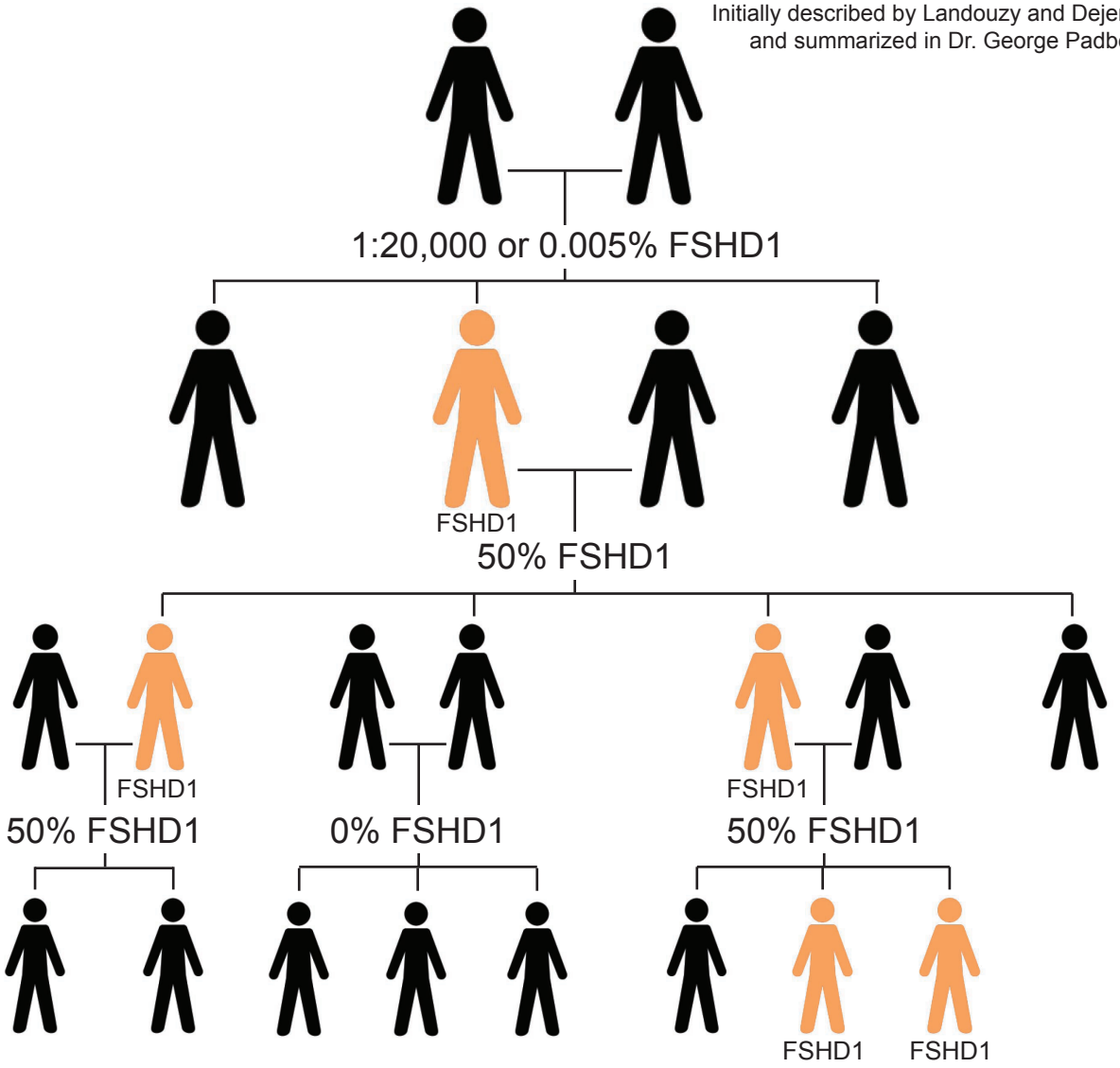
FSHD1 Inheritance (Pt 1)

Simplified (hopefully) FSHD1 inheritance.

FSHD1 is monogenic and has autosomal dominant inheritance.

Initially described by Landouzy and Dejerine (1885)
and summarized in Dr. George Padberg's Thesis (1982)



The chance of being FSHD1 with no family history (i.e., being the first one in the family with FSHD1) is 1:20,000 or 0.005%.

If you have FSHD1 in the family, all FSHD1 family members have the same size deletion.

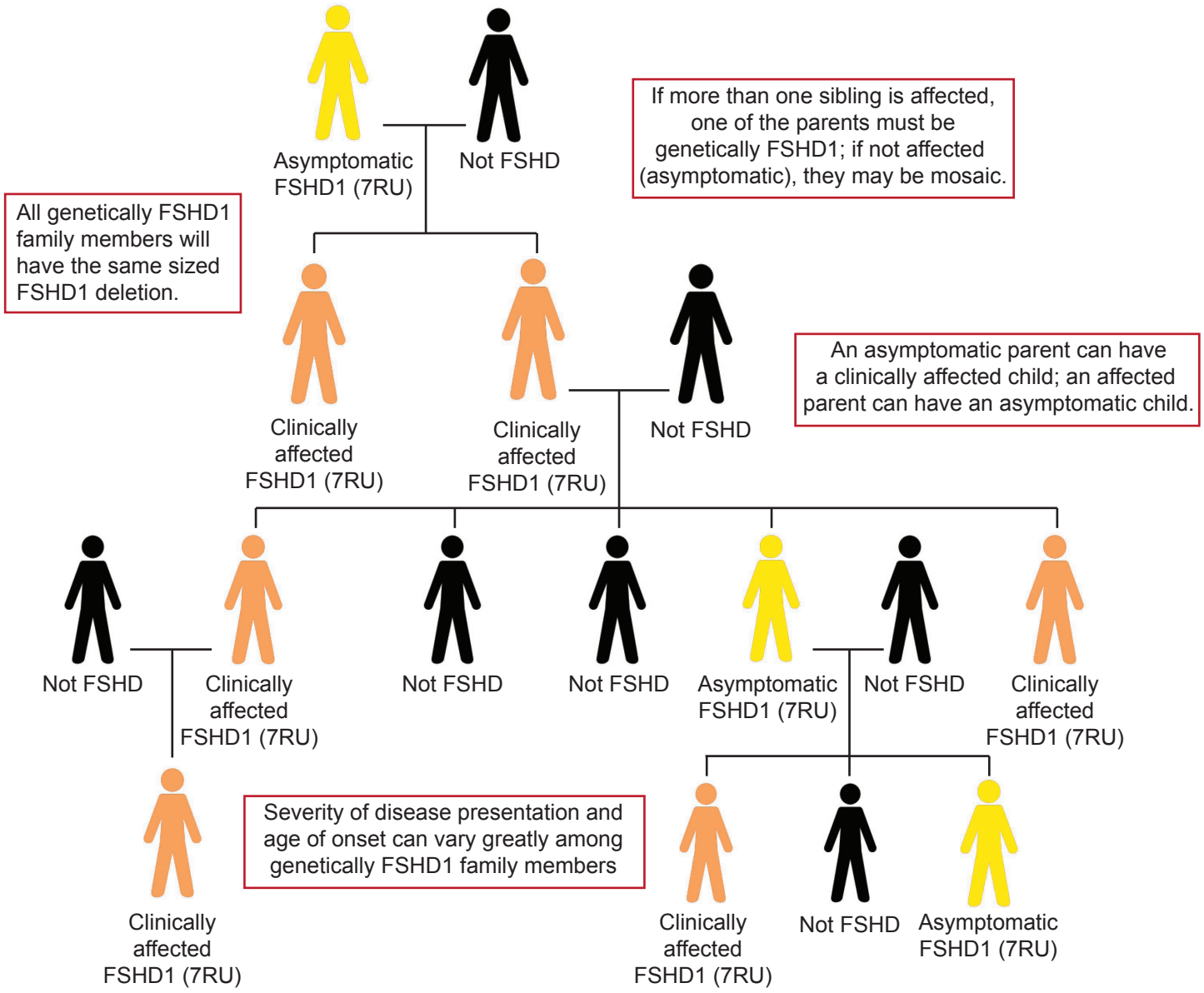
If you are FSHD1, there is a 50% chance of passing on the FSHD1 mutation to each child; however, someone who is FSHD1 may have all healthy (non-FSHD1) children, or alternatively, more than 50% FSHD1 children. It is like flipping a coin -- on average over time each side comes up equally, but sometimes you can get four heads in a row instead of 2 and 2.

The incidence for one child does not affect the chances for the other children (i.e., having the first child FSHD1 has no bearing on the second child, and vice versa).

FSHD1 Inheritance (Pt 2)

FSHD1 is monogenic and has autosomal dominant inheritance; however, there can be low penetrance of clinical symptoms.

Many references, including: *Med Genetics* (2004) 42:e12, *Neuromuscular Disorders* (2004) 14:33, *Human Molecular Genetics* (2012) 21:4419-30, *Orphanet J Rare Diseases* (2015) 10:2, and *Neurology* (2018) 91:e444-54.



Within an FSHD1 family, all members with genetic FSHD1 will have the same sized deletion (e.g., 7RU above). However, there can be high variability of disease presentation within families.

In some people, the clinical symptoms of FSHD may not appear until late in life (if ever) despite being genetically FSHD1. These individuals appear asymptomatic, at least at the time of having children, and is why some feel FSHD can skip a generation. Genetically, FSHD1 does NOT skip generations.

Shorter deletions (resulting in 6-10 D4Z4 repeat units) tend to be the ones more likely to present as asymptomatic or mild late in life. This is also the size range with the most familial variability.

FSHD1 Inheritance (Pt 3)

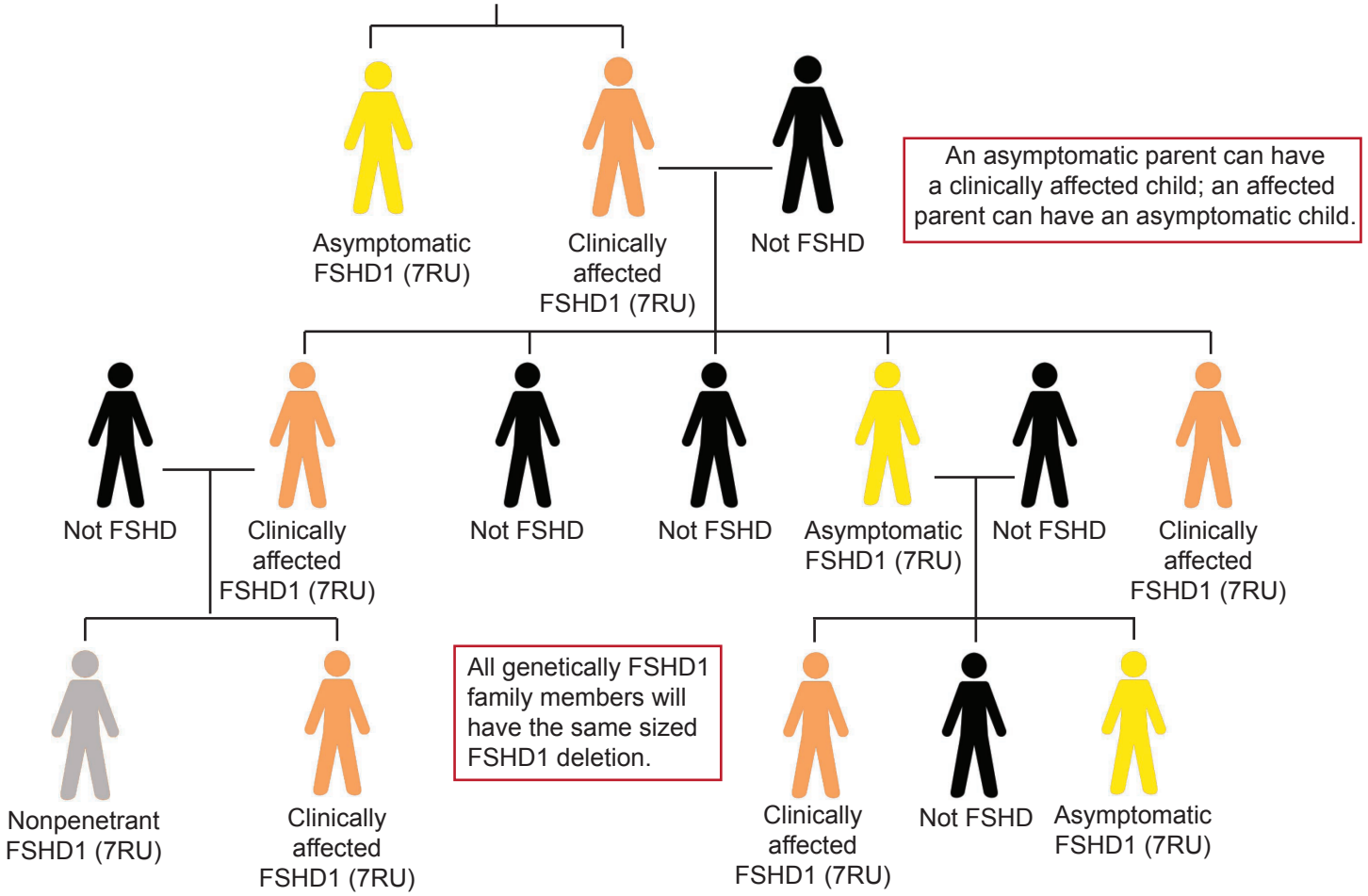
FSHD1 can be asymptomatic and nonpenetrant within families.

Asymptomatic individuals are genetically FSHD1 and have no reported muscle weakness but do have signs of FSHD upon clinical evaluation.

Nonpenetrant mutation carriers are people who are genetically FSHD1 but do not have signs of muscle weakness upon clinical evaluation.

A recent study showed that when 69 subjects from families with 4-9 D4Z4 RUs were grouped as:
(1) symptomatic, with muscle weakness reported and also found upon examination,
(2) asymptomatic, with no muscle weakness reported but FSHD symptoms upon examination,
(3) nonpenetrant, with no muscle weakness reported and no FSHD symptoms upon examination.
Results: ~25% were asymptomatic carriers and 17% were nonpenetrant carriers. Overall, ~83% of individuals meeting the FSHD genetic criteria show symptoms by 30 years, 95% of males, and 69% of females.

Neurology (2018) 91:e444-54.



If you have a blood relative that is FSHD1 and you are planning on having children, you may want to get officially tested for FSHD1 regardless of whether you are experiencing any symptoms so that you can understand the genetic risk. There are family planning options available, if interested.