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A point mutation in *Celsr3* linked to Tourette Syndrome impacts basal dendrite patterning of pyramidal neurons in the mouse somatosensory cortex

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Abstract

The cause of Tourette Syndrome (TS) is thought to be due to a combination of multiple genetic as well as environmental factors. To improve genetic counseling outcomes for these patients, it's imperative that we continue the search for risk genes associated with the condition. A recent trio-based study using whole exome sequencing (WES) uncovered de novo variations in the gene *Celsr3* associated with TS.[1] *Celsr3* is known to be involved in neurite patterning, synapse formation, and interneuron migration, and is highly expressed in striatal cholinergic interneurons (CINs).[2,3,4] Our preliminary data using a mouse model of the R774H point mutation which was discovered in the previously mentioned trio study show that *Celsr3* mutant CINs are more complex in their branching patterns when compared to wild type CINs. To further study how this point mutation effects the cortico-striatal-thalamo circuit (CSTC) I looked at a population of neurons within the cortex known as the pyramidal neurons. Given the changes we saw in the mutant CINs, I hypothesized that cortical pyramidal neurons which harbor a point mutation in *Celsr3* would changes to dendrite morphogenesis.

Introduction

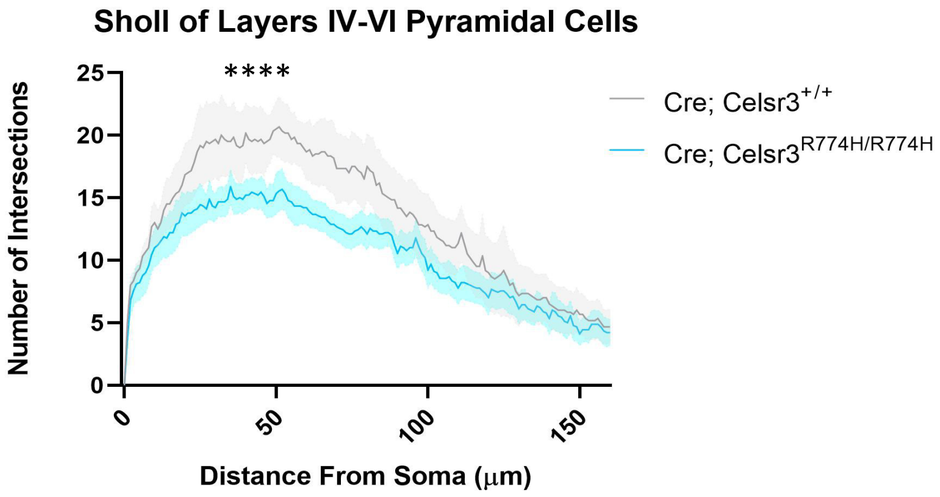
- TS is an inherited neurodevelopmental disorder classified by the presence of multiple motor and one or more vocal tics.
- The prevalence of TS is 0.3-1% and it is more prevalent in males with a 4.3:1 male-to-female ratio. [5]
- TS is comorbid with conditions such as attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD).[5]
- Whole exome sequencing (WES) and *de novo* mutation analysis in TS trios (unaffected parents, affected child) has identified *Celsr3* as a high confidence risk gene. [1,6]

Methods

- Creating the mouse line
- Viral labeling
- Immunofluorescent labeling and imaging
- Cell morphological analysis

Results

The *Celsr3*^{R774H} point mutation caused changes to dendrite morphogenesis in cortical pyramidal neurons. It revealed decreased dendritic complexity among mutant pyramidal neurons meaning mutant animals appeared to have less dendritic intersections when compared to wild types.



Discussion

- Reduced dendritic arborization in mutant pyramidal cells may prevent the pyramidal neuron from forming appropriate synapses with neighboring cells
- The data suggest that the R774H point mutation affects the way that different neuronal populations communicate within the CSTC circuit
- Future studies are needed to further understand the severity of the R774H point mutation in humans, but hopefully in the future *Celsr3* will become an understood risk gene for TS that can be included on genetic testing panels to help families understand the cause and recurrence risk their TS.

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