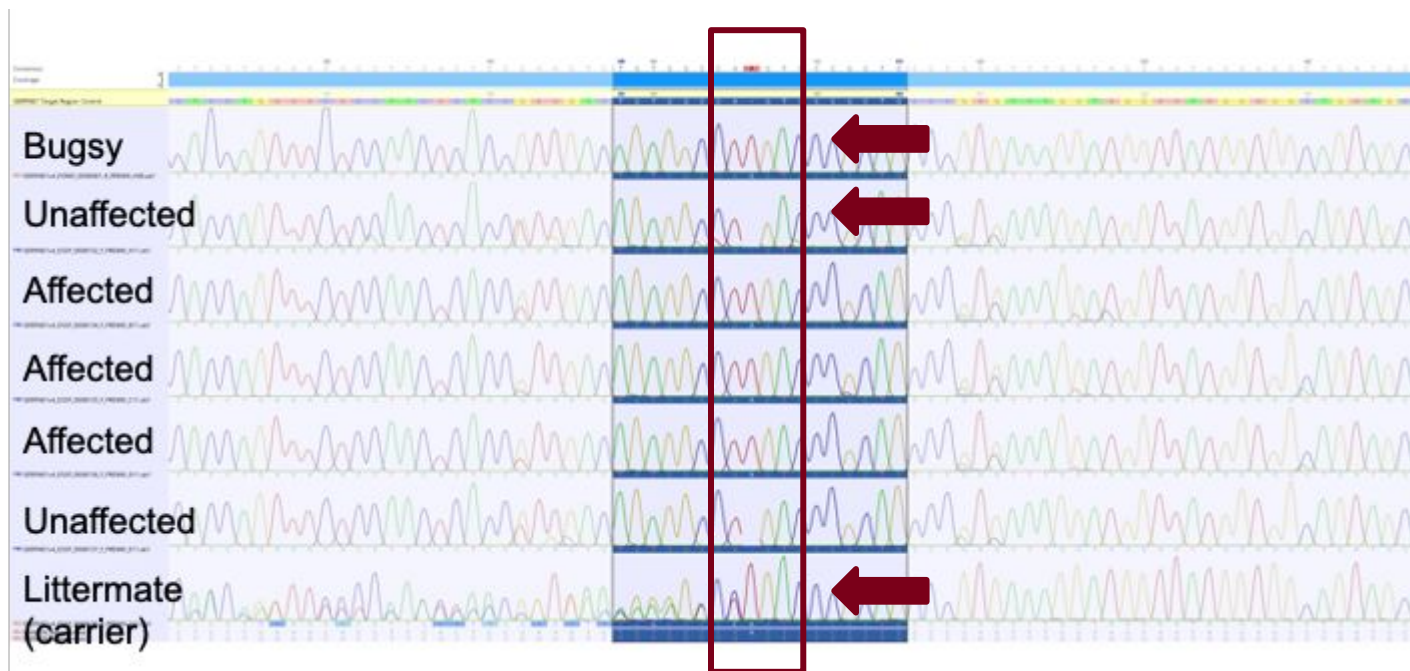
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Additional sequencing results





Additional sequencing results

- 197 English Springer Spaniels
 - Collected years ago for an epilepsy study
 - No phenotyping for bleeding
- Identified 2 additional carriers
 - One copy of the mutation
- No additional homozygous dogs





Clinical interpretation

- Dogs with two copies of the mutation are likely to experience excessive bleeding following trauma or surgery
 - Unlikely to cause spontaneous bleeding
- Difficult to diagnose by most veterinarians
- Treatable
 - Better to know/treat prophylactically
 - Can treat after the fact
 - Lifelong therapy not likely required



Genetic interpretation

- Rare condition
- Likely a small number of dogs with one copy of the mutation in the general breeding and pet population
- Opportunity to eliminate this condition entirely through informed breeding practices



Get your dog tested!

- z.umn.edu/ESSPFIB
 - \$65/dog
 - \$58/dog for 4+ dogs

Submitting a sample

[Expand all](#)

+ Step 1 - Select instructions for your sample type

+ Step 2 - Complete the online submission form

+ Step 3 - Fees & Payment

+ Step 4 - Ship your sample(s)

+ Result interpretation



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Acknowledgements

- Lab members
 - Jonah Cullen
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 - Many others...





Questions?



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