

## A Possible Link Between Tic Disorders Associated with Beta Thalassemia Minor and Sickle Cell Disease

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### Abstract

**Background:** Genetic linkages with psychiatric disorders have been documented. In our clinical practice, we noticed a high propensity for blood disorders in female patients with certain neuropsychiatric phenomenon, specifically Tourette Syndrome (TS) or Trichotillomania (TTM). With this clinical observation, we hoped to better understand a possible genetic correlation, namely the role of chromosome 11 which encodes for both the B globulin gene and human dopamine receptor D4 (DRD4) gene.

**Method:** This is a retrospective case series of six children found to have a blood disorder and neuropsychiatric diagnosis in our clinic. We used family interview, lab results, and the patient's medical chart for data collection

**Results:** Our case series reveals six children with a repetitive neuropsychiatric disorder and a blood disorder.

**Conclusions:** Currently, there are no definitive susceptibility genes that have been identified to date for TS or TTM. We postulate that blood disorders found on chromosome 11 may play a role as a susceptibility factor, particularly in females, for repetitive neuropsychiatric disorders.

**Keywords:** Tourette syndrome; Tics; Trichotillomania; Sickle cell trait; Beta thalassemia minor

### Introduction

The aim of this report is to describe a possible genetic link between tic disorders and trichotillomania, and blood disorders as they may have a common link associated with chromosome 11. We present six cases of school-aged children (4 females) who had one of these repetitive psychiatric disorders and a blood disorder of either beta thalassemia minor or sickle cell trait. This report builds on the existing literature which has identified genetic links and familial overlap between obsessive compulsive spectrum disorders and blood disorders. Identification of the etiological factors of these disorders will lead to a greater understanding of their pathogenesis and treatment options.

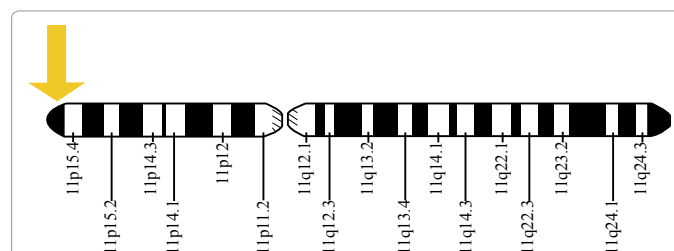
### Background

Psychiatric disorders, like many other medical disorders have potential genetic links. Obsessive compulsive spectrum disorders, such as Obsessive Compulsive Disorder (OCD), tics, and trichotillomania (TTM) may share a common genetic susceptibility as many studies cite high rates of familial overlap [1]. Once presumed rare, the prevalence of Tourette syndrome (TS) is now estimated to range between, 1 to 10 per 1000, in school-aged children and across all ethnic groups with males affected about three to four times more often than females [2]. OCD is a common co morbid condition found in patients with tics with prevalence in adolescents reported to be between 2 to 3%. The lifetime prevalence of TTM is between 1 to 3% [3,4]. TTM is similarly related to OCD and TS as these disorders can involve a negative reinforcement paradigm in which there is a premonitory urge and temporary relief after completion of an action.

In the United States it is estimated that two million people have thalassemia trait, either alpha or beta [5], and sickle cell trait is found in 7 to 9 African Americans [6]. Beta thalassemia minor and sickle cell trait (HbSC) often present with anemia that is mistakenly thought to have little clinical significance to overall health of the affected individual. Chromosome 11 encodes a gene specific for B globulin, "Hemoglobin Beta" or the HBB gene, which are both affected in beta thalassemia minor and sickle cell disease. In beta thalassemia minor, the

production of the beta chain is affected resulting in mild-to-moderate microcytic anemia. Sickle Cell Disease (SCD) produces a mutant form of beta globulin, due to a point mutation at the sixth position of its beta chain, in which glutamic acid is replaced with valine. This mutation results in a sickled, incorrectly functioning red blood cell (RBC). The sickle cell trait form of the disease (HbSC) occurs when only one of the hemoglobin genes is sickled. The HBB gene is located at 11p15.5 and more precisely from base pair 5,203,271 to base pair 5,204,876 (Figure 1).

Chromosome 11 has been implicated as having a linkage associated with multiple psychiatric disorders such as Attention Deficit Hyperactivity Disorder (ADHD), Tourette syndrome, and bipolar disorder. Over the past 10 years there have been several studies indicating there may be a link between chromosome 11q 23-24 and Tourette syndrome [7]. The human dopamine receptor D4



**Figure 1:** HBB gene is located at 11p15.5 and more precisely from base pair 5,203,271 to base pair 5,204,876.

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(DRD4) gene like the HBB gene is located on chromosome 11p15.5. This dopamine gene has been found to be specifically located from base pair 637,304 to base pair 640,705. The DRD4 gene is one of the most variable human genes known and has been linked to multiple psychiatric disorders such as ADHD, a common co morbid diagnosis with TS, and impulse control disorders such as TTM [8].

Minor or heterozygote blood disorders are not necessarily benign and are a source of controversy in the medical literature. Some view the trait form of the disease as a milder or intermediary form of sickle cell disease but each have their own medical complications. Sick cell disease patients are at an increased risk of bacteremia particularly from encapsulated organisms, splenic sequestration, vaso-occlusive crisis, stroke, renal disease, and pulmonary hypertension [9]. Sick cell trait (HBSC) has been associated with sudden idiopathic death/ and or rhabdomyolysis during intense exercise, splenic infarctions at elevated altitudes, hematuria, hyposthenuria, bacteriuria, and renal medullary carcinoma in children and young adults [10]. Minor hemoglobinopathies have been linked to have a higher prevalence of asthma [11]. Cognitive dysfunction has been linked to various anemias and more specifically an association between low hemoglobin and neurocognitive impairment has been found in children with sickle cell disease [12].

Case Reports

Case A is an 11-year-old female diagnosed with TS, ADHD-combined type, and remitted OCD. At the age of 10 years her tics became so severe that a pediatric neurologist diagnosed her with Sydenham chorea, a movement disorder caused by Group A *Streptococcus*. Her tics consisted of wiggling her nose, head bobbing, grunting and a need to straighten out her arms. She has beta thalassemia minor with anemia and the patient’s maternal grandmother and mother also have beta thalassemia minor. She is of Sicilian descent from her mother who is second generation Sicilian and father is from Honduras. There is no history of anemia on the father’s side of the family. A maternal uncle has TS and her father has unspecified tics.

Case B is a 13-year-old female diagnosed with TS at the age of 12 years. Her parents report that they had concerns of tic behaviors since she was a young child but only sought treatment after the tics became impairing. Her tics consisted of grunting, throat clearing, and neck, leg and arm jerking. She has both alpha thalassemia minor and beta thalassemia minor. Her mother is known to have alpha thalassemia minor and is of European and Cherokee descent. The father’s history is unknown as this patient was conceived thru insemination.

Case C is a 7-year-old African/American/Caucasian female diagnosed with ADHD-combined type, OCD, and Chronic Motor Tic Disorder. Her symptoms consisted of being impulsive, hyperactive, distractible and making disruptive noises at times. She preferred to do things in sets of three and was perfectionist in her homework, erasing letters up to 50 times until they look right to her. Her tics consisted of head and jaw movements. She has sickle cell trait and a family history of blood disorders was not obtainable due to patient being lost to follow-up.

Case D is a 17-year-old Caucasian female diagnosed with Trichotillomania, Major Depressive Disorder and Generalized Anxiety Disorder. She began to pull hair from her scalp and eyebrows when she was 12 years-old. She has beta thalassemia minor, which was inherited from her father.

Case E is an 8-year-old African American boy diagnosed with TS

and ADHD-combined type. He began having vocal tics in kindergarten which lasted a few months. Motor tics began at age 8 and consisted of eye blinking, eye rolling and neck jerks. He has sickle cell trait which was inherited from his father who is of Sicilian descent. His family history is significant for a paternal uncle with ADHD and tic disorder.

Case F is an 8-year-old African American boy diagnosed with transient tic disorder. He developed a neck jerking tic concurrent with a GAS infection that remitted after a few months. He has sickle cell trait, which his mother, sister and maternal grandmother also have. There is no family history of a tic disorder (Table 1).

Discussion

We present a case series of children diagnosed with a repetitive neuropsychiatric disorder such as tics, OCD, or hair pulling also diagnosed with beta thalassemia minor or sickle cell trait. It is possible that having one of these blood disorders was an incidental finding or that these disorders had a contributory role in developing TS or TTM. It is interesting that four of the six cases were female whereas tic disorders are much less commonly represented compared with males. The 15p.5 area on chromosome 11 is a highly imprinted area and could possibly explain the greater incidence of females in this case series. Many studies of families have indicated a greater risk of developing TS in first degree relatives compared to the general population [13] yet only two of our 6 cases had a reported family history of a tic disorder. Only one of our cases (F) had a sibling, a sister, with the same hemoglobinopathy but did not have any psychiatric diagnosis. The concurrent hematological carrier state may increase risk for neuropsychiatric illness expression such as tics and trichotillomania or perhaps some other unknown factor contributed to a greater risk for both.

Research supports overlapping co morbidities of TTM, ADHD, tic disorder, anxiety, impulse control disorders, and mood disorders [14]. A recent genetic study of families with TS found there may be a heritable phenotype with those that had a combination of TS, OCD, and ADHD [15]. A 2008 study of 133 adolescents identified with a primary diagnosis of TTM found that 38.3 % had co-morbid psychiatric diagnoses. The most common were anxiety disorder (24.1%), mood disorder (18.8%), attention-deficit disorder with or without hyperactivity (16.5%), and tic disorder (4.5%) [16].

Chromosome 11 has been implicated to have a linkage associated with multiple psychiatric disorders such as ADHD, Tourette syndrome, impulse control disorders, and bipolar disorder. Over the past 10 years there have been several studies indicating there may be a link between

Cases	A	B	C	D	E	F
Age	11	13	7	17	8	8
Gender	Female	Female	Female	Female	Male	Male
Psychiatric DX	TS OCD ADHD	TS	ADHD OCD CMT	TTM MDD GAD	TS ADHD	TTD
Blood disorder	BTM	A/BTM	HbSC	BTM	HbSC	HbSC
Family member w/BD	Mother, MGM	Mother	unknown	Father	Father	Mother MGM, S
Family history of Tics	Yes	No	No	No	Yes	No

ADHD: Attention Deficit Hyperactivity Disorder; A/BTM: Alpha and Beta Thalassemia Minor; BD: Blood Disorder; BTM: Beta Thalassemia Minor; CMT: Chronic Motor Tic; GAD: Generalized Anxiety Disorder; HbSC: Sickle Cell Trait; MD: Major Depression; MGM: Maternal Grandmother; OCD: Obsessive Compulsive Disorder; S: Sister; TTD: Transient Tic Disorder; TTM: Trichotillomania; TS: Tourette Syndrome

Table 1: Characteristics of the patients.

chromosome 11q 23-24 and TS. Dopaminergic abnormalities in frontal-sub cortical circuits have been hypothesized as the underlying pathophysiological mechanism in TS, impulse control disorders, and ADHD. Recently, a certain dopamine receptor, found on the DRD4 gene, which is located in chromosome 11p15.5, has also been linked to ADHD. In addition, chromosome 11 has also been linked with bipolar disorder [17] and multiple case reports discuss a possible linkage between bipolar disorder and Beta Thalassemia minor [18,19].

In addition, ADHD is often a common co morbid diagnosis found with TS and OCD and has significant impact in academics and intellectual function. Cognitive dysfunction has been linked to various anemias, and three out of the six cases were diagnosed with ADHD combined type. Cognitive dysfunction in areas such as sustained attention, executive function, coordination, and visual motor speed are found to be impaired in children who have subclinical or silent strokes which are common complications of SCD. These infarctions can appear on MRI without any history of a neurological event [20] and have a prevalence rate in children with the HBSS form between 20% to 25% [21].

Another study compared cognitive processing and academic functioning in both HBSS and HBSC with non-diseased siblings and found significantly lower scores in both HBSS and HBSC of sickle cell disease compared to their siblings [22]. A study from 2007 reported cognitive dysfunction in adult patients with beta-thalassemia minor by evaluating event related potentials. Patients with beta thalassemia minor had P300 latency that was significantly longer than in the control group and had lower amplitudes, suggestive of cognitive dysfunction [23]. These studies argue that the minor forms of both hemoglobinopathies should not be overlooked as medical diagnoses with little or few clinical repercussions.

This case review was intended to increase understanding between the localization of a gene or genes involved in the expression of TS and TTM. Four of our six cases had no clear genetic history of a neuropsychiatric disorder and these specific cases suggest that blood disorders might play a role as a susceptibility factor in obsessive compulsive spectrum disorders, specifically tic disorders and trichotillomania. With the low prevalence of females reported in the literature with TS, this additional dysfunction of the beta globulin gene on chromosome 11 may add a predisposing risk factor for females to develop these disorders. We also suggest that with the well established findings of cognitive dysfunction in patients with sickle cell disease and thalassemias that many children with just the trait form of each disease may be having cognitive dysfunction secondary to the hematologic disease which needs to be further explored.

There are many limitations to our study such as the small sample size, missing family medical and psychiatric data, lack of genetics and neuro-imaging. Potential considerations for future research include: a) replication surveys of microcytic anemia and the thalassaemic trait in psychiatric populations from high prevalence areas; b) surveys of tic disorder and impulse control disorders among subjects with an already established diagnosis of heterozygous  $\beta$ -thalassemia or sickle cell anemia and; c) family studies of patients with TS and TTM and an established thalassaemic trait; d) genetic microarrays; and e) imaging that would examine cerebral vasculopathy in children, such as transcranial doppler ultrasonography. This imaging could aid in determining what effects compromised red blood cells have neurologically as there is little literature examining this. A future prospective study examining children with tic disorder and blood disorder versus a control population of children with only tic disorder is warranted.

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