



## CLINICAL CASE ROUNDS

# Case Report of Childhood-Onset Psychosis in a Patient with a Known WNT10A Mutation

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## Abstract

**Objective:** To report on a patient with childhood-onset psychosis at age 12 with a known WNT10A mutation. **Methods:** Case report. **Results:** The patient is a 12-year-old male who presented with an acute onset of psychosis in the context of a known WNT10A mutation. **Conclusion:** WNT genes have only been previously linked to schizophrenia on a theoretical basis. To our knowledge, this is the first case report of an association between a childhood-onset psychosis and a WNT10A mutation. We conclude that there is a possibility that WNT10A may be one of the many genes contributing to the development of childhood-onset schizophrenia.

**Key Words:** *childhood-onset, schizophrenia, WNT10A*

## Résumé

**Objectif:** Faire rapport sur un patient chez qui la psychose est apparue à 12 ans et qui a une mutation connue du WNT10A. **Méthodes:** Rapport de cas. **Résultats:** Le patient est un garçon de 12 ans qui a présenté un début de psychose aiguë dans le contexte d'une mutation connue du gène WNT10A. **Conclusion:** Les gènes WNT n'ont précédemment été liés qu'à la schizophrénie sur une base théorique. À notre connaissance, ceci est le premier rapport de cas d'une association entre une psychose apparue dans l'enfance et une mutation du WNT10A. Nous en concluons qu'il existe une possibilité que le WNT10A soit l'un des nombreux gènes qui contribuent au développement de la schizophrénie apparue dans l'enfance.

**Mots clés:** *apparition dans l'enfance, schizophrénie, WNT10A*

## Introduction

Schizophrenia is one of the most disabling and economically catastrophic medical disorders; it contributes 13.4 million years of life lived with disability to burden of disease globally (Charlson et al., 2018).

Childhood-onset schizophrenia is defined as beginning before the age of 13. Such an early presentation is exceedingly rare. A study in the United States of America estimated a prevalence of 0.04% (McKenna, Gordon, & Rapoport,

1994; Rapoport & Gogtay, 2011); while another in Germany estimated 0.01% (Kallmann & Roth, 1956) no significant inter-group differences have been found either with respect to twin concordance rates or with respect to the schizophrenia rates for the parents (12.5% and 9.2%. This is in contrast with the overall prevalence of the disease, estimated to be about 1% worldwide. The pathogenesis of childhood-onset schizophrenia is not thought to be much different from the adult-onset form of the disease; however, the illness has

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proven to be more severe and debilitating than the adult-onset type (Ordóñez, Luscher, & Gogtay, 2016).

It has long been known that schizophrenia has a substantial genetic component; with heritability being estimated from ~65-80% (Sullivan, Kendler, & Neale, 2003). Through the recent advent of Genome-Wide Association Studies (GWAS) over 100 different forms of DNA variation—including both SNPs (single nucleotide polymorphisms) and CNVs (copy number variants)—have been associated with schizophrenia (Aberg et al., 2013; Ripke et al., 2013, 2014; Shi et al., 2009; Stefansson et al., 2009) a devastating psychiatric disorder, has a prevalence of 0.5-1%, with high heritability (80-85%; however, there are no confirmed causal mutations, nor families where schizophrenia segregates in a Mendelian fashion (Harrison, 2015). Overall, GWAS has identified a large number of susceptibility loci each having a very small effect, meaning that schizophrenia has proven to be a highly complex, heterogeneous and polygenic disease (Henriksen, Nordgaard, & Jansson, 2017). The WNT pathway has theoretically been thought to play a role in schizophrenia given its role in neuronal migration and programmed cell death during development, yet no WNT gene mutation has ever been associated with the development of schizophrenia (Harrison, 2015; Panaccione et al., 2013). Epidemiologic and family studies looking at genetics in childhood-onset schizophrenia have been limited due to the low prevalence of this illness as described earlier. We report on a patient with a known WNT10A mutation who presented with psychosis at the age of 12. To our knowledge this is the first case of childhood-onset psychosis in a patient with a known WNT10A gene mutation.

## Case Report

A 12-year-old male presented to our centre with a one-month history of odd beliefs and behaviour. He lived at home with his parents and ten-year-old sister. In the Emergency Room he began the interview by consistently repeating that he was “dead” and saying, “I don’t want to be here. I am not safe. I am drowning.” He tried to leave the room multiple times and required redirection. He was uncooperative, suspicious and guarded and his speech was often unintelligible. His thought content was consistent with paranoid delusions. No hallucinations were reported and the patient did not seem to be responding to any internal stimuli.

The patient was born post-term after an uncomplicated pregnancy except for antepartum fetal distress necessitating a C-section and concern for small birth weight. His mother was not on any medications during pregnancy and there was no exposure to alcohol, smoking, or drugs. Neonatal course was unremarkable except for jaundice requiring phototherapy. Motor milestones were normal, with walking at ten months, but the patient was drooling into his first year of life and had a language delay. He was found to have normal receptive language but considerable expressive language

delay and articulation problems necessitating speech therapy from the age of two. At the time of presentation, he had a diagnosed reading disability and was in grade seven with an individualized education plan.

His past medical history was significant for asthma, eosinophilic esophagitis (well controlled for years with steroid medication), food protein enteropathy, and multiple IgE-mediated food allergies. He was evaluated by the Genetics Team for abnormal dentition in addition to developmental delay, failure to thrive, and feeding difficulties and was found to have two heterozygous mutations in WNT10A in trans, one of which is associated with tooth abnormalities and possibly hypohydrosis (variant p.F228I, Coding DNA c.682 T>A) and one of which is a variant of uncertain significance (variant p.G165R, Coding DNA c.493 G>A). His past psychiatric history was significant for being under the care of a community psychiatrist for generalized anxiety and social anxiety for the last two months.

His medications on presentation were: lansoprazole, inhaled budesonide (1mg/2mL inhalation suspension taken every three days), mometasone nasal spray, ciclesonide nasal spray, salbutamol and Co-enzyme Q10. Parents denied any substance use.

Parents had noticed a cognitive decline over the last three months. They described a more disrupted sleep cycle, and an increase in uncooperative behaviour that teachers were calling defiance but the parents felt was more consistent with confusion. For example, the patient would be walking in a familiar place and all of a sudden look around completely lost to his surroundings.

In the last month, he had started to voice a number of paranoid thoughts: the presence of hidden cameras, teachers putting ‘body parts’ in the closets, and snipers on the roof of the house. His parents also noticed new strange behaviours including waking up in the middle of the night screaming and hitting his mother and himself. At other times he seemed disconnected and parents found his emotional expression difficult to read. The night the family presented to the Emergency Room, the patient’s mother found him awake just after midnight packing a suitcase full of clothing and a kitchen knife. He was insisting on leaving the house (inappropriately dressed for the winter weather) because he felt unsafe.

Family history was significant for one episode of psychosis in the maternal uncle which had resolved with medication.

As this was a first presentation of childhood psychosis, our group adhered to the Canadian Schizophrenia Guidelines (Pringsheim & Addington, 2017) and the NICE (National Institute for Health and Care Excellence) Psychosis and Schizophrenia in Children and Young People Guidelines (National Institute for Health and Care Excellence, 2016) for a comprehensive diagnostic work-up. There were no significant abnormal findings found on blood work as seen

**Table 1. Laboratory values at presentation**

Red Blood Cells (4.5-5.1x10 <sup>12</sup> /L)	<b>4.11</b>	Thyroid stimulating hormone (0.7-6.4 mIU/L)	2.20
White Blood Cells (3.5-12.0x10 <sup>9</sup> /L)	4.1	Prolactin serum males (1-20 µg/L)	12
Hemoglobin (112-165 g/L)	122	Aspartate Aminotransferase (AST) (7-40 IU/L)	<b>52</b>
Platelets (150-400x10 <sup>9</sup> /L)	264	Alanine Aminotransferase (ALT) (5-35 IU/L)	11
Na <sup>+</sup> serum (135-145 mmol/L)	143	Ceruloplasmin (200-600 mg/L)	212
K <sup>+</sup> serum (3.4-4.7 mmol/L)	<b>5.2</b>	Vitamin B12 (149-772 pmol/L)	585
Cl <sup>-</sup> serum (96-106 mmol/L)	104	Folate (>27.6 nmol/L)	<b>21.5</b>
Ca <sup>2+</sup> ionized (1.16-1.36 mmol/L)	1.17	Anti-nuclear antibody	negative
Mg <sup>2+</sup> (0.65-1.05 mmol/L)	0.88	Urinalysis	negative
Glucose fasting (3.9-6.1 mmol/L)	4.5	Urine toxicology	negative
Creatinine serum (50-110 µmol/L)	<b>41</b>	Serum toxicology	negative
All values are reported as the patient's value (reference range)			
Values outside of the normal range have been <b>bolded</b> .			

in Table 1 or on brain MRI and EEG. The patient did have a slight hyperkalemia on presentation (K<sup>+</sup> 5.2) that normalized without treatment on subsequent bloodwork.

With a negative neurological exam, cerebral spinal fluid testing (for toxicology and anti-NMDA receptor antibodies) was not pursued. The patient was started on Olanzapine and has achieved partial improvement one year later.

## Discussion

We described a patient, with a known WNT10A mutation, who presented with psychosis at age 12. Our assessment included a full psychiatric, medical, psychological, psychosocial, and developmental investigation. Given that our medical work-up was negative, our diagnosis of exclusion was that this was indeed a first presentation of psychosis of psychiatric origin. Possible etiological factors of this early onset psychosis include hypoxia at the time of birth and the WNT10A mutation. Although oral steroid medications are well known to cause neuropsychiatric side effects including psychosis (Dubovsky, Arvikar, Stern, & Axelrod, 2012) these side effects have not been associated with inhaled corticosteroid use (Toogood, 1998). Therefore, steroids were ruled out as the cause in our patient given that he had been maintained on a stable dose of inhaled budesonide over several years. The patient's mild hyperkalemia on presentation that normalized without treatment was also ruled out as a potential cause as hyperkalemia is not known to have psychotic manifestations and there was no improvement in our patient's behaviour upon normalization (Shrimanker & Bhattarai, 2019).

Historically, mutations in the WNT10A gene have been associated with three syndromes: Tooth agenesis, Schopf-Schulz-Passarge syndrome, and Odonto-onycho-dermal dysplasia (National Institute of Health, 2018). Classically,

the WNT10A gene has not been associated with childhood-onset schizophrenia.

To our knowledge this is the first case of childhood-onset psychosis in a patient with a known WNT10A gene mutation. It is important to recognize that the specific mutations seen in our patient (variant p.F228I, Coding DNA c.682 T>A and variant p.G165R, Coding DNA c.493 G>A) have a frequency of 0.00599 and 0.00220 respectively in the population and there have been no cases thus far reporting psychosis (National Center for Biotechnology Information, n.d.-a, n.d.-b). Further, databases of human genetic variation demonstrate that there are individuals who are homozygous for these particular mutations, and they have not been reported to have psychosis (National Center for Biotechnology Information, n.d.-a, n.d.-b). In addition, the WNT10A gene has been shown to have a lack of intolerance to variation (pLI=0.000) meaning that a high amount of genetic disturbance is needed in order to produce a different phenotype (gnomAD browser, n.d.).

Therefore, we would like to emphasize that our finding does not imply causality. Rather, we are reporting on an association between a WNT10A gene mutation and childhood-onset psychosis. It is possible that our patient has an otherwise high genetic risk score for the development of childhood-onset schizophrenia. However, given the theoretical link between the WNT pathway and schizophrenia with its role in neuronal migration and programmed cell death during development, we cannot discount that these heterogeneous mutations in the WNT10A gene in our patient may be contributing to his presentation of childhood-onset psychosis. We conclude that there is a possibility that WNT10A may be one of the many genes contributing to the development of childhood-onset schizophrenia. Further research is needed to examine if there is truly a causal relationship and

whether it can be attributed to one particular mutation. Given how rare childhood-onset schizophrenia is, future case reports and case series may provide insight into answering this question.

## Consent

Witnessed consent was obtained on March 15<sup>th</sup> 2018 to present this case for academic purposes.

## Acknowledgements / Conflicts of Interest

The authors have no known conflicts of interest in this case presentation.

## References

- Aberg, K. A., Liu, Y., Bukszar, J., McClay, J. L., Khachane, A. N., Andreassen, O. A.,...van den Oord, E. J. (2013). A comprehensive family-based replication study of schizophrenia genes. *JAMA Psychiatry*, 70(6), 573-581. <https://doi.org/10.1001/jamapsychiatry.2013.288>
- Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., Scott, J. G.,...Whiteford, H. A. (2018). Global epidemiology and burden of schizophrenia: Findings from the global burden of disease study 2016. *Schizophrenia Bulletin*, 44(6), 1195-1203.
- Dubovsky, A. N., Arvikar, S., Stern, T. A., & Axelrod, L. (2012). The Neuropsychiatric Complications of Glucocorticoid Use: Steroid Psychosis Revisited. *Psychosomatics*, 53(2), 103-115. <https://doi.org/10.1016/j.psym.2011.12.007>
- Genome-wide association study identifies five new schizophrenia loci. (2011). *Nature Genetics*, 43(10), 969-976. <https://doi.org/10.1038/ng.940>
- gnomAD browser. (n.d.). WNT10A wingless-type MMTV integration site family, member 10A. Retrieved July 9, 2019, from [https://gnomad.broadinstitute.org/gene/ENSG00000135925?dataset=gnomad\\_r2\\_1](https://gnomad.broadinstitute.org/gene/ENSG00000135925?dataset=gnomad_r2_1)
- Harrison, P. J. (2015). Recent genetic findings in schizophrenia and their therapeutic relevance. *Journal of Psychopharmacology (Oxford, England)*, 29(2), 85-96. <https://doi.org/10.1177/0269881114553647>
- Henriksen, M. G., Nordgaard, J., & Jansson, L. B. (2017). Genetics of Schizophrenia: Overview of Methods, Findings and Limitations. *Frontiers in Human Neuroscience*. Retrieved from <https://www.frontiersin.org/article/10.3389/fnhum.2017.00322>
- Kallmann, F. J., & Roth, B. (1956). Genetic Aspects of Preadolescent Schizophrenia. *American Journal of Psychiatry*, 112(8), 599-606. <https://doi.org/10.1176/ajp.112.8.599>
- McKenna, K., Gordon, C. T., & Rapoport, J. L. (1994). Childhood-Onset Schizophrenia: Timely Neurobiological Research. *Journal of the American Academy of Child & Adolescent Psychiatry*, 33(6), 771-781. <https://doi.org/10.1097/00004583-199407000-00001>
- National Center for Biotechnology Information. (n.d.-a). ClinVar, Variation ID 334399. Retrieved July 9, 2019, from <https://preview.ncbi.nlm.nih.gov/clinvar/variation/334399>
- National Center for Biotechnology Information. (n.d.-b). ClinVar, Variation ID 4462. Retrieved July 9, 2019, from <https://preview.ncbi.nlm.nih.gov/clinvar/variation/4462>
- National Institute for Health and Care Excellence. (2016). Psychosis and schizophrenia in children and young people: Recognition and management.
- National Institute of Health. (2018). Genetics Home Reference WNT 10A gene.
- Ordóñez, A. E., Luscher, Z., & Gogtay, N. (2016). Neuroimaging Findings from Childhood Onset Schizophrenia Patients and their Non-Psychotic Siblings. *Schizophrenia Research*, 173(3), 124-131. <https://doi.org/10.1016/j.schres.2015.03.003>
- Panaccione, I., Napoletano, F., Maria Forte, A., Giorgio, K., Del Casale, A., Rapinesi, C.,...Sani, G. (2013). Neurodevelopment in Schizophrenia: The Role of the Wnt Pathways. Bentham Science Publishers.
- Pringsheim, T., & Addington, D. (2017). Canadian Schizophrenia Guidelines: Introduction and Guideline Development Process. *The Canadian Journal of Psychiatry*, 62(9), 586-593. <https://doi.org/10.1177/0706743717719897>
- Rapoport, J. L., & Gogtay, N. (2011). Childhood onset schizophrenia: Support for a progressive neurodevelopmental disorder. *International Journal of Developmental Neuroscience*, 29(3), 251-258. <https://doi.org/https://doi.org/10.1016/j.ijdevneu.2010.10.003>
- Ripke, S., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K.-H., Holmans, P. A.,...Huang, H. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, 511(7510), 421.
- Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J. L., Kahler, A. K., Akterin, S.,...Sullivan, P. F. (2013). Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nature Genetics*, 45(10), 1150-1159. <https://doi.org/10.1038/ng.2742>
- Shi, J., Levinson, D. F., Duan, J., Sanders, A. R., Zheng, Y., Pe'er, I.,...Gejman, P. V. (2009). Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature*, 460(7256), 753-757. <https://doi.org/10.1038/nature08192>
- Shrimanker, I., & Bhattarai, S. (2019). Electrolytes. In *In StatPearls [Internet]*. StatPearls Publishing.
- Stefansson, H., Ophoff, R. A., Steinberg, S., Andreassen, O. A., Cichon, S., Rujescu, D.,...Collier, D. A. (2009). Common variants conferring risk of schizophrenia. *Nature*, 460(7256), 744-747. <https://doi.org/10.1038/nature08186>
- Sullivan, P., Kendler, K., & Neale, M. (2003). Schizophrenia as a Complex Trait: Evidence From a Meta-analysis of Twin Studies. *Archives of General Psychiatry*, 60(12), 1187-1192. <https://doi.org/doi:10.1001/archpsyc.60.12.1187>
- Toogood, J. H. (1998). Side effects of inhaled corticosteroids. *Journal of Allergy and Clinical Immunology*, 102(5), 705-713.