Too much or too little of one gene, CHRNA7, is associated with many neuropsychiatric disorders

In the human genome, certain regions are unstable and are found to have missing (deletions) or extra (duplications) pieces of chromosome. Many of these deletions and duplications have been implicated in neurological disease, including autism spectrum disorder (ASD), intellectual disability, and schizophrenia.

Chromosome 15 is a hotspot for deletions and duplications (Fig. 1). On chromosome 15, at 15q13.3, we see deletions or duplications of varying sizes in patients with neuropsychiatric disease. Often, these changes will include the same genes. However, we observe the genetic phenomenon of variable expressivity among patients, with the same genetic changes manifesting as different neuropsychiatric conditions (e.g. ASD, bipolar disorder, epilepsy), and at different levels of severity.Additionally, these changes also exhibit incomplete penetrance, with not all individuals carrying the deletions or duplications having neurological disease. Affected children often inherit these genetic changes from unaffected parents.

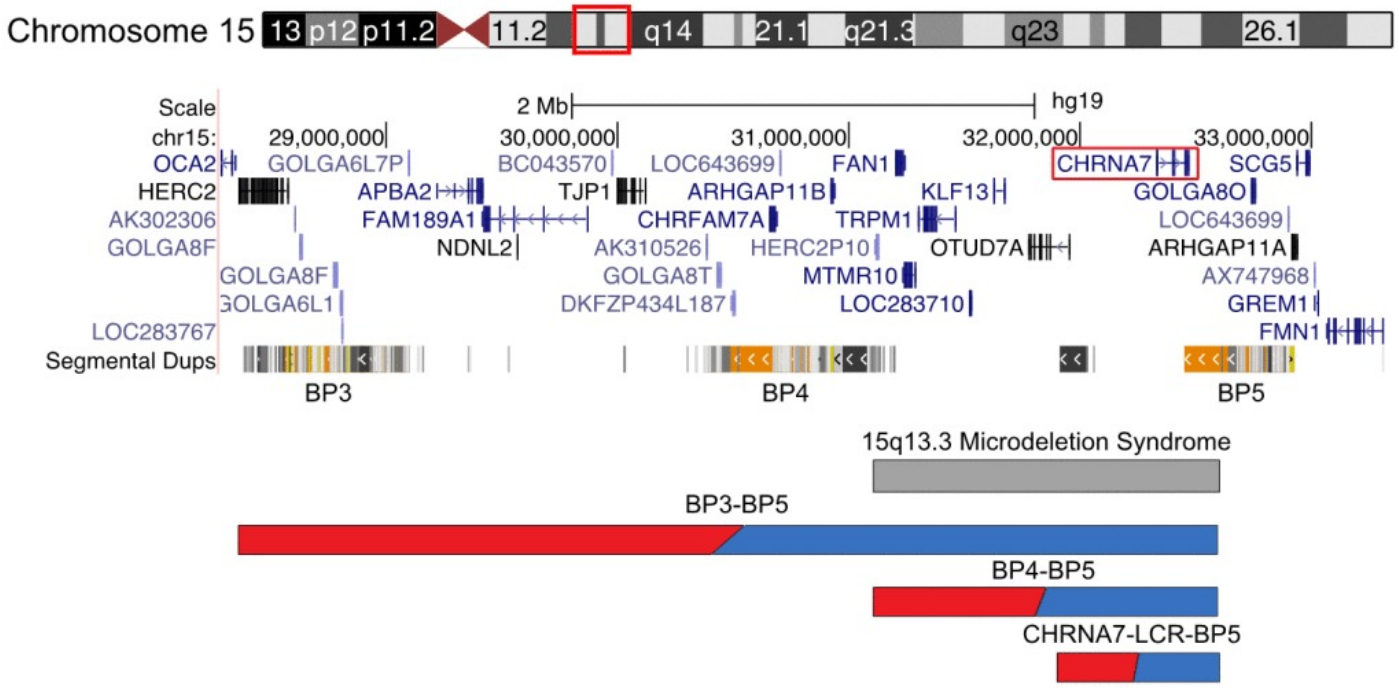

Fig. 1. Multiple deletions (red) and duplications (blue) occur at chromosome 15q13.3 due to the presence of six breakpoints (BPs) along 15q13, with BP3–BP5 shown. The genetic coordinates for 15q13.3 microdeletion syndrome are shown in gray. CHRNA7 is highlighted by a red box. Adapted from UCSC Genome Browser.

Deletions and duplications change the number of copies of several genes (shown in Figure 1). One gene, *CHRNA7*, typically has two copies in humans. We have found patients in the literature with zero to four copies of the gene with a range of clinical severity. *CHRNA7* is a promising candidate gene for causing at least a subset of the neurological conditions identified in patients, as it encodes for the ?7 nicotinic acetylcholine receptor, which is highly expressed in the human brain and is involved in signaling that plays a role in learning and memory. The smallest deletions and duplications at 15q13.3 include only *CHRNA7*.

By reviewing the literature, we determined the traits that are associated with different numbers of *CHRNA7*, suggesting that the gene is sensitive to how many copies are present (Fig. 2). Rare individuals with zero copies of *CHRNA7* have the most severe condition consisting of severe intellectual disability, seizures, and changes in brain morphology. More commonly, we identify individuals with one copy of *CHRNA7* deleted, which we term 15q13.3 Microdeletion Syndrome. These patients have intellectual disability, seizures, and language impairment. Duplications and triplications (having 4 copies total) of *CHRNA7* have much milder neurological manifestations, with mild learning problems, ASD, ADHD, and mood disorders such as bipolar disorder or depression. These duplications are also prevalent in the normal population.

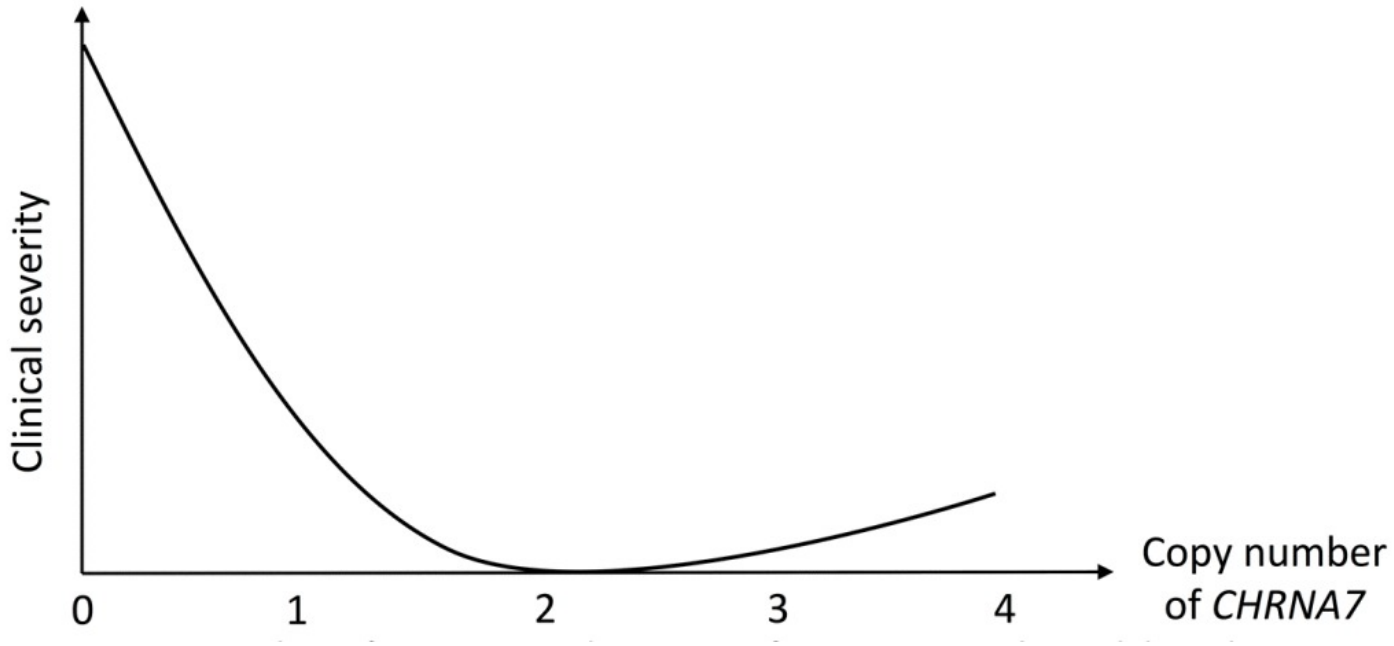

Fig. 2. Copy number of CHRNA7 and severity of patient neurological disorders. Typically, individuals have two copies of the gene. Patients having zero copies have the most severe disorders; with one copy of CHRNA7 being deleted also having a considerable effect. In contrast, extra copies of CHRNA7 appear to have a milder impact.

There are several potential mechanisms to account for the variable neurological conditions we observe. These include other genetic or epigenetic changes at different regions or within *CHRNA7*, although they do not seem to play a significant role. The most likely factor in the wide range of conditions we see in these patients are other genes modifying the ?7 nicotinic acetylcholine receptor, which is currently being explored.

Understanding the clinical conditions of patients who have differing copy numbers of *CHRNA7* is very important for physicians, affected individuals, and their families. We hope that we provide information that can help provide better counseling and anticipatory guidance to individuals and families affected by these copy number changes.

Publication

The human clinical phenotypes of altered CHRNA7 copy number.
Gillentine MA, Schaaf CP
Biochem Pharmacol. 2015 Oct