

Update on the Genetics of Tourette Syndrome



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Epidemiology of TS

- Involuntary motor & vocal tics beginning about age 7
- Part of a spectrum of tic disorders
- Frequently co-occurs with OCD and ADHD
- Prevalence of TS approximately 1/2000 to 1/100
- Frequency of tics in population 3-18%
 - transient tics or chronic single motor tics
- Male to female ratio
 - 3:1 for TS
 - 2:1 for tics



Genetic epidemiology of TS

- Overall risk of TS in relatives is 10.7%
 - Male relatives 17.7%
 - Female relatives 5.2%
- Concordance rate for TS
 - MZ twins 53%
 - DZ twins 8%
- Concordance rate for CMT
 - MZ twins 77%
 - DZ twins 23%



Tourette Syndrome

Inheritance patterns

- TS is genetic, but the genetics are not simple
 - Probably not a one-gene disorder
- May be multiple genes acting together
 - Some combination of multiple genes
- May be that only one gene is necessary, but could be different genes in different people/families
- May be that it's a combination of genes plus environment



Complicating factors for genetic studies

- Not everyone who has TS will have a genetic form of TS
 - TS can occur in other disorders, where it is probably secondary, such as mental retardation, or autism
- Not everyone who has TS will have the same genetic form of TS
 - PANDAS is probably genetic, but may have a different genetic cause than TS itself
- Not everyone who has the TS gene will have TS
 - Many of your parents or children don't have TS



Genetic Strategies

- Searching the genome is like proof-reading a book for mistakes
 - The chromosomes are the chapters
 - The genes are the paragraphs
 - The mutations in the DNA sequence are the letters
- First, you have to find the right chapter
- Then, you have to find the right paragraph
- Then, you have to read every word very carefully to find the mistakes
 - Some “mistakes” don’t have any effect (spelling behaviour vs behavior, for example)
 - Some mistakes make a big difference (missing a word or a sentence, spelling “of” instead of “if”, forgetting a period)



Genetic Strategies

- Three approaches
- Candidate gene approaches assume you know the right chapter
- Genome searches require you to read the whole book
- Chromosome abnormalities assume that part of the important chapter is rearranged, and that this messes up the important sentence or gene



Candidate gene approaches

- Assume you know the right chapter
- Based on the idea that genes that we know are involved in treatment pathways might be important
- For example, dopamine-related genes
 - Dopamine blocking agents are useful in treating TS
- So far, this approach hasn't worked very well for TS



Genome searches

- Require you to read the whole book or genome
- Doesn't assume that you know anything about what causes TS
- Safer approach (more likely to be successful)
- More likely to identify multiple genes working either together or in different families
- Takes much longer and is expensive



Chromosome abnormalities

- Assume that part of the important chapter is rearranged, and that this messes up the important sentence or gene
- High potential for success, assuming you find the right kind of families
 - Requires families with a chromosome abnormality and also with TS
- Chromosome abnormalities usually go along with lots of other problems that can complicate the search
 - Did we find a gene for TS or for autism?, for example
- Or, they can be “red herrings”, and not be associated with anything



Types of genetic studies

- Family-based studies
 - Requires large families with multiple people affected with TS
- Case-control studies
 - Individuals with TS and unrelated controls without TS
- Affected sib pair studies
 - Two or more sibs from the same family, both with TS
- Parent-child trios
 - Child has TS, parents may or may not
 - Works like case-control studies, but parents act as controls
- Special cases
 - Chromosome rearrangements
 - Studies in genetic isolates



Genetics of TS: What do we know?

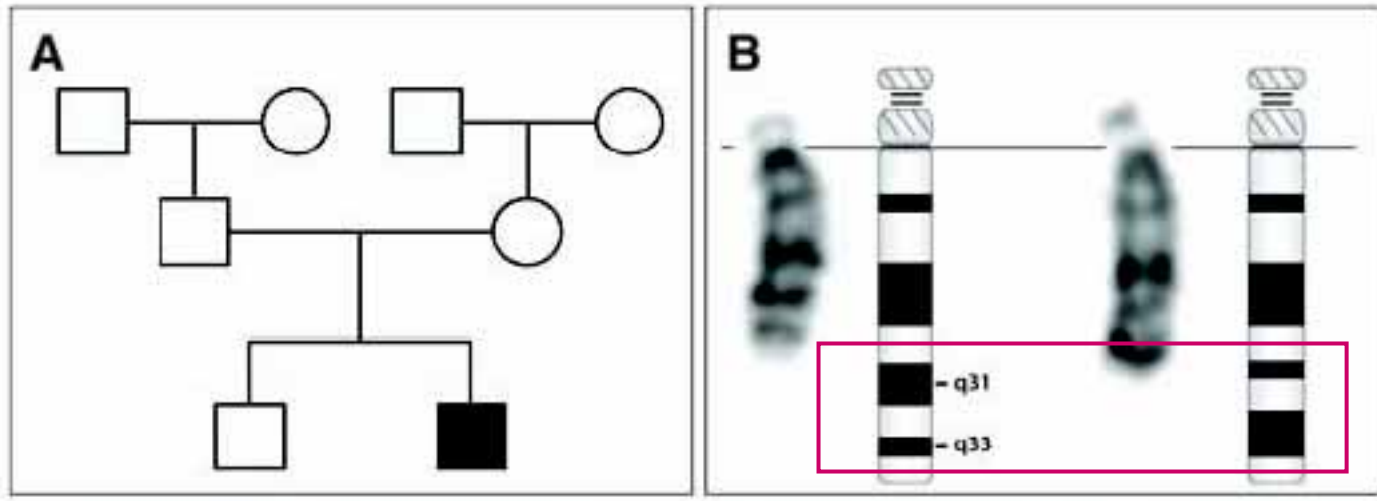
- TSA International Consortium for Genetics
 - International collaboration of scientists and clinicians to find genes that cause TS
 - Supported by the TSA and the NIH
 - Everyone sharing information and resources
- We are using all approaches with the idea that together they will be successful
 - Focus on families with two or more sibs with TS and on parent-child trios (only child needs to have TS)
 - Other approaches complement these



TS and the SLITRK1 gene

- Initial family identified through the TSA
 - 6 year old boy with TS and ADHD
 - Chromosome 13 inversion (flip)
 - Not carried by the parents
 - No other medical abnormalities
- Three genes near the breakpoint of the inversion
 - One was SLITRK1
 - Good candidate because it is located in brain regions important in TS

Chromosome 13 inversion



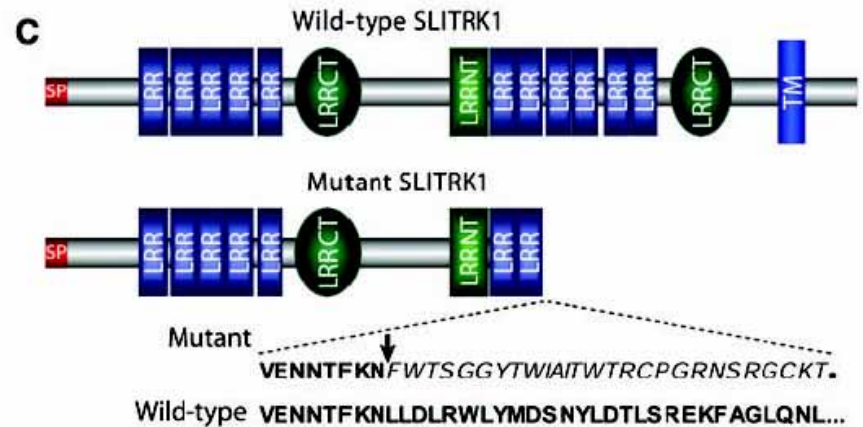
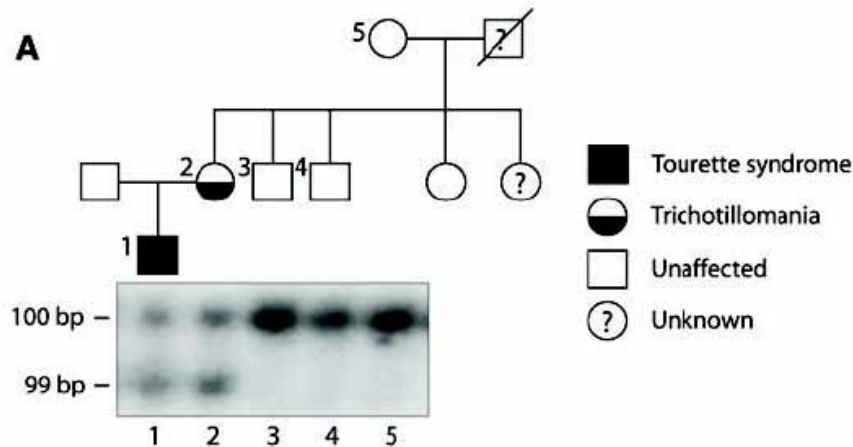
- SLITRK1 near the inversion (not in the breakpoint)
- SLITRK1 normal in boy with TS
- May be a position effect (what other genes are nearby is also important)
- In its new position in this boy, SLITRK1 might be less active



Follow-up in others with TS

- Not enough just to find it in one boy
- Need to follow up with others with TS to make sure its not a coincidence
- Examined SLITRK1 in 174 people with TS
- Found three with abnormalities in SLITRK1

SLITRK1 abnormalities found



- One person with TS (and his mother with trichotillomania) had a shortened SLITRK1
- Like missing an entire part of a sentence, with only the beginning and end left
- This copy of SLITRK1 doesn't function at all



More SLITRK1 abnormalities in TS subjects

- Two additional people with TS of the 174 studied had a SLITRK1 abnormality
- This one was a point mutation
 - Like changing one letter in a word (“of” to “if”)
 - This one might or might not be important
- In this case, it changes how the DNA gets made (translated) into a protein
 - Micro-RNA binding site
 - Results in less SLITRK1 protein being made (maybe 10% less)
- Not 100% related to TS, even in these families
 - In one of the two families, mother with tics had it, sister with tics did not



Where to go next?

- SLITRK1 abnormalities are present in only 3/174 TS cases studied (~2%)
- How do you prove that it is a TS gene?
 - Need to look at how SLITRK1 affects brain function
 - Can't really do this in humans
 - Can do it in mice or neuronal cells in the lab



SLITRK1 and brain

- SLITRK1 is expressed in the regions of human brain associated with TS
- Put SLITRK1 into mouse neurons
 - No SLITRK1
 - Normal SLITRK1
 - Abnormal SLITRK1
- Results:
 - No SLITRK1==normal neurons
 - Normal SLITRK1==bushy neurons
 - Abnormal SLITRK1==scrawny neurons



So is *SLITRK1* a gene for TS?

- It's a good story, but we're not sure yet
- Lots of evidence for it being a TS gene
- Some evidence against it being a TS gene
 - Not seen in all family members with tics in those families who carry the mutation
 - Only seen in 2% of TS patients studied
- Could still be a coincidence
- Need to confirm the findings in other samples



What else is there?

- If SLITRK1 is a gene for TS, it only accounts for $\leq 2\%$ of individuals with TS
- Need to look for other genes
- More chromosomal abnormalities
 - This is limited by the availability of people with TS and a chromosome abnormality
- Back to genome searches



Tourette Syndrome Association International Consortium for Genetics

- Sib pair study done by TSAICG
- Over 400 families so far (over 1000 people)
- Also looked at large families with TS
- Complete genome screen (looking at the entire book)
- Found several regions of interest, most interesting is on chromosome 2
- No proof yet, just evidence that we need to look closer!



Other studies/areas of interest

- Chromosome 17
 - Some evidence in large families
 - Some evidence in genetic isolates
 - Some evidence from subset of sib pairs (associated with hoarding)
- Case control study in the genetically isolated Afrikaner population in South Africa
- Found three chromosomal regions of interest
 - Chromosome 8
 - Chromosome 2
 - Chromosome 11
- Just like the other findings, there is no proof of any of these yet!



Future Plans

- We have submitted a grant to the NIH to continue this work
- We will follow up on the areas of interest and look for additional areas
- We will eventually need additional families for follow-up and confirmation of all the regions of interest
- Best families are parent-child trios
 - Child or adult with TS
 - One or both parents available
 - Parents do not have to have TS



How do I get involved?

- Recruitment for genetic studies still ongoing
- We will refer you to someone in your area for screening and evaluation
- Cornelia Illman PhD
- cillmann@partners.org
- 1-800-471-2730



What is the risk that a family member will have TS if I do?

- Not a simple answer, because we don't know the genes that cause it
- The risk to the general population is 1/2000 to 1/100, or 0.05% to 1%
- In general, risk to first-degree relatives is 10-20%
 - First-degree relative is child, sibling or parent
 - Boys have a higher risk of getting TS than girls
 - Girls are more likely to get OCD
- If you don't have TS, but someone in your family does, the risk is substantially lower
 - Depending on who it is, maybe between 1-5%



What is the risk to my children if I have TS?

- Risk for TS is about 10%
- Risk for a tic disorder is about 30%
- Risk of OCD is about 30%
- Risk of ADHD is about 40%
- Risk of any of the three is about 60%
- Not necessarily severe symptoms
 - 20% of the time a parent with TS doesn't notice tics in their child
- Higher risk if both parents have TS
 - 75% of having a tic disorder
 - 50% of having TS
 - 95% of having tic, OC, or ADHD diagnosis (including mild symptoms)



Family planning

- How does this compare to the risk of other disorders?
 - Risk of ADHD is 10%
 - Risk of bipolar disorder (manic depressive illness) is 2%
 - Risk of being left-handed is 10%
 - Risk of heart disease is 20%
 - Risk of diabetes is 30-40%
 - Risk of breast cancer is 12.5%
 - Risk of prostate cancer is 20%