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CASE REPORT

# NTRK2-related obesity, hyperphagia, and developmental delay: case report

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## ABSTRACT

**Background:** The Neurotrophic receptor tyrosine kinase 2 (*NTRK2)* is a group of neurological disorders characterized by epilepsy and developmental delay. Neurodevelopmental disorders and obesity are linked to various inherited disorders and are often missed or diagnosed late. Our aim was to review obesity, hyperphagia, and developmental delay which overlap with a wide range of neurodevelopmental disorders with obesity. Also, variable expressivity can mislead the diagnosis, especially if there is a parent with a similar phenotype but a milder presentation.

**Case presentation:** A 8-year-old girl presented with a 6-year history of increased weight. On a neurodevelopmental examination, she was found to have a speech delay and autistic features. Parents deny sphincter dysfunction and cognitive delay. Family history was negative for members with a similar presentation. Genetic testing identified a novel mutation in the *NTKR2* gene. Parents were examined and underwent segregation analysis which came back negative, so it is de novo.

**Conclusion:** Obesity and neurodevelopmental delay are features that are seen in a wide range of inherited disorders, either chromosomal or single-gene disorders. Here we highlight the importance of thorough history, examination, and the application of genetic testing sooner than later to avoid delaying the diagnosis and report a possible novel variant in the *NTRK2* gene. Functional studies would be our next step.

**Keywords:** *NTRK2*, obesity, developmental delay.

## Introduction

The neurotrophic receptor tyrosine kinase 2 (*NTRK2*) gene (OMIM#600456) also known as Tropomyosin receptor kinase B (TRKB) [receptor for brain-derived neurotrophic factor (BDNF)] contains 24 exons and is located on chromosome 9q21 (1). It is a membrane-bound receptor that phosphorylates both itself and other mitogen-activated protein kinases (MAPK) pathway participants, upon binding neurotrophin. This kinase signaling pathway promotes cell differentiation. Obesity and mood disorders have been linked to mutations in this gene. There are several transcript variations because of alternative splicing Reference Sequence [RefSeq contributed this in May 2014] (2). It is expressed in the human brain and acts through the regulation of neuron survival, proliferation, migration, differentiation, and synapse formation and plasticity (3). It found that it regulates energy hemostasis in rodents (4).

Developmental and epileptic encephalopathy and Obesity, hyperphagia, and developmental delay (OBHD) are two conditions linked to *NTRK2*. G-protein-coupled receptors Pathway and dysregulation in Hippo-Merlin signaling are two of its associated pathways (3).

OBHD is a rare neurodevelopmental genetic disorder characterized by obesity and a generalized developmental delay especially cognitive and verbal. Seizures may happen in some patients (1). There are similarities in phenotypes between these patients and the mouse model of TrkB deficiency reported by Xu et al. (5).We report a case of OBHD due to a possible novel variant in *NTRK2*, describing the phenotypes and comparing them with previously reported cases.

## Case Presentation

8-year-old Saudi girl presented to our clinic due to progressive weight gain, which started at age of 2 years,

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associated with mild intellectual disability, inattention, and speech delay, being able to say only 3 words sentences.

She developed snoring at the age of 4 years and was diagnosed with adenoid hypertrophy and sleep apnea, also, her parents noticed eye squint at age of 5 years with autistic features like preferring to play with herself. She is seen by ophthalmology which reveals exotropia, mixed astigmatism, and error refraction in the right eye 6/9.5.

She is a product of full-term, spontaneous vaginal delivery with a birth weight of 2.5 kg and was initially hypotonic and had a delay in walking and setting but now she catches up.

Parents are first cousins once removed with no family history of a similar condition (Figure 1).

We suggest encouraging the family to help her to decrease food intake and increase physical activity but has easy fatigability with long distances of walking. She is in the second grade of primary school in a special school with fair performance and obeys simple commands.

On examination she is looking obese, not dysmorphic**,** no eye-to-eye contact with acanthosis nigricans around the neck and abdominal striae. Her weight is 76.8 kg which is above the 97th percentile, her height is 136.4 cm, and her Body Mass Index is 41, vitally stable and other systemic examinations are unremarkable. She is not on medication. She is investigated thoroughly and all labs are within normal including Tandem Mass Spectrometry, Adrenocorticotropic Hormone, Insulin, cortisol, and urine for organic acid except mild elevation of Hemoglobin A1C (HbA1C), ALT, and Triglyceride (Table 1). Abdominal ultrasound is unremarkable.

She has a moderate delay in adaptive behavior skills. The result of Vineland adaptive behavior scales: communication=48 (moderate deficit), socialization=52 (moderate deficit), daily living skills =44 (moderate deficit), composite score=45 (moderate deficit).

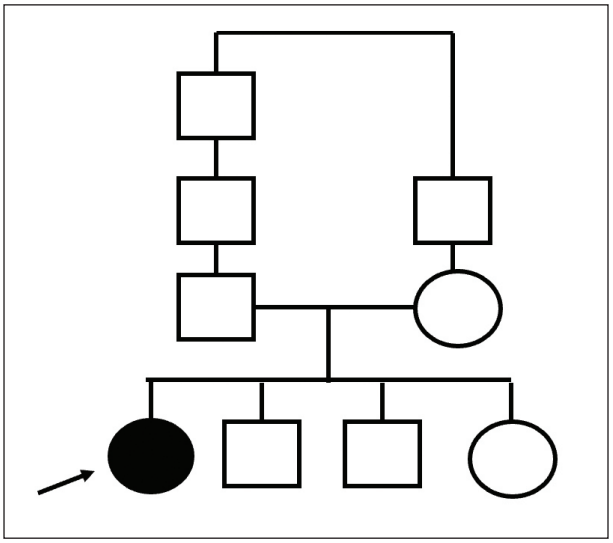

***Figure 1.*** *Family pedigree of index case, filled symbols represent affected individuals, open symbols represent unaffected individuals, and the studied proband is indicated with an arrow.*

A sleep study confirmed obstructive sleep apnea. Chromosomal analysis (46,XX), chromosomal microarray and methylation test for Prader-Willi syndrome are negative but the whole exome sequence (WES) shows she is a carrier for the following pathogenic variants (*CLN5, ANO5, HMGCS2*) which are autosomal recessive in nature. Also, she has two variants of uncertain significance (VUS) in *NTRK2* and *NLGN1*. Both are heterozygous. Regarding (*NLGN1*:c.1171G>T, p. Glu391*), it causes susceptibility to autism 20 which consists partially of our patient.

*NTRK2* variant (c.2168A>C:p.Tyr723Ser) which is fit the phenotype of OBHD. Although no functional analysis of the *NTRK2* variant was carried out, the allele frequency of this variant is Absent according to the gnomAD database with a Combined Annotation Dependent Depletion score of 28 so it becomes a more candidate variant. Sanger sequence for variant done outsource.

Segregation analysis for parents reveals that the father is heterozygous in *NLGN1* and *CLN5* and negative for *HMGCS2*, *ANO5,* and *NTRK2* and the mother is homozygous in *ANO5* and negative for others.

Management implications have included a referral to a clinical psychologist, dietician, and endocrinologist to address a trial of weight loss medication or the need for bariatric surgery.

## Discussion

*The NTRK2* gene encodes a member of the *NTRK* family, a membrane-bound receptor that, upon neurotrophin binding, phosphorylates itself and members of the MAPK pathway.

Receptor tyrosine kinase controls neuron survival, proliferation, migration, differentiation, and the creation and plasticity of synapses during the maturation of the central and peripheral nervous systems (by similarity); receptor for Neurotrophin 4 and BDNF. A different option is to bind neurotrophin-3, which is less effective at activating the receptor but controls neuron survival through *NTRK2* (6).

Diseases associated with *NTRK2* include OBHD, developmental and epileptic encephalopathy (DEE58, OMIM#6117830), pilomyxoid astrocytoma, infantile spasms syndrome, and nonspecific early-onset epileptic encephalopathy.

In this study, we describe a novel mutation affecting the *NTRK2* gene using next-generation sequence analysis for a Saudi patient.

Clinical investigation for our patient revealed morbid obesity class 3 associated with hyperphagia and cognitive and speech delay. Obesity with developmental delay is often erroneously diagnosed with Prader-Willi syndrome.

DNA sequence quality metrics were carried out using the FASTQC version:0.11.7. Human reference assemblies were aligned against GRCh37.p13. QIAGEN Clinical Insight-interpret software was used in sequence analysis and interpretation. Variants are reported according to Human Genome Variation Society nomenclature and were classified following American

***Table 1.*** *Lab profile of the patient.*

| Lipid profile | Patient value | Reference range |
|---|---|---|
| Total cholesterol | 4.26 mmol/l | <4.4mmol/l |
| Triglyceride | 1.14 mmol/l(High) | <0.8 mmol/l |
| High-density lipoprotein | 0.87 mmol/l (Low) | >1.2mmol/l |
| Low-density lipoprotein | 2.9 mmol/l (Borderline) | <2.8mmol/l |
| Serology | | |
| C-peptide | 1,109 pmol/l | |
| HbA1C | 6.46% | 6 or less% |
| Total 25 Hydroxyvitamin D | 34.8nmol/l (Low) | >75nmol/l |
| Thyroid function tests | | |
| Thyroid-stimulating hormone (TSH\|) | 3.55 mIU/l | 0.27-4.2 mIU/l |
| Free T4 | 13.5 pmol/l | 12-22pmol/l |
| Biochemistry | | |
| Random glucose | 4.2 mmol/l | <11.1 mmol/l |
| CBC | | |
| WBC | $9*10^9$ | $4.5\text{-}13.5*10^9$ |
| RBC | 5.39 | $4\text{-}5.2*10^{12}$ |
| HGB | 11.8 | 11.5-15.5 g/dl |
| MCV | 76 | 77-95fl |
| PLT | $549*10^9$ (High) | $15\text{-}450*10^9$ |

College of Medical Genetics and Genomics(ACMG) guidelines WES revealed that she carried de novo novel variant (chr9:87570428,g.87570428A>C,NM_006180.6:c.2168A>C:p.Y723S) in *NTRK2* gene which is not reported in Human Gene Mutation Database/Clinically relevant variation and the mode of inheritance is expected to be autosomal dominant in the absence of family history. Additionally, the *NTRK2* gene variant occurs at an allele frequency of 0% in our in-house database Furthermore, the ACMG; Tandem-based scoring system for variant classification (PM2, PP3) of the *NTRK2* gene variants which suggesting its deleterious nature and possible contribution to the phenotype in our patients.

The other VUS in *NLGN1* was detected in the father, and he is healthy which led to exclude this variant as a cause of her condition.

It must be kept in mind that no functional studies have been carried out for *NTRK2* variants so far. However, with the increase in the number of reported cases having *NTRK2*-related clinical features, it is evident that *NTRK2* plays an important role in disease pathogenesis.

There are four reported cases before in different countries worldwide (7-10) and share almost all in learning difficulties, speech delay, and autistic features. Two of them have a seizure disorder and are controlled with medication and those two have a motor developmental delay. Only one has an extended spectrum of presentation in the left coronal synostosis and streak ovaries and uterus (Table 2). The reported variant in our patient is 3 base pairs different than the case reported by Yeo et al (7). Also, the Hamdan et al. case (9) had a mutation that was adjacent to the Yeo et al. case (7) and our case which give us more evidence to support the pathogenicity of the NTKR2 variant detected in our patient.

Considering the presence of OBHD, a hereditary disorder was suspected; genetic testing revealed a variant of insignificant *NTRK2* which is only present in this patient and correlates with clinical presentation.

When disease-causing mutations are found in *NTRK2* patients, it may have a significant influence on patient care since it enables early intervention and follow-up to decrease weight gain and secondary comorbidity of obesity.

Overall, *NTRK2* is a candidate gene that has been reported in patients associating obesity and Global Developmental Delay and/or learning disability as a novel candidate. We need to investigate the expression level of the mutated variant and then compare it with normal control which will support the potentially damaging effects of this mutation in the future.

## Limitations

Lack of functional assay to support a finding.

### *Recommendations and clinical implications of your report*

It may help in the differential diagnosis of hereditary monogenic obesity and describe the definite phenotype of OBHD.

***Table 2.*** *Summary of the clinical features, development, and mutation of all reported cases 0f OBHD.*

| Reference | Our patient | Patient 4(10) | Patient 3(9) | Patient 2(8) | Patient 1 (7) |
|---|---|---|---|---|---|
| Age | 8 years | 44 years | 11-year-old | 7.5-year-old | 8 years |
| sex | Girl | Female | Girl | Girl | Boy |
| country | Saudi Arabia | Caucasian | Guatemala | - | United Kingdom |
| Onset of obesity | 2 years | Late teenagers | After 3 years of age | - | 6 months |
| Fasting insulin | - | - | - | - | Normal |
| Thyroid function tests | Normal | - | - | - | Normal |
| Dysmorphic features | Negative | - | - | Left coronal synostosis at 12 months with facial asymmetry, strabismus | Negative |
| Seizure disorder | Negative | | Yes, on carbamazepine and controlled | - | Absence of seizures in the second and third years of life only. |
| Development | Speech and cognitive delay | Intellectual disability and learning disorder | Global developmental delay | Moderate learning difficulties with speech and language delay | Motor function, speech, and language |
| Nociceptive stimuli. | - | - | - | - | Blunted |
| behaviors | Poor communication and plays with herself | Depression and anxiety, binge eating disorder | Moderate to severe Intellectual disability, autism spectrum disorder. | Progressive onset of aggressive outbursts and ritualized behaviors, temper tantrums | - |
| Pelvic US | - | - | - | Streak ovaries and uterus | - |
| mutation | c.2168A>C:p. Tyr723Ser | c.C2000G:p. S667W | c.2159C>T:p. Thr720Ile | c.1330G>T; p. Gly444* | c.722A>G,p.Y722C |

* Stop codon.

## Conclusion

This clinical case highlights a novel variant detected in the *NTRK2* gene. Affected individuals showed a range of phenotypes that varied in severity which can be often misdiagnosed with other diseases.


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**List of Abbreviations**

ACMG American College of Medical Genetics and Genomics
HbA1C Hemoglobin A1C
OBHD Obesity, hyperphagia, and developmental delay
VUS Variant of uncertain significant
WES Whole exome sequence.


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**Consent for publication**
Due permission was obtained from the father of the patient to publish the case.

**Ethical approval**
Ethical approval is taken from our institution to publish this case report.


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