What is a syndrome?

- A clinically based definition
- Look alike
- Same medical issues
- Same developmental strengths and weaknesses
- Assumed to have the same cause

It is important to understand the term syndrome. A syndrome is defined by a collection of clinical features. It is also identified when it becomes clear that a certain combination of clinical features frequently occur together and are therefore presumed to have a single cause. These clinical features may be facial features, medical issues, or developmental strengths and weaknesses. This is often the point at which a syndrome is named.

Once a syndrome is identified, the next task is to identify its underlying cause. Once a genetic cause is discovered, the syndrome name and the identified genetic cause are often used interchangeably. This is technically inappropriate because the "syndrome" describes a series of clinical features—not the underlying cause. And to complicate things even more, one clinically-recognized syndrome can actually have multiple underlying causes.

**Special points of interest:**

- Defining a syndrome.
- TCF4 and Pitt Hopkins
- Dominant and recessive genes

**Inside this issue:**

- TCF4 and Pitt Hopkins Syndrome
- Pitt Hopkins by Recessive Genetic Mechanism
- What is 18q-?
- 18q- or Pitt Hopkins?

**Pitt Hopkins Syndrome**

This is the case with Pitt Hopkins syndrome. The constellation of clinical characteristics that make up Pitt Hopkins syndrome can actually be caused by any of three different genetic defects—three different genes on three different chromosomes.

We believe the most common cause of Pitt Hopkins syndrome involves the gene *TCF4* located on the large arm of chromosome 18. *TCF4* causes Pitt Hopkins syndrome by several mechanisms.

- **TCF4** (18q21.2) – dominant loss of function
  - Only one copy has an inactivating mutation or is deleted.
- **CNTNAP2** (7q35) – recessive
  - Both copies of the gene have a mutation.
- **NRXN1** (2p16.3) – recessive
  - Both copies of the gene have a mutation.
This diagram illustrates the point. The top yellow genes depict the normal state and normal result. One of the blue genes has a deletion of the TCF4 gene so this person will have Pitt Hopkins syndrome. One of the pink genes has a mutation (red star) of the TCF4 gene so this person will also have Pitt Hopkins syndrome.

Both copies of TCF4 must be functional for normal development to occur. This defines a dominant condition. Most dominant conditions are inherited from one parent, but we presume that almost all cases of Pitt Hopkins syndrome—with such a significant clinical presentation—are the result of a new mutation or new deletion in the child and that neither parent had the condition. These families are at low risk for having more than one child with Pitt Hopkins Syndrome.

Pitt Hopkins by Recessive Genetic Mechanism

The other two causes of Pitt Hopkins syndrome involve genes on other chromosomes—ENTHAP2 (7q35) and NRXN1 (2p16.3). Both of these genes can cause Pitt Hopkins syndrome but by a recessive genetic mechanism.

At the top of the diagram to the right, two normal copies of the gene are shown resulting in no disease. In a recessive condition, neither the deletion or mutation of one of the two genes causes disease. However, people with these DNA changes are carriers for the condition and probably have no idea they are a carrier.

In a recessive condition both copies of the gene must somehow be defective in order for disease to result. A person with Pitt Hopkins syndrome caused by one of these two recessive genes is likely to have parents who are both carriers of the disease. These families are at risk for having more children with Pitt Hopkins syndrome and should see a genetic counselor for a consultation. By the way, each of us is probably harboring 200 recessive mutations making us carriers for many conditions.

What is 18q-?

18q- is not a syndrome but is defined as a deletion of a portion of chromosome 18. There are no uniform deleted regions or sets of clinical characteristics.

18q- is not a syndrome. It is not defined by any clinical characteristics at all. It is defined by a genetic test that identifies a deletion of a portion of the long arm of chromosome 18. All persons with 18q- have different deleted regions and sizes of deletions. This means that there is no characteristic clinical picture for 18q-. Consequently, people with 18q deletions have a very broad range of medical issues and abilities. For example, IQs range from 120, which is well above average, to immeasurably low. But if you look at individuals 175, 181 and 127, they share no deleted region in common. Consequently, their clinical pictures are very different. We have studied almost 300 persons with 18q- and no two unrelated people have the exact same deletion—so no two people would be expected to have the exact same characteristics as a result of their deletions; though they may have overlapping general features, such as developmental delays or hypotonia.
People whose deletions include the TCF4 gene can be thought of as having “Pitt Hopkins syndrome” because their characteristics are similar to persons with Pitt Hopkins. However, technically speaking, none of them have Pitt Hopkins syndrome. In this illustration, individuals 30, 181 and 239 all have deletions that include TCF4 as well as other genes. Therefore technically, they have 18q-. But anything we learn about Pitt Hopkins syndrome will probably apply to these three individuals. So they are likely to benefit from any Pitt Hopkins syndrome research. However they may not be allowed to participate in some of the Pitt Hopkins research because their deletions involve genes in addition to TCF4.

We have found that those persons with large deletions of 18q that include TCF4 are not substantially different from those with deletions of TCF4 alone. But from a scientific perspective, these persons do not have Pitt Hopkins syndrome, as it is defined by a deletion of or mutation on TCF4 alone.

For more information, you may contact the authors and principal investigators of the Chromosome 18 Clinical Research Center at the phone numbers or email shown to the left.

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