“Drop attacks”

A 27 year old man comes to the BWH Adult Genetics Clinic with his fiancé to discuss a longstanding medical problem.

At age 14 he experienced an acute paralytic event, which resolved without any persisting deficits. He continued to suffer identical periodic events — which he describes as “drop attacks” — until the age of 19. He has not had any such attacks for the past eight years. He has never lost consciousness during these events and a seizure disorder has been ruled out.

Other than these “drop attacks,” his past medical history includes wisdom teeth extraction without complications.

He is a marathon runner, and he occasionally has transient weakness and tingling in his fingers that can last for 1-2 hours and then resolve completely.

His family history is significant for a 29 year old brother with a similar history of “drop attacks” and transient episodes of acute weakness in his fingers. His brother also has a problem with progressive weakness. His father is 60 and is wheelchair bound due to a progressive myopathy that has caused significant weakness. His father had his first “drop attack” at age 16. His great uncle (paternal grandmother's brother) is said to have had drop attacks and progressive weakness, but he died many years ago and the recorded story is not entirely clear. His mother and two sisters (ages 21 and 24) are completely well. There is no family history of surgical problems related to anesthesia.

He has no allergies and is currently taking no medications, although he has taken acetazolamide in the past.

On physical examination his vital signs and neurological exam are completely normal, and his muscle strength is completely normal. His heart and lung exam is also normal.

He recalls that his serum potassium level has been measured during one of his drop attacks as a teenager. He can’t recall whether the level was high or low, but he remembers that it was abnormal.

He and his fiancé come to clinic at this time because they hope to start a family and they want to know about potential risks to the next generation and what, if anything, can be done to avoid this problem in the next generation.
Questions:

What are the genetic diagnoses you would consider in this family?

Draw and annotate a pedigree of the family. Does the family history fit one of the diagnoses you are considering? What is the mendelian inheritance pattern?

What genes are associated with the diagnoses? What is the pathophysiology of the disease?

Describe the mechanism of action of carbonic anhydrase inhibitors, and how this class of drugs could be used to alter the patient’s physiology to treat this disorder.