

Schizophrenia and Nail Patella Syndrome: The Dopamine Connection

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ABSTRACT: **Background:** Nail-patella syndrome (NPS) is characterized by changes in the nails, knees, and elbows, as well as the presence of iliac horns detected by X-ray of the pelvis. A higher occurrence of psychiatric disorders has also been suggested in NPS. Heterozygous mutations in the gene encoding the LIM-homeodomain transcription factor (*LMX1B*) are identified in most patients with typical clinical findings of NPS.

Objective: To report on the association between NPS and schizophrenia.

Methods: Genomic DNA was isolated from a patient's venous blood and collected on ethylenediaminetetraacetic 5% with the Genra Puregene Blood Kit. All exons and flanking regions of the *LMX1B* gene (*LMX1B*: NM_001174146.1) were amplified by standard polymerase chain reaction and analyzed by direct DNA sequencing with BigDye Terminators on an ABI 3100 sequencer. Sequence chromatograms were analyzed using SeqScape software version 1.1. Mutation analysis and characterization of variants was performed with the Alamut Software Version 2.1.

Results: We report a patient presenting to the psychiatry department with schizophrenia. Clinical examination revealed characteristic findings consistent with NPS. Since NPS was suspected, based on clinical findings, sequencing of all coding exons of *LMX1B* gene was completed. Results revealed a novel heterozygous mutation in the proband: c.546_547insACCG(het); p.Glu183Thrfs*11.

Conclusions: Based on *LMX1B* expression in brain regions that are implicated in neuropsychiatric illness, and especially in the development of dopaminergic neurons, we hypothesize that schizophrenia may be part of the clinical spectrum of NPS.

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in rare cases [1]. *LMX1B* plays a role in the development of various organs during the embryonic period, including limbs, kidneys, and eyes. *LMX1B* also plays a role in the development of the central nervous system (CNS), including the development of dopaminergic and serotonergic neurons in the midbrain and hindbrain and in the dorsal interneurons of the spinal cord [2].

The prevalence of NPS has been estimated at 1:50,000; however, may be higher as it is likely that some individuals with milder clinical manifestations do not seek medical attention and thus go undiagnosed.

In accordance with the developmental role of *LMX1B*, NPS is characterized by changes in the limbs as well as the nails (in 98% of patients nails may be hypoplastic, dystrophic, absent, discolored, thin or thickened), knees (in 74% of patients the patellae may be irregular, hypoplastic, absent, dislocated), and elbows (in 70% of patients limited range of motion, cubitus valgus). The presence of iliac horns may be detected in X-rays of the pelvis. The clinical spectrum of NPS can also include nephropathy (30–50% of patients) and glaucoma. Neurologic manifestations may also be expressed as peripheral neurological symptoms and a higher prevalence of epilepsy (6% of patients) [3].

A higher occurrence of psychiatric disorders has also been suggested in NPS. One report showed attention deficit disorder/attention deficit hyperactivity disorder in 11 of 50 patients and depression in 20 of 50 patients [4]. The co-occurrence of depression in NPS is still debated since additional research found no evidence of depression or other mood disorders in NPS patients [2].

Schizophrenia is a psychiatric disorder with variable symptoms including psychosis, negative behavior, and cognitive impairment. Schizophrenia has a very significant genetic component, and first degree relatives have an incidence of schizophrenia an order of magnitude higher than the general population. It is a complex disorder with multifactorial modes of inheritance in which the combined effect of many genes, as well as non-genetic factors, each confer a small increase in risk to develop the illness. Thus, no causal disease genes of major effects have been identified. Several of the genes that are strongly associated with schizophrenia are directly involved in dopaminergic transmission and other brain developmental processes [5].

Nail-patella syndrome (NPS) is an autosomal dominant disorder caused by mutations in the *LMX1B* gene encoding the LIM-homeodomain transcription factor. Heterozygous mutations are identified in most patients with typical clinical findings, although homozygous inheritance has been suggested

It has been shown that *LMX1B* plays a crucial role in the development of the dopaminergic neurons. A variant of the *LMX1B* gene has been associated with schizophrenia [6]. Surprisingly, to the best of our knowledge, there are no reported cases of psychosis in NPS.

In this article we report on a patient presenting with schizophrenia to the psychiatry department of a local mental health facility. Clinical examination revealed characteristic findings consistent with NPS, and gene sequencing displayed a novel mutation in *LMX1B*. Based on *LMX1B* expression in brain regions that are implicated in neuropsychiatric illness and especially in dopaminergic neurons, we hypothesized that schizophrenia may be part of the clinical spectrum of NPS.

PATIENTS AND METHODS

We discuss the case of a 30 year old Jewish male patient. He had no family history of mental illness. He was born by cesarean section, one of a triplet, following an uneventful pregnancy. Motor and cognitive development was described as normal. He reported stuttering from young age. His academic skills are described as excellent, but he always had major social difficulties.

He served in the army during which, at the age of 19, he was exposed to a traumatic event. After the event, he started engaging in philosophical and religious ideas and gradually, during a course of 10 years, he became isolated, withdrawn, anxious, and argumentative. One year prior to his hospitalization he became suspicious of his parents, saying that they poisoned his food. He became verbally and physically aggressive and attacked one or more of the family members.

At the age of 29, he was hospitalized in a psychiatric ward for the first time. During his hospitalization he was anxious and suspicious, showed disturbances in his thought processes including circumstantial speech and tangentially, and displayed delusions of persecution and reference such as thinking that someone had poisoned his food with a substance that makes his thoughts transparent. He was diagnosed with an acute psychotic episode.

Extended physical, laboratory, and radiological examinations were conducted due to the presentation of a first psychotic episode. Physical examination revealed hypoplastic and dystrophic finger nails and toe nails and mild contractures on both elbows, thus he cannot fully extend his arms. A previous knee X-ray demonstrated a small, chronically dislocated patellae.

Complete blood count, blood chemistry including renal functions, thyroid functions, hepatitis B, hepatitis C, anti-nuclear antibody, venereal disease research laboratory test, and urine toxicology, were normal. Urine examination was normal and there was no proteinuria. A toxicological urine screen was negative. Ceruloplasmin levels were low on two examinations, and ophthalmological examination did not show Keiser–Fleisher ring. Neurological examination, elec-

troencephalography, and brain magnetic resonance imaging were normal.

Based on findings of delusions of persecution and disorganized speech for at least 1 month, continuous psychotic signs for at least 6 months, and a progressive social and occupational functional decrease over the last 10 years, he received a diagnosis of schizophrenia. There were no affective or autistic symptoms, and he denied alcohol or substance abuse in the past and during his hospitalization.

After treatment with risperidone (5 mg/day), he was discharged with no delusions and an improvement in his speech. The diagnosis stayed stable in recurrent hospitalizations. The abnormal physical and radiological examination raised the suspicion of NPS and he underwent ambulatory genetic counseling, followed by genetic testing.

Genomic DNA was isolated from venous blood and collected on ethylenediaminetetraacetic 5% with the Gentra Puregene Blood Kit (Qiagen, Valencia, CA, USA). All exons and flanking regions of the *LMX1B* gene (*LMX1B*: NM_001174146.1) were amplified by standard polymerase chain reaction and analyzed by direct DNA sequencing with BigDye Terminators on an ABI 3100 sequencer (Applied Biosystems, Foster City, CA, USA). Sequence chromatograms were analyzed using SeqScape Software Version 1.1 (Applied Biosystems). Mutation analysis and characterization of variants was performed with the Alamut Software Version 2.1 (Interactive Biosoftware, Rouen, France).

RESULTS

Since NPS was suspected based on clinical findings, sequencing of all coding exons of *LMX1B* gene was completed. The results revealed a novel heterozygous mutation in the proband: c.546_547insACCG(het); p.Glu183Thrfs*11. To the best of our knowledge, this mutation has not been reported before in public databases (EXAC, ClinVar, ESP, and COSMIC) and prediction algorithms showed high functional effect. Based on reports of similar mutations, we expected the mutations to lead to nonsense-mediated decay of the mRNA, resulting in a reduction of protein levels.

DISCUSSION

We report the case of a patient with co-occurrence of schizophrenia and NPS caused by a novel mutation in the *LMX1B* gene. Based on *LMX1B* expression in embryonic dopaminergic neurons, we hypothesized that schizophrenia might be part of the clinical spectrum of NPS.

NPS is caused by loss of function mutations in the *LMX1B* gene that are suspected to cause reduction in *LMX1B* activity by different mechanisms. Since the different types of mutations (nonsense, frameshift, splice site, missense and exonic deletions, and duplications) result in the same NPS

phenotype, it is hypothesized that NPS is a result of *LMX1B* haploinsufficiency. *LMX1B* transcripts bearing nonsense or frameshift mutations (as the mutation reported here) are postulated to lead to nonsense-mediated mRNA decay resulting in a reduction of protein amounts. Other mutations within the homeodomain or LIM domains of the protein reduce *LMX1B* activity by eliminating DNA binding.

Knock out experiments in mice showed that in the developing CNS, *LMX1B* is required for formation and survival of the dopaminergic neurons during the embryonic period [7].

LMX1B has been previously linked to schizophrenia by Bergman and colleagues [6], showing preliminary evidence that polymorphisms in *LMX1B* are associated with schizophrenia. They hypothesize that schizophrenia may be associated with *LMX1B*-mediated decrease in the density of the dopaminergic neurons [6].

We report on a patient with co-occurrence of schizophrenia and NPS caused by a novel mutation in *LMX1B*. We propose that since *LMX1B* has a dual role in the development of tissues implicated in the syndrome and in the development of dopaminergic neurons, schizophrenia might be part of the clinical spectrum of NPS.

CONCLUSIONS

The true incidence of mental disorders, and schizophrenia in particular, in NPS is unknown, as only a minority of affected individuals have undergone appropriate evaluation. Thus, we cannot exclude that the co-occurrence of NPS and schizo-

phrenia in this case is a mere coincidence. Future studies need to address whether there is a predisposition for schizophrenia in NPS and to provide the best evidence to guide clinical surveillance in these patients.

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Capsule

Uncomplicating malaria

Severe malaria is caused by the parasite *Plasmodium falciparum*. Infections can result in organ failure and life-threatening hematological or metabolic abnormalities. Lee et al. sequenced patient and parasite transcriptomes from 46 *P. falciparum*-infected Gambian children to better understand host-pathogen interactions. The immune response in severe

malaria, compared with that in uncomplicated malaria, was not necessarily dysregulated but instead reflected high parasite loads, although there was a distinct neutrophil response.

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Eitan Israeli

“When you waste a moment, you have killed it in a sense, squandering an irreplaceable opportunity. But when you use the moment properly, filling it with purpose and productivity, it lives on forever”

Rabbi Menachem Mendel Schneerson, (1902–1994), known to many as the Rebbe, was a Russian Empire-born American Orthodox Jewish rabbi, and the last rebbe of the Lubavitcher Hasidic dynasty. He is considered one of the most influential Jewish leaders of the 20th century

“There is no end to education. It is not that you read a book, pass an examination, and finish with education. The whole of life, from the moment you are born to the moment you die, is a process of learning”

Jiddu Krishnamurti, (1895–1986), Indian public speaker, author