Neuropsychiatr Invest. 2025; 63:1-4

Case Report
10.5152/NeuropsychiatricInvest.2025.25015

Autosomal Recessive Omodysplasia (GPC6-Related) with Treatment-Resistant Schizophrenia

Elif Poyraz[1], Sümeyye Firidin[2], Digdem Göverti[2], Berk Ulu[1], Alper Bülbül[3], Tolgahan Özer[4]

[1]*Department of Psychiatry, Erenköy Training and Research Hospital for Mental Health and Neurological Disorders, İstanbul, Türkiye*

[2]*Department of Psychiatry, Kocaeli University Faculty of Medicine, Kocaeli, Türkiye*

[3]*Department of Psychiatry, Newham Center for Mental Health, East London NHS Foundation Trust, London, England*

[4]*Department of Genetics, Kocaeli University Faculty of Medicine, Kocaeli, Türkiye*

ABSTRACT

Omodysplasia is an extremely rare short-limb skeletal dysplasia characterized by severe micromelic dwarfism with predominantly rhizomelic shortening of the upper and lower limbs. Type 1 omodysplasia, also known as autosomal recessive omodysplasia, is caused by a mutation in the *GPC6* gene. This is the first case of a patient with schizophrenia genetically diagnosed with omodysplasia type 1. A 27-year-old, university graduate, bilingual, single white woman was brought to the emergency psychiatry clinic with psychomotor agitation, anxiety, persecutory delusions, and hallucinations. On the basis of the patient's background, she was diagnosed with omodysplasia type 1 in early childhood. In addition, she was diagnosed with schizophrenia 8 years ago. Informed consent was obtained from the patient and her mother, who had an advance directive. Schizophrenia is a neurodevelopmental disorder caused by both genetic and environmental factors. *GPC6* is also associated with formal thought disorder (FTD), which is a common symptom of schizophrenia. *GPC6* gene mutation in FTD is located on chromosome 13, such as that of autosomal recessive omodysplasia. Although this case could be coincidental, it may contribute to current genetic studies that have an important place in the etiology of schizophrenia.

Keywords: ***GPC6*** protein, glypicans, omodysplasia type 1, schizophrenia

Corresponding author:
Elif Poyraz

E-mail:
poyraz.elif@yahoo.com

Received: March 5, 2025
Revision Requested: June 10, 2025
Last Revision Received: July 17, 2025
Accepted: July 18, 2025
Publication Date: October 28, 2025

INTRODUCTION

Omodysplasia is an extremely rare skeletal dysplasia characterized by severe congenital micromelia with shortening and distal tapering of the extremities. Type 1 omodysplasia (autosomal recessive omodysplasia) is caused by a mutation in *GPC6*.[1] The mammalian genome contains 6 members of the glypican family *(GPC1–GPC6*). *GPC4* and *GPC6* play roles in the formation of excitatory synapses in the central nervous system. It is based on their ability to form part of the synapse-organizing protein complexes.[2]

Schizophrenia is a neurodevelopmental disorder associated with genetic and environmental risk factors which affects synaptic connectivity.[3] Some strong candidate schizophrenia susceptibility genes

Cite this article as: Poyraz E, Firidin S, Göverti D, Ulu B, Bülbül A, Özer T. Autosomal recessive omodysplasia (GPC6-related) with treatment-resistant schizophrenia. *Neuropsychiatr Invest.* 2025, 63, 0015, doi:10.5152/NeuropsychiatricInvest.2025.25015.

were identified, including *COMT, DTNBP1*, *NRG1*, *DISC1*, and 22q11 deletion. Recent studies show that schizophrenia is a result of problems during neural development that lead to improper function of synaptic transmission at glutamatergic, GABAergic, dopaminergic, and cholinergic synapses and plasticity, and in agreement, many of the susceptibility genes encode proteins critical for neural development.[4] *GPC6* produces heparan sulfate proteoglycan (HSPGs), which plays a role in regulating synaptogenesis, has been associated with formal thought disorder (FTD) in schizophrenia, and is located in the critical genetic region 13q32, which is a susceptibility loci for schizophrenia.[5]

In the present case, schizophrenia developing in a patient with omodysplasia (*GPC6*-related) may support the neurodevelopmental hypothesis and indicate the importance of synaptic regulation in etiopathogenesis.[6]

CASE PRESENTATION

A 27-year-old bilingual woman with a university degree was brought to the emergency psychiatry clinic with psychomotor agitation, anxiety, persecutory delusions, and olfactory hallucinations persisting for the past year. She was hospitalized in the psychiatric inpatient clinic at Erenköy Training and Research Hospital for compulsory treatment with these symptoms. The patient who was diagnosed with schizophrenia 8 years ago exhibited increased persecutory and grandiose delusions for several months and was suspicious of her eating and drinking routine. Her parents were consanguineous, her mother had a history of hospitalization for major depression with psychotic features, and her sister had mild intellectual disability.

She displayed a blunted affect, a suspicious and defensive attitude, and refused to remove her coat and hood. She thought of pregnancy with the prophet's child, being the prime minister's wife, and being followed and poisoned by them. She partially refused food for 2 months and experienced olfactory hallucinations (smoke odor from plug sockets). She reported seeing compressed babies in the hospital walls. Attention and concentration were impaired. She presented visual, auditory, and tactile hallucinations and suspicious delusions. Judgment and insight were poor. Speech was reduced in terms of both rate and tone. Her mood was anxious, and her affect appeared constricted. Eye contact was limited. In addition, she reported decreased sleep and appetite. Her intelligence quotient was determined as normal.

She appeared consistent with her stated age. Her physical features, including frontal bossing, depressed nasal bridge, long philtrum, low-set ears, rhizomelia, short humerus, hypoplastic distal humeri, elbow dislocation, radioulnar diastasis, short first metacarpal, and short stature, were notable, which are presented in autosomal recessive omodysplasia (*GPC6*-related) (Figures 1 and 2). Her length and weight were 123 cm and 35 kg, respectively, corresponding to below the 1st percentile on standard adult female growth charts.

Cranial magnetic resonance imaging findings: minimal enlargement of the fourth ventricle (16.5 mm), widened subdural space at the vertex level, slightly prominent cerebellar folia, cavum septum pallidum vargae variation at the midline (Figures 3 and 4).

Whole exome sequencing analysis was performed on the blood sample taken from the patient for genetic analysis. The mutation analysis

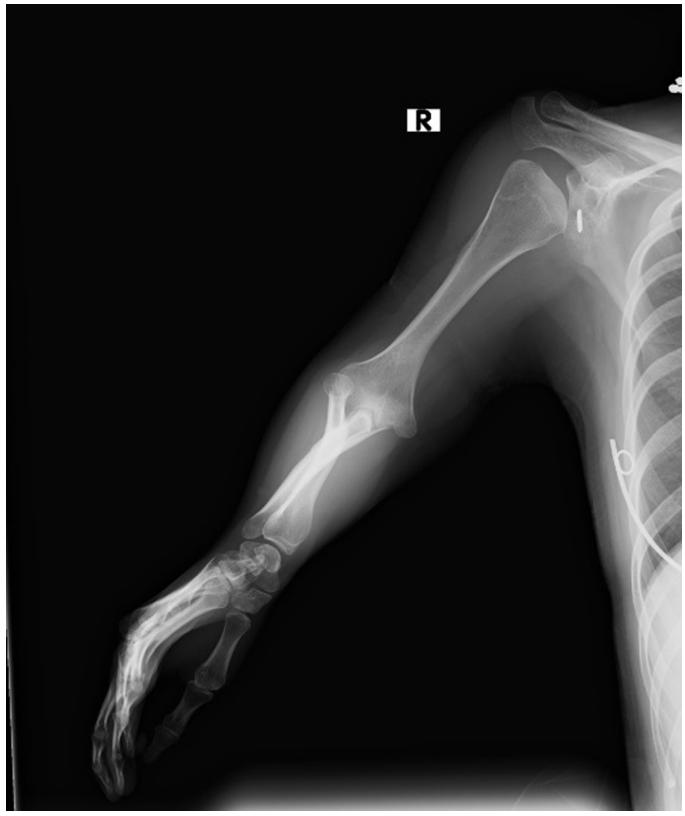

Figure 1. Micromelic dysplasia with dislocation of radius and rhizomelic shortening of the upper limbs.

revealed a homozygous exon 4-6 deletion in *GPC6*, associated with omodysplasia type 1 (autosomal recessive). These results confirm the diagnosis of *GPC6*-related autosomal recessive omodysplasia.

In clinical follow-up, after being given 2 antipsychotics, her psychotic symptoms persisted Positive and Negative Symptoms Scale (PANSS: 132). Due to treatment resistance and disrupted oral intake, electroconvulsive therapy (ECT) and Clozapine were initiated. After 8 ECT sessions, she was discharged on clozapine 200 mg/day with residual negative symptoms and followed by an outpatient clinic.

Informed consent was obtained from the patient and her mother, who was an advance directive.

DISCUSSION

Omodysplasia is classified into 2 types: autosomal recessive (*GPC-6* related) and autosomal dominant (*FZD-2* related). Currently, psychotic features are not observed in autosomal recessive omodysplasia. However, 1 reported case exhibited autistic behaviors, and some individuals were diagnosed with intellectual disability.[3]

Heparan sulfate proteoglycans play crucial roles in several biological processes, including growth factor signaling, cell adhesion, and intracellular membrane trafficking.[7] *GPC6* is a member of the glypican subfamily, which consists of 6 glycosylphosphatidylinositol-linked HSPGs.[7] Proteoglycans, particularly HSPGs, have been recognized as regulators of synapse formation and neural plasticity by regulating glutamate receptor expression, with *GPC6* showing increased expression in the cerebellum during the postnatal period.[7] Furthermore, their dysfunction is linked to neurodevelopmental

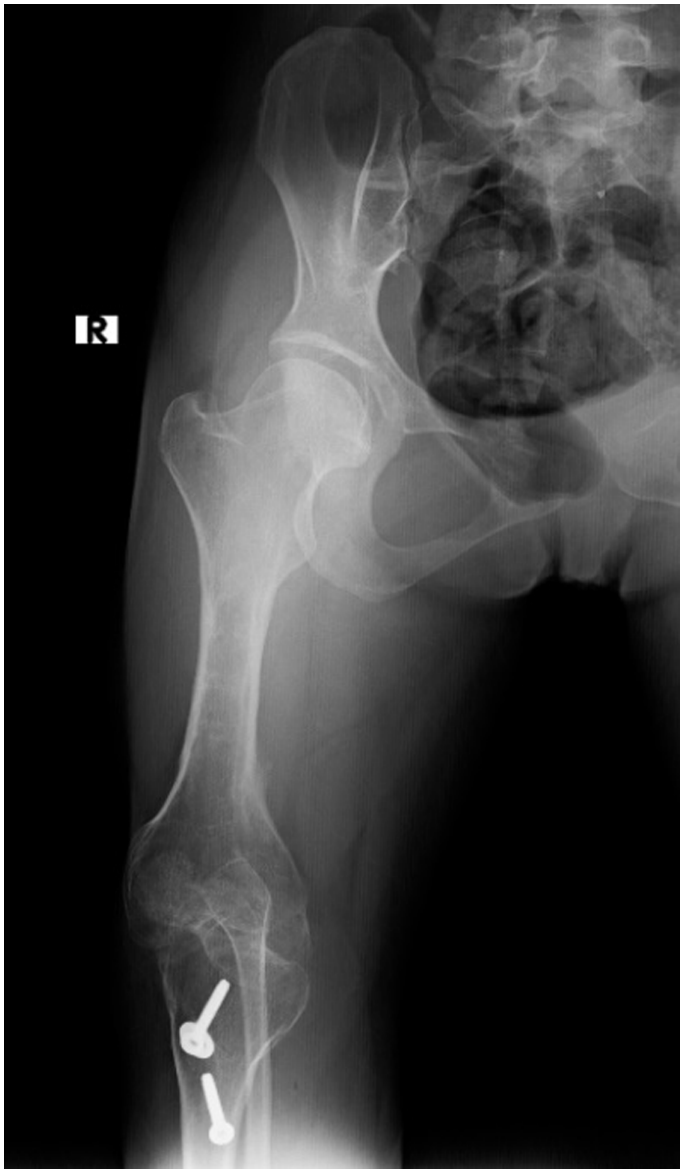

Figure 2. Rhizomelic shortening of the lower limbs.

disorders such as autism, intellectual disability, and schizophrenia.[8] In a study, *GPC6* has also been linked to FTD in schizophrenia. Formal thought disorder is a core symptom of schizophrenia and is associated with reduced reactivity to stimulation and heightened activity at rest. Additionally, left frontal language regions demonstrate hyperactivity at rest without structural deficits. Notably, an important locus for FTD was identified in *GPC6* at 13q32.[5] Markers on chromosome 13q32 have been significantly linked to schizophrenia in psychotic family members.[9] Moreover, recessive omodysplasia maps to chromosome 13.[6] Recently, a sequence from the 13q34 region was utilized to identify the *DAOA* locus, which has been associated with schizophrenia and bipolar disorder.[10]

The midline structural abnormalities in the brain particularly, were seen in schizophrenia and mood disorders.[11] The septum pellucidum, a dual midbrain structure, separates the lateral ventricles. The cavity between its leaflets, termed cavum septum pellucidum (CSP), may extend posteriorly as cavum vergae (CV).[12] The septum pellucidum typically fuses in 85% of individuals by 3-6 months of age and in more than 99% of individuals by adulthood.[12] Failure of

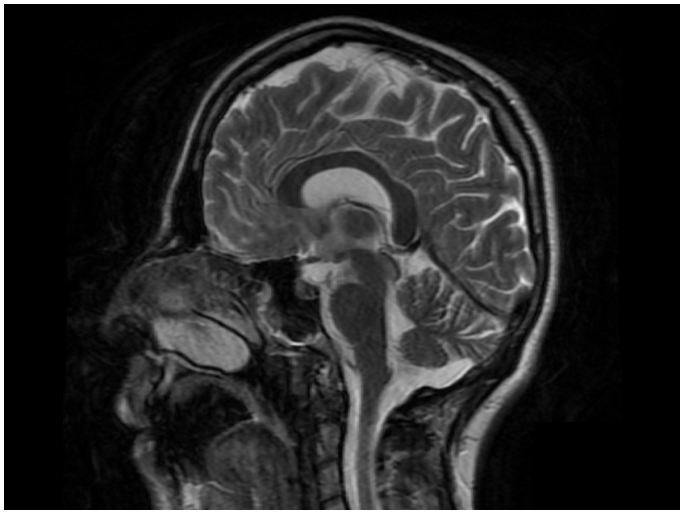

Figure 3. Widened subdural space at the vertex level, slightly prominent cerebellar folia.

leaflet fusion can lead to CSP and CV, which have been implicated in neurodevelopmental disorders, particularly schizophrenia.[12] The individuals with CV often demonstrate a later onset of illness, lower intelligence quotientIQ, and greater deterioration of executive function and memory.[11] When CSP and CV co-occur, earlier onset and poor treatment response may be expected.[12] This patient was affected by psychotic symptoms at the age of 20 years and exhibited a poor response to treatment.

Synaptic dysfunction is a key hypothesis in schizophrenia etiology, disrupting links between the prefrontal cortex, limbic system, striatum, and thalamus, leading to an excitatory-inhibitory imbalance.[12] Even minor dendritic spine changes affect synaptic function,

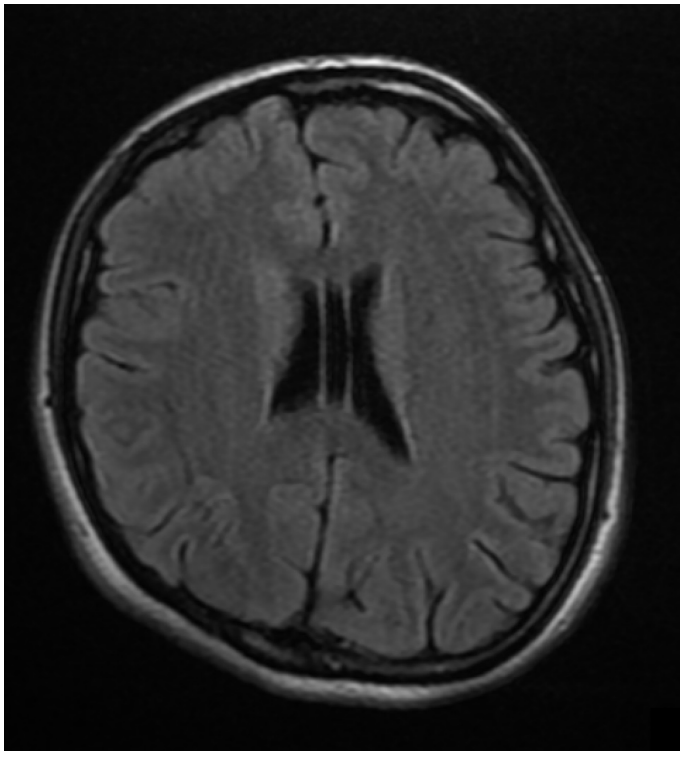

Figure 4. Cavum septum pellicidum vargae variation at midline.

plasticity, and connectivity.[13] Post-mortem studies suggest that spine density changes contribute to grey matter loss in schizophrenia, possibly due to reduced stability or excessive pruning.[13] Mutant DISC1 may cause synaptic dysfunction via transcriptional dysregulation.[12] *NRG1* and *ERBB4* regulate spine structure, and *ERBB4* overexpression is linked to increased excitatory synaptic expression.[13] Glutamatergic synapses, crucial for normal cognition, rely on dendritic spine structure and are responsible for most of the fast excitatory transmission.[12] A study found that syndecan and Dallylike, homologs of mammalian *GPC4* and *GPC6*, play key roles in glutamatergic type 1 bouton formation at the neuromuscular junction.[7]

CONCLUSION

This is the first case presentation about schizophrenia and omodysplasia type 1, autosomal recessive (*GPC6* related). Although *GPC6* has been associated with FTD, which is one of the main symptoms seen in schizophrenia, there are few studies on genetic variants in FTD. Further research is needed to understand the relationship between schizophrenia and *GPC6* expression.

Data Availability Statement: The data that support the findings of this study are available upon request from the corresponding author.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.G.; Design – D.G.; Supervision – D.G., A.B.; Resource – B.U., E.P.; Materials – D.G., T.Ö.; Data Collection and/or Processing – B.U., E.P., T.Ö.; Analysis and/or Interpretation – D.G., S.F., A.B.; Literature Search – D.G., E.P., S.F.; Writing – D.G., E.P., S.F.; Critical Reviews – D.G.

Declaration of Interests: The authors declare no conflicts of interest.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Elçioglu NH, Gustavson KH, Wilkie AO, Yüksel-Apak M, Spranger JW. Recessive omodysplasia: five new cases and review of the literature. *Pediatr Radiol*. 2004;34(1):75-82. [CrossRef]
2. Maroteaux P, Sauvegrain J, Chrispin A, Farriaux JP. Omodysplasia. *Am J Med Genet*. 1989;32(3):371-375. [CrossRef]
3. Schmitt A, Falkai P, Papiol S. Neurodevelopmental disturbances in schizophrenia: evidence from genetic and environmental factors. *J Neural Transm (Vienna)*. 2023;130(3):195-205. [CrossRef]
4. Yin DM, Chen YJ, Sathyamurthy A, Xiong WC, Mei L. Synaptic dysfunction in schizophrenia. *Adv Exp Med Biol*. 2012;970:493-516. [CrossRef]
5. Wang KS, Zhang Q, Liu X, Wu L, Zeng M. PKNOX2 is associated with formal thought disorder in schizophrenia: a meta-analysis of two genome-wide association studies. *J Mol Neurosci*. 2012;48(1):265-272. [CrossRef]
6. Pantelis C, Papadimitriou GN, Papiol S. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511(7510):421-427. [CrossRef]
7. Campos-Xavier AB, Martinet D, Bateman J, et al. Mutations in the heparan-sulfate proteoglycan glypican 6 (GPC6) impair endochondral ossification and cause recessive omodysplasia. *Am J Hum Genet*. 2009;84(6):760-770. [CrossRef]
8. Kamimura K, Maeda N. Glypicans and heparan sulfate in synaptic development, neural plasticity, and neurological disorders. *Front Neural Circuits*. 2021;15:595596. [CrossRef]
9. Wildenauer DB, Schwab SG, Maier W, Detera-Wadleigh SD. Do schizophrenia and affective disorder share susceptibility genes? *Schizophr Res*. 1999;39(2):107-160. [CrossRef]
10. Chumakov I, Blumenfeld M, Guerassimenko O, et al. Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. *Proc Natl Acad Sci U S A*. 2002;99(21):13675-13680. [CrossRef]
11. Rajasekharan C, Karthik V, Harikrishnan M, Lekshmi S. Cavum vergae and psychiatric illness: substantive or serendipity? *BMJ Case Rep*. 2018;2018:bcr2018225511. [CrossRef]
12. Achalia R, Bhople KS, Ahire P, Andrade C. Late-onset schizophrenia with isolated cavum vergae: case report and literature review. *Indian J Psychiatry*. 2014;56(4):399-401. [CrossRef]
13. Habela CW, Song H, Ming GL. Modeling synaptogenesis in schizophrenia and autism using human iPSC-derived neurons. *Mol Cell Neurosci*. 2016;73:52-62. [CrossRef]