Overview of Clinical Symptoms of 17q12 Deletions and Duplications

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Overview

1. How frequent is it to have a 17q12 deletion or duplication (also known as copy number variant - CNV)?
2. How likely is it to have clinical features if the CNV is there?
3. Do these CNVs run in families?
4. Are the features the same for deletions and duplications?
5. What are the clinical features?
   - Brain and behavior
   - Facial features
   - Kidneys
   - Hormone system
   - Others?
6. Conclusions

How frequent is it to have a 17q12 deletion or duplication?

- It all depends on where we look
- General population
  - deletion: 1 out of ~7,000 people
  - duplication: 1 in ~2,000
- People with developmental delay
  - deletion: 1 out of ~1000
  - duplication: 1 out of ~800
- The frequency is similar in **boys** and **girls**
- The frequency is similar across different **ethnicities**

How likely is it to have clinical features?

- Deletion is about **7 times** as frequent in people with developmental delay compared to the general population
- Duplication is about **3 times** as frequent
- Not everyone with the deletion or the duplication has clinical features (**penetrance**)
- Not everyone with the deletion or the duplication with clinical features have the same ones, or to the same degree (**expressivity**)

Do the 17q12 deletions and duplications run in families?

- Most of the time, the deletions and duplications arise *de novo*, meaning none of the parents have them
- However, the CNVs can also be inherited from a parent who may or may not have clinical features
- Although the clinical features tend to be similar in family members with the same CNV, this may not always be the case

Are the clinical features the same for deletions and duplications?

- Although some of the same symptoms are present in people with the deletion and the duplication, each CNV has some particular clinical features
- People with the deletion tend to have more significant clinical features than people with the duplication

Known syndromes associated with 17q12 deletion

- Renal Cysts and Diabetes (RCAD) Syndrome
- Maturity onset diabetes of the young type 5 (MODY5)
- Müllerian agenesis or Mayer-Rokitansky-Kuster-Hauser (MRKH) Syndrome: Partial absence of the cervix, uterus, and vagina.

17q12 deletions and duplications – Shared features

Brain and behavior - Developmental delay:

- Common but not universal, variable degree ranging from mild to severe.
- One of the symptoms that prompts clinical attention.
- Motor delay is frequent, difficulties walking, or with fine motor skills.
- Learning disabilities and intellectual functioning deficits may be present, but widely variable. Some patients require special school, while others successfully graduate from college.
  - "He was delayed globally but has caught up in most areas." ☐ 4 years
  - "Developmental delay compared with her peers in fine motor skills and language development, but cognitive tests have her in average ranges." ☐ 6 years
  - "Delayed motor skills, but otherwise entirely normal development." ☐ Adult

17q12 deletions and duplications – Shared features

Brain and behavior - Communication, speech and language:

- One of the areas most likely to be affected.
- May be seen as early as young babies, decreased social smile or reciprocal babbling.
- Delayed onset of language, may be limited once gained.
- More prominent in people with the deletion than in those with the duplication.
  - "The area he continues to struggle in is speech and socialisation. He communicates with words in full sentences but does have difficulties with some sounds, such as r, th and l. We did use sign language and a communication board but he does not use these any more. We also do listening/music therapy. His language comprehension is better than his expression, but both are good now. Early intervention is key, and you must do work at home as well. The therapists are only with the children for a limited amount of time."

17q12 deletions and duplications – Shared features

Brain and Behavior - Autism Spectrum Disorders:

- Deficits in communication, social interaction, and restricted interests and repetitive patterns of behavior, seen before 3 years of age.
- Present in about half of the patients with the deletion, less common in those with the duplication.
  - "He can't look people in the eye and has difficulty answering questions if people are new to him. Even with those who know him well, he will have a warm-up period every time he sees them. He has a hard time meeting new children and playing with others. He does better with adults than children. He never kissed us until after he was 2 and today still has poor eye contact, difficulty recognizing non-verbal cues and difficulty empathizing with others. He was diagnosed with autism at the age of one. Today he likes routine and to know what is going to happen. With age he has more empathy toward others and has become more caring." ☐ Boy, 4 years

17q12 deletions and duplications – Shared features

Brain and Behavior - Schizophrenia:

- Abnormal perception of reality (hallucinations, paranoia), decreased sociability, and disorganized thoughts, seen in early adulthood.
- The deletion and the duplication have been associated with schizophrenia in large populations, but detailed descriptions of people with schizophrenia and these CNVs are not yet available.

17q12 deletions and duplications – Shared features

Brain and Behavior – Other features:

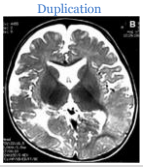
- Less common - Anxiety, bipolar disorder, frequent mood changes, short attention span, unusual phobias, hyperactivity, obsessive-compulsive behaviors, irritability, self injurious behaviors, mostly described in people with deletions. However, some have no behavioral problems.
- Seizures can be observed in about 10% of people with these CNVs, but seem to be more common in those with the duplication. They can be focal complex, generalized, or associated with fever.

17q12 deletions and duplications – Shared features

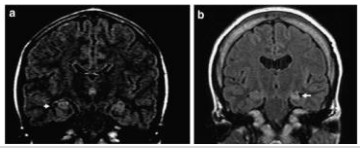
Brain and Behavior – Other features:

- Mild cerebral and hippocampal atrophy and ventricular dilatation in patients with deletion
- Non-specific periventricular white matter changes in patient with duplication
- None of these features are specific to the 17q12 deletions or duplications

Duplication



Deletion



Facial Features – People with 17q12 deletion

Most prominent facial features

- High forehead
- Macrocephaly (large head size)
- Downslanting eyes
- Small jaw that enlarges later in life
- Low nasal bridge

Facial Features – People with 17q12 duplication

Most prominent facial features

- High forehead
- Microcephaly (small head size)
- Arched eyebrows
- Upslanting eyes
- Low nasal bridge
- Bushy eyebrows
- Thin upper lip

Other systems affected

- **Kidneys** – Renal cysts, impaired renal function and urinary tract malformations (Dr. Jamie Alton Green). Much higher frequency of renal involvement in people with the deletion, occasional but rare in people with duplication.
- **Genital and reproductive system malformations**: mostly affecting women with the deletion. Rare in women with duplication, or in men with either deletion or duplication. Agenesis of uterus and vagina.
- **Endocrine** – Difficulty regulating blood sugars leading to diabetes at young adulthood in about half of the patients with the deletion. Not evident in patients with the duplication.
- **Musculoskeletal** – Scoliosis and increased joint mobility in patients with the deletion, no clear data on patients with duplication.

Conclusions

- People with 17q12 deletions and duplications have variable clinical features in several areas including brain and behavior, facial features, kidneys, endocrine system
- Clinical features range from very mild to severe, and may be absent from some people with the CNVs. These features tend to be more significant in patients with the deletion when compared with the duplication.
- Although many symptoms are common in patients with the deletion and duplication, some are more frequent in each of the groups – such as kidney abnormalities in the deletion group and seizures in the duplication
- There are subtle but characteristic facial features in people with the deletion, which are less evident in people with the duplication.
- Early intervention and surveillance is key!

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