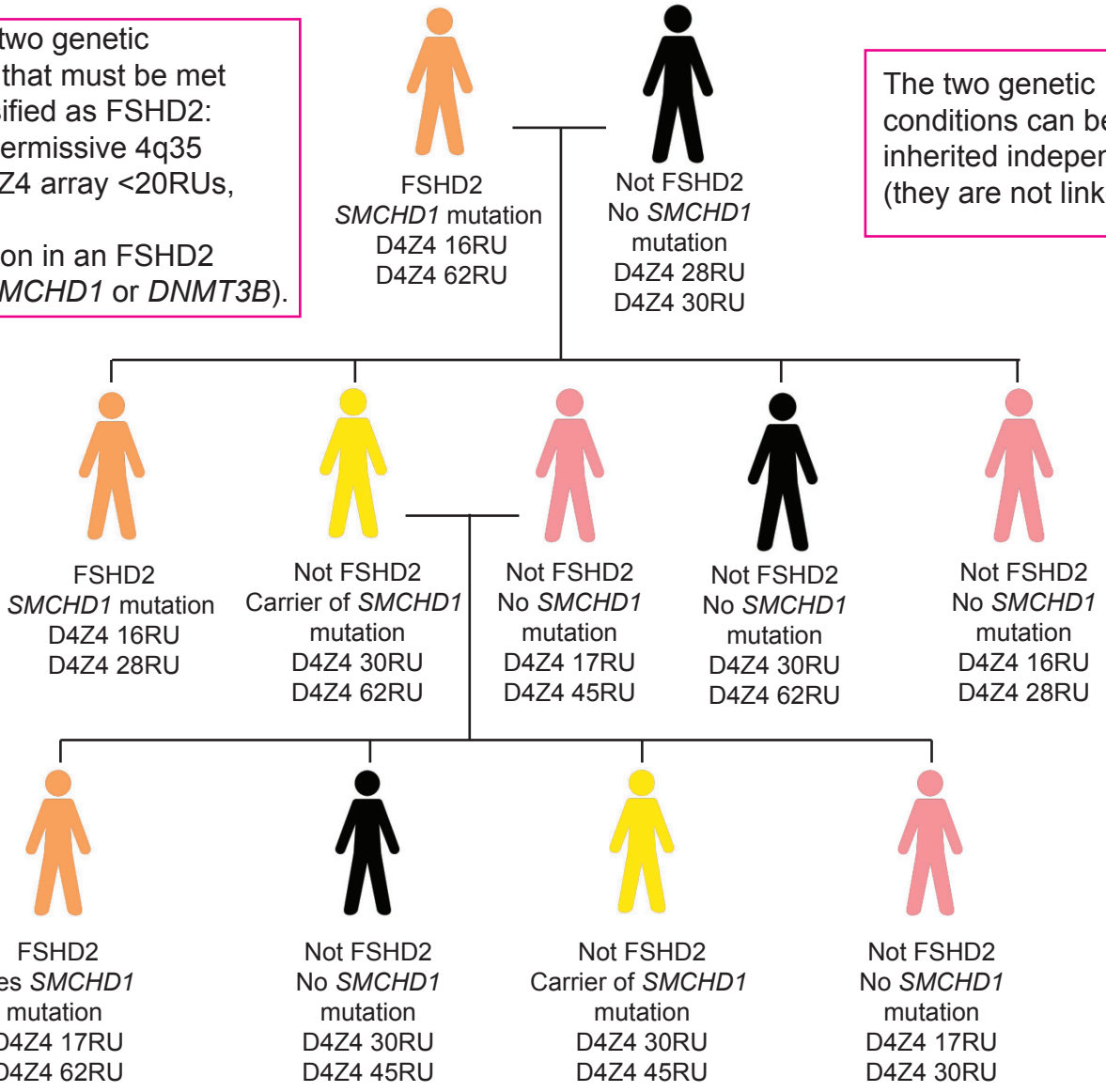
FSHD2 Inheritance

FSHD2 is digenic and thus, can seemingly skip generations.

There are two genetic conditions that must be met to be classified as FSHD2:
1) FSHD permissive 4q35 on a D4Z4 array <20RUs,

2) a mutation in an FSHD2 gene (*SMCHD1* or *DNMT3B*).



The two genetic conditions can be inherited independently (they are not linked).

FSHD2 is digenic -- requires two genes -- and thus two unaffected (not FSHD2) parents, neither of which meet the genetic requirements for FSHD2, can produce a child that is FSHD2. Each parent contributes one of the genetic requirements: *SMCHD1* mutation (yellow), and FSHD2 sized D4Z4 array (pink).

In the example above, one parent has FSHD2; the other parent does not and also has two long 4q35 D4Z4 arrays (28RU and 30RU). Together, they produce four potential scenarios (from 8 genotypes): FSHD2 (orange), unaffected FSHD2 carrier (yellow), unaffected not an FSHD2 carrier with long 4q D4Z4 RUs (black), and unaffected not an FSHD carrier but with an FSHD2-sized 4q D4Z4 (pink).

In the next generation, an unaffected carrier with the familial *SMCHD1* FSHD2 mutation (yellow) by chance has kids with a healthy individual with an FSHD2 appropriate 4q D4Z4 array (17RU) producing the same four possible outcomes as above, including clinically affected FSHD2.

One can see how being clinically affected with FSHD2 can seemingly skip a generation and be difficult to predict or track through a family.