Obesity, Hyperphagia, and Developmental Delay (MONDO:0013483) — Comprehensive Disease Dossier

MONDO:0013483 · OMIM:613886 · Orphanet:99704 · MeSH:C563938 · UMLS:C3151303 · MedGen:462653 Causal gene: NTRK2 (TrkB) · HGNC:8032 · NCBI Gene 4915 · UniProt Q16620 · Ensembl ENSG00000148053 · chr9q21.33

Summary

Obesity, Hyperphagia, and Developmental Delay (MONDO:0013483; OMIM:613886; Orphanet:99704; "OBHD") is a rare, autosomal-dominant, typically *de novo* Mendelian syndrome caused by **heterozygous loss-of-function variants in *NTRK2* (HGNC:8032)**, the gene encoding **TrkB (tropomyosin receptor kinase B)**, the high-affinity receptor for **brain-derived neurotrophic factor (BDNF)**. BDNF–TrkB signaling is a critical anorexigenic ("satiety brake") node in the hypothalamic leptin–melanocortin pathway, acting *downstream* of the melanocortin-4 receptor (MC4R) in paraventricular (PVH) and dorsomedial (DMH) hypothalamic neurons. When TrkB is disabled, this satiety signal fails, producing insatiable hyperphagia and severe early-onset obesity, while TrkB's broader role in neuronal survival, differentiation, and synaptic plasticity produces global developmental delay, intellectual disability, behavioral abnormalities, hypotonia, impaired nociception, and (in some patients) seizures.

A central discovery of this investigation was a **mid-course correction**: the disease was initially mapped to *SIM1* and the 6q16 Prader–Willi-like syndrome, which is phenotypically very similar. However, the authoritative MONDO/OMIM definition of MONDO:0013483 specifies ***NTRK2*** as the causal gene. The *SIM1* and *NTRK2* disorders are distinct entities that converge on the same hypothalamic circuit — SIM1 builds the PVH and supports MC4R/oxytocin output, while TrkB transduces the satiety signal downstream — explaining their overlapping clinical pictures. This report is organized around *NTRK2*/TrkB as the definitive cause while preserving the SIM1 mechanistic insights as context for the shared circuit and differential diagnosis.

The gene shows a striking **allelic series**: loss-of-function (truncating/structure-disrupting) variants cause the milder obesity–hyperphagia–developmental delay phenotype (this disease), whereas gain-of-function variants in the transmembrane cholesterol-binding motif (recurrent p.Tyr434Cys) cause a *distinct, severe* neurodevelopmental disorder with therapy-refractory epilepsy and blindness. *NTRK2* is extremely intolerant to loss-of-function (gnomAD pLI = 1.00, LOEUF = 0.219), consistent with dominant haploinsufficiency. Diagnosis is molecular (NGS obesity gene panels, whole-exome/genome sequencing, chromosomal microarray), and management is multidisciplinary and supportive; mechanism-based melanocortin-agonist therapy is of uncertain benefit because the TrkB lesion lies downstream of MC4R.

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1. Disease Information

Overview. OBHD is a syndromic monogenic obesity disorder defined by the triad of **early-onset severe obesity, hyperphagia (insatiable appetite), and global developmental delay**, with characteristic impairment of short-term memory and language. The MONDO record (EBI OLS) defines it as *"A syndromic disease caused by a variation in the NTRK2 gene, characterized by early-onset severe obesity, hyperphagia, and global developmental delay with specific impairment of short-term memory and language delay."*

Key identifiers.

Resource	Identifier
MONDO	MONDO:0013483
OMIM	613886
Orphanet	ORPHA:99704
MeSH	C563938
UMLS	C3151303
MedGen	462653
Causal gene	*NTRK2* / TrkB (HGNC:8032; NCBI Gene 4915; Ensembl ENSG00000148053)

Synonyms / alternative names. OBHD; Obesity-Hyperphagia-Developmental Delay syndrome; Early-onset obesity–hyperphagia–severe developmental delay syndrome; NTRK2-related obesity.

Data source type. Information is derived from **aggregated disease-level resources** (OMIM, Orphanet, MONDO, HPO, ClinVar, gnomAD) combined with **individual-patient case reports and a 44-individual genotype–phenotype cohort**. The index case was a single detailed patient report (PMID: 15494731); the allelic-series delineation came from an aggregated cohort (PMID: 39540377).

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2. Etiology

Primary cause — genetic. The disease is caused by **heterozygous loss-of-function variants in *NTRK2***. The index patient carried a *de novo* missense variant **p.Tyr722Cys (Y722C)** that, as the authors state, *"markedly impaired receptor autophosphorylation and signaling to MAP kinase"* (PMID: 15494731). The larger cohort established that **truncating variants, or variants that disturb the 3D protein structure leading to loss of function**, produce *"a remarkably milder phenotype of developmental delay, obesity, and hyperphagia"* (PMID: 39540377).

Genetic risk factors. The causal variants are the risk factors; there are no recognized common susceptibility loci for this specific Mendelian entity. On the ligand side of the same axis, *BDNF* haploinsufficiency (e.g., WAGR 11p14 deletions) causes an overlapping obesity phenotype, confirming the pathway: WAGR patients with *BDNF* deletion *"had significantly higher BMI z scores throughout childhood than did patients with intact BDNF"* (PMID: 18753648).

Environmental risk factors. As a highly penetrant Mendelian disorder, environmental contribution to *causation* is minimal. However, general obesogenic exposures (hypercaloric diet, sedentary behavior) plausibly modify the *severity* of weight gain. Rodent data show early-life hypercaloric diet alters BDNF/TrkB signaling and feeding behavior, illustrating gene–environment convergence on the same molecular axis (PMID: 32926590).

Protective factors. No specific genetic protective alleles are established for this disorder. Environmentally, dietary restriction and structured feeding management reduce weight gain but do not correct the underlying hyperphagia driver.

Gene–environment interactions. The shared node is BDNF/TrkB tone. Reduced BDNF/TrkB signaling (genetic) and obesogenic diet (environmental) both push the same circuit toward hyperphagia, suggesting additive/synergistic weight gain in affected individuals exposed to obesogenic environments.

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3. Phenotypes

The official HPO disease annotation for **OMIM:613886** (JAX HPO) and the index/cohort reports define the phenotype spectrum below. Frequencies "1/1" reflect the single annotated index proband; the cohort confirms the core triad broadly.

Phenotype	HPO term	Type	Frequency (annotation)	Onset / notes
Obesity	HP:0001513	Physical/metabolic	1/1	Early-onset, severe
Hyperphagia / polyphagia	HP:0002591	Behavioral	1/1	Insatiable appetite
Severe global developmental delay	HP:0011344	Neurodevelopmental	1/1	Infantile onset
Intellectual disability	HP:0001249	Neurodevelopmental	Core	Variable severity
Hypotonia	HP:0001252	Neuromuscular	1/1	Infantile onset
Motor stereotypy	HP:0000733	Behavioral	1/1	—
Autistic behavior	HP:0000729	Behavioral	Reported	—
Reduced eye contact	HP:0000817	Behavioral	Reported	—
Generalized non-motor (absence) seizure	HP:0002121	Neurological	1/1	—
Seizure (general)	HP:0001250	Neurological	Very rare	—
Facial asymmetry	HP:0000324	Physical	Reported	—
Delayed myelination	HP:0012448	Neuroimaging	Very rare	—
Impaired pain sensation	HP:0007328	Sensory	Index case	Blunted nociception
Impaired short-term memory	HP:0009074	Cognitive	Index case	—
Impaired learning	HP:0001328	Cognitive	Index case	—
Language delay	HP:0000750	Neurodevelopmental	Core	—

The index report emphasized that *"the associated impairment in memory, learning and nociception seen in the proband reflects the crucial role of TrkB in the human nervous system"* (PMID: 15494731). The loss-of-function cohort confirmed *"developmental delay, obesity, and hyperphagia"* as the **core triad**, with cognitive impairment milder than in the gain-of-function group (PMID: 39540377).

Phenotype characteristics. Onset is **infantile/early childhood** (HP:0003593 infantile onset). Severity ranges from moderate to severe; obesity and hyperphagia are typically severe and progressive if unmanaged, whereas developmental delay is static/non-progressive. **Quality-of-life impact** is substantial: insatiable hyperphagia dominates daily functioning (analogous to other MC4R-pathway hyperphagic diseases, where patients describe "unrelenting hunger"; PMID: 42821228), and developmental delay/ID impairs independence, learning, and communication lifelong.

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4. Genetic / Molecular Information

Causal gene. ***NTRK2*** (neurotrophic receptor tyrosine kinase 2), encoding **TrkB**. HGNC:8032; chromosome **9q21.33** (GRCh38 chr9:~84.67–85.10 Mb); Ensembl ENSG00000148053; UniProt Q16620.

Pathogenic variants. - **Index variant:** c.2165A>G, **p.Tyr722Cys (Y722C)**, *de novo* heterozygous missense in the tyrosine kinase domain. As reported: *"An 8-year-old male with a complex developmental syndrome and severe obesity was heterozygous for a de novo missense mutation resulting in a Y722C substitution"*; the variant functionally impairs autophosphorylation and MAPK signaling (**loss of function**) (PMID: 15494731). - **LoF group (this disease):** *"The second group had truncating variants or variants that presumably disturb the 3D structure of the protein leading to loss of function"* → obesity/hyperphagia/developmental delay (PMID: 39540377). - **GoF group (distinct disease):** variants in the transmembrane cholesterol-binding motif, recurrent **c.1301A>G p.(Tyr434Cys)** → upregulation of TrkB activity → severe DD/ID, refractory epilepsy, blindness (PMID: 39540377).

Variant classification & burden. ClinVar (retrieved 2026-10-17): *NTRK2[gene]* returns **978 total variant records**, of which **130 are Pathogenic/Likely pathogenic**, and **49 records annotated to an obesity phenotype**. Classifications follow ACMG/AMP criteria. As the cohort noted, *"Heterozygous pathogenic variants in NTRK2 (HGNC: 8032) have been associated with global developmental delay"* (PMID: 39540377).

Allele frequency. Pathogenic variants are **ultra-rare/absent in gnomAD**, consistent with *de novo* dominant disease. *NTRK2* is **extremely LoF-constrained**: gnomAD v2 pLI = **1.00**, LOEUF (oe_lof_upper) = **0.219**, observed/expected LoF = 0.138 (13 observed vs 94.5 expected), LoF-Z = 7.11; also missense-constrained (missense-Z = 5.63, oe_mis = 0.60).

Somatic vs germline. Germline (de novo or, rarely, inherited). Not a somatic/cancer entity in this context.

Functional consequences. Loss of function / haploinsufficiency for this disease (impaired kinase activity, autophosphorylation, and downstream MAPK/PI3K signaling). The allelic series demonstrates that *gain* of function produces a mechanistically and clinically opposite neurological disorder.

Modifier genes / epigenetics / chromosomal abnormalities. No established Mendelian modifier genes specific to *NTRK2* OBHD. Epigenetic regulation of *BDNF*/*NTRK2* (e.g., diet-induced HDAC5 changes in rodents; PMID: 32926590) may modulate pathway tone but is not a primary disease mechanism. Large 9q21 deletions encompassing *NTRK2* would be detected by chromosomal microarray (DECIPHER/ClinVar), though point variants predominate in reported cases.

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5. Environmental Information

- **Environmental factors:** No toxicological, radiation, or occupational cause. This is a monogenic disorder.
- **Lifestyle factors:** Diet and physical activity modify the *degree* of obesity but not its genetic cause. Hyperphagia makes dietary control exceptionally difficult.
- **Infectious agents:** Not applicable.

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6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. A **heterozygous loss-of-function variant in *NTRK2*** (de novo) **results in** a TrkB receptor with impaired kinase activity (e.g., Y722C abolishes autophosphorylation) — *demonstrated in vitro* (PMID: 15494731).
2. Impaired TrkB **leads to** failure of **BDNF→TrkB signal transduction** (reduced MAPK/ERK and PI3K-AKT and PLCγ signaling) in TrkB-expressing neurons — *demonstrated for MAPK; PI3K/PLCγ inferred by homology to canonical TrkB signaling*.
3. In the **hypothalamic PVH and DMH**, loss of TrkB signaling **removes an anorexigenic "satiety brake"** that normally operates **downstream of MC4R** — *demonstrated by mouse circuit genetics* (PMID: 32265438, PMID: 30718415).
4. Absent satiety signaling **results in hyperphagia** (insatiable appetite), which **precedes** weight gain — *demonstrated in Nkx2.1-Ntrk2 mice* (PMID: 26629410).
5. Sustained hyperphagia, with **no compensatory increase in energy expenditure**, **leads to** positive energy balance and **severe early-onset obesity**, with secondary **hyperinsulinemia, hyperglycemia, and hyperleptinemia** — *demonstrated in mice* (PMID: 26629410).

Branch (neurodevelopment): In parallel, loss of TrkB signaling in **broader CNS neurons impairs** neuronal survival, differentiation, and synaptic plasticity, **leading to** global developmental delay, intellectual disability, impaired memory/learning, behavioral abnormalities, hypotonia, and blunted nociception — *inferred from TrkB's established neurobiology and index-patient phenotype* (PMID: 15494731).

Mechanistic detail

- **Molecular pathways.** Canonical TrkB signaling: **MAPK/ERK** (demonstrated defective in Y722C), **PI3K-AKT-mTOR**, and **PLCγ**. These transduce BDNF's anorexigenic and neurotrophic effects. KEGG: *Neurotrophin signaling pathway* (hsa04722); MAPK (hsa04010); PI3K-AKT (hsa04151).
- **Cellular processes.** Synaptic plasticity, neuronal survival/differentiation (neurotrophic support), and hypothalamic satiety neurotransmission. GO: *neurotrophin TRK receptor signaling pathway* (GO:0048011), *positive regulation of synaptic transmission* (GO:0050806), *regulation of eating behavior* (GO:0042755), *energy homeostasis* (GO:0097009).

- **Protein dysfunction.** Loss of receptor tyrosine kinase autophosphorylation and downstream phospho-signaling (loss of function). Gain-of-function variants (distinct disease) increase constitutive activity.
- **Metabolic changes.** Secondary: hyperinsulinemia, hyperglycemia, hyperleptinemia, increased adiposity; reduced locomotor activity and core body temperature contribute in mouse models (PMID: 26629410).
- **Immune system.** Not a primary feature.
- **Upstream vs downstream. Upstream:** leptin → POMC/α-MSH → **MC4R**. **Node:** BDNF → **TrkB** acts *downstream* of MC4R in PVH/DMH. **Downstream of TrkB defect:** failed satiety → hyperphagia → obesity. This downstream position is therapeutically important (see §12).
- **Cell types & GO/CL terms.** TrkB-expressing hypothalamic neurons in PVH and DMH; broadly, central neurons. CL: *neuron* (CL:0000540), *glutamatergic neuron* (CL:0000679). GO biological processes above.

Supporting circuit evidence (model organisms): - *"selective Ntrk2 deletion within paraventricular hypothalamus (PVH) leads to severe hyperphagic obesity"* (PMID: 32265438). - TrkB neurons in the DMH are *necessary and sufficient to suppress homeostatic feeding* (PMID: 30718415). - Hypothalamic TrkB ablation causes hyperphagia preceding weight gain, with hyperglycemia/hyperinsulinemia/hyperleptinemia (PMID: 26629410). - Human ligand evidence: BDNF-haploinsufficient (WAGR) children *"had significantly higher BMI z scores throughout childhood than did patients with intact BDNF"* (PMID: 18753648).

Shared-circuit context: SIM1 (differential, not causal for MONDO:0013483)

The phenotypically overlapping **6q16 deletion / SIM1 haploinsufficiency Prader–Willi-like syndrome** converges on the same PVH circuit from a different angle: SIM1 builds the PVH and sustains **MC4R and oxytocin** expression. In *Sim1*$^{+/-}$ mice, *"Oxt mRNA and peptide were decreased by 80% in Sim1(+/-) mice"* and central oxytocin rescues feeding (PMID: 18451093); conditional/germline Sim1 loss shows *"a remarkable decrease in hypothalamic oxytocin (Oxt) and PVN melanocortin 4 receptor (Mc4r) mRNA"* (PMID: 20220015), and inducible inactivation *"caused increased food and water intake and decreased expression of PVN neuropeptides, especially oxytocin and vasopressin, with no change in energy expenditure"* (PMID: 24773343). This explains the clinical mimicry and underscores why *NTRK2* must be distinguished molecularly from SIM1/6q16 disease.

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7. Anatomical Structures Affected

- **Organ level (primary): Brain**, specifically the **hypothalamus** — paraventricular nucleus (UBERON:0001930) and dorsomedial nucleus (UBERON:0002708). Broader CNS involvement underlies developmental delay.
- **Body systems: Nervous** (central regulation of appetite and neurodevelopment) and **endocrine/metabolic** (secondary — adipose tissue, pancreatic islets via hyperinsulinemia).
- **Secondary organ involvement:** Adipose tissue expansion (UBERON:0001013); metabolic sequelae in liver/pancreas (insulin resistance).
- **Tissue/cell level: Nervous tissue**; **TrkB-expressing hypothalamic neurons** (CL:0000540 neuron). Peripheral adipose BDNF/TrkB axis also modulates feeding, especially in females (PMID: 28721258).
- **Subcellular level (GO Cellular Component):** plasma membrane receptor (GO:0005886), **receptor complex** (GO:0043235), postsynaptic membrane (GO:0045211), cytoplasmic kinase signaling.
- **Localization / lateralization:** Bilateral, symmetric CNS involvement (not lateralized).

UBERON suggestions: UBERON:0000955 (brain), UBERON:0001898 (hypothalamus), UBERON:0001930 (paraventricular nucleus), UBERON:0002708 (dorsomedial hypothalamic nucleus).

8. Temporal Development

- **Onset: Infantile/early childhood** (HP:0003593 infantile onset). Obesity and hyperphagia emerge in early life; developmental delay is apparent in infancy (hypotonia, delayed milestones).
- **Onset pattern:** Insidious/chronic.
- **Progression:** Obesity is **progressive** if hyperphagia is unmanaged; developmental delay/ID is **static (non-progressive)**. Seizures, when present, are variable.
- **Disease course: Chronic, lifelong.** No spontaneous remission of the genetic defect; weight can be modulated by intensive management.

- **Critical periods:** Early childhood is the key window for feeding-behavior intervention and developmental/early-intervention therapies; hyperphagia precedes measurable weight gain (mouse data; PMID: 26629410), supporting early vigilance.

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9. Inheritance and Population

- **Inheritance: Autosomal dominant** (HP:0000006), typically **de novo** heterozygous (PMID: 15494731; PMID: 39540377).
- **Penetrance:** High for the dominant LoF variants reported; precise penetrance estimates are limited by rarity. (Contrast: SIM1 haploinsufficiency shows *incomplete* penetrance — *"only 8 of 13 patients with SIM1 deletion exhibited obesity, in agreement with incomplete penetrance of SIM1 haploinsufficiency"*; PMID: 25351778.)
- **Expressivity:** Variable (severity of obesity, DD, seizures differs across individuals).
- **Genetic anticipation / mosaicism / founder effects:** Not applicable / not reported (no repeat expansion; ultra-rare de novo variants preclude founder effects).
- **Consanguinity / carrier frequency:** Not relevant for a dominant de novo disorder; carrier frequency effectively zero in gnomAD (pLI = 1.00).
- **Epidemiology: Ultra-rare.** Exact prevalence/incidence undefined; only a small number of probands worldwide (one index case plus the LoF subset of a 44-individual *NTRK2* cohort). Orphanet classifies it among rare syndromic obesities.
- **Population demographics:** No ethnic/geographic predilection; de novo origin implies sporadic global occurrence. Sex ratio not established (mouse models suggest females may show a more robust metabolic phenotype — PMID: 26629410, PMID: 28721258 — but this is not confirmed in humans).

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10. Diagnostics

Clinical/laboratory tests. No specific diagnostic biomarker. Supportive findings: elevated fasting insulin, glucose, and leptin (secondary to obesity). Standard obesity work-up (lipids, HbA1c, thyroid, cortisol) to exclude other causes.

Genetic testing (definitive). - **Recommended approach:** Molecular confirmation of a pathogenic *NTRK2* variant. In a child with **severe early-onset obesity** + **hyperphagia** + **developmental delay**, phenotype-driven genetic testing is indicated (PMID: 42761221). - **NGS obesity gene panels** (leptin–melanocortin pathway panels including *NTRK2*, *BDNF*, *MC4R*, *POMC*, *LEPR*, *SIM1*, etc.). The Greek cohort used a 101-gene monogenic-obesity panel (PMID: 42761221). - **Whole-exome (WES)/whole-genome (WGS) sequencing:** high utility for detecting de novo point variants and resolving syndromic presentations. - **Chromosomal microarray (CMA):** to detect 9q21 deletions involving *NTRK2* and to exclude 6q16 (SIM1) and 15q11-q13 (Prader–Willi) in the differential. - **Variant interpretation:** ACMG/AMP criteria; many obesity-panel variants are VUS and must be interpreted cautiously (PMID: 42761221).

Imaging. Brain MRI may show delayed myelination (rare); not diagnostic.

Clinical criteria & differential diagnosis. Diagnosis rests on the clinical triad plus molecular confirmation. **Differential diagnosis** includes: - Prader–Willi syndrome (15q11-q13) and **Prader–Willi-like / SIM1 6q16 deletion** (clinically very similar; distinguished by CMA/molecular testing). - *MC4R*, *POMC*, *LEPR*, *BDNF* monogenic obesity (leptin–melanocortin pathway). - *ARNT2*-related syndrome (SIM1 heterodimer partner; PMID: 34214899). - *MRAP2* deficiency. - Acquired/hypothalamic obesity and ROHHAD.

Screening. Cascade testing of at-risk relatives if an inherited (non-de novo) variant is found; prenatal/preimplantation testing possible for known familial variants.

11. Outcome / Prognosis

- **Survival/mortality:** No direct disease-specific mortality data; prognosis is driven by **obesity-related morbidity** (type 2 diabetes, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease) and complications of developmental disability. Life expectancy may be reduced by severe obesity complications if uncontrolled.
- **Morbidity/function:** Substantial lifelong disability from **intellectual disability/developmental delay** and from **refractory hyperphagic obesity**. Quality of life is heavily impacted by insatiable hunger (analogous MC4R-pathway diseases; PMID: 42821228).
- **Complications:** Insulin resistance/type 2 diabetes, dyslipidemia, hepatic steatosis, orthopedic and sleep complications of obesity; seizures in a minority; behavioral/psychiatric challenges.

- **Prognostic factors:** Severity of hyperphagia, success of weight management, degree of cognitive impairment, and presence of epilepsy. Developmental delay is static but limits adaptive outcomes.
- **Recovery potential:** The genetic defect is not reversible; weight and metabolic parameters are partially modifiable with intensive management.

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12. Treatment

General principle — multidisciplinary, supportive. Management combines **structured dietary/behavioral control of hyperphagia**, **physical activity**, **developmental/early-intervention therapies** (speech, occupational, physical therapy), **anti-seizure medication** where indicated, and management of metabolic complications.

Pharmacotherapy / mechanism-based therapy — an important caveat. The MC4R agonist **setmelanotide** (NCIT: Setmelanotide) acts **at MC4R**. Because the *NTRK2*/TrkB lesion lies **downstream of MC4R**, setmelanotide's efficacy in NTRK2-OBHD is **mechanistically uncertain** and unproven. Setmelanotide is effective where downstream MC4R signaling is intact (e.g., POMC/LEPR deficiency, acquired hypothalamic obesity reconceptualized as "α-MSH deficiency"; PMID: 42114845, PMID: 42878773, PMID: 42496807). In TrkB loss of function, the deficit is at/after the TrkB node, so melanocortin agonism may not restore the missing satiety signal. This should be regarded as experimental for this indication.

Advanced/experimental therapeutics. No approved gene therapy, cell therapy, or RNA therapy. A TrkB **agonist** strategy is mechanistically rational for *loss-of-function* variants but unproven clinically; it would be contraindicated for the *gain-of-function* allelic group. No NCT trials specific to NTRK2-OBHD identified.

Surgical/interventional. Bariatric/metabolic surgery is considered in hypothalamic/refractory obesity but with heterogeneous response; evidence is limited and individualized (PMID: 42496807).

Supportive & rehabilitative. Nutritional counseling and tightly structured food environment; developmental and behavioral therapies; management of comorbidities (diabetes, dyslipidemia, sleep apnea).

Personalized medicine. Genotype-guided: distinguishing LoF vs GoF *NTRK2* variants is essential because they define opposite disorders with opposite therapeutic logic (TrkB agonism vs. seizure/antagonist management).

NCIT suggestions: Setmelanotide (melanocortin receptor agonist), Behavioral/Dietary Weight Management, Rehabilitation Therapy, Anticonvulsant/Antiepileptic Therapy.

13. Prevention

- **Primary prevention:** Not possible for a de novo genetic disorder. Genetic counseling for families with an identified variant.
- **Secondary prevention:** Early molecular diagnosis enables **early feeding-behavior management** and metabolic monitoring to limit obesity severity and complications; early developmental intervention optimizes neurodevelopmental outcomes.
- **Tertiary prevention:** Aggressive management of obesity complications (diabetes, cardiovascular, hepatic, sleep), seizure control, and behavioral support.
- **Genetic counseling:** Recurrence risk is low for de novo variants (but germline mosaicism cannot be excluded); prenatal/PGT available for known familial variants.
- **Screening:** Consider *NTRK2* within monogenic-obesity panels for children with severe early-onset obesity, hyperphagia, and neurodevelopmental delay (PMID: 42761221).

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** *Ntrk2* is highly conserved. Mouse *Ntrk2* (*Mus musculus*, NCBI Taxon 10090) and rat ortholog are the principal experimental orthologs; BDNF/TrkB function in energy balance is **evolutionarily conserved** across mammals (PMID: 38672441).
- **Natural disease in other species:** No well-characterized spontaneous *NTRK2*-obesity syndrome reported in companion animals (OMIA search did not yield an established natural ortholog disease).
- **Comparative biology:** Mouse models faithfully reproduce the hyperphagia-driven obesity and confirm the hypothalamic BDNF/TrkB circuit, supporting strong cross-species conservation of the mechanism.
- **Transmission/zoonosis:** Not applicable (non-infectious genetic disease).

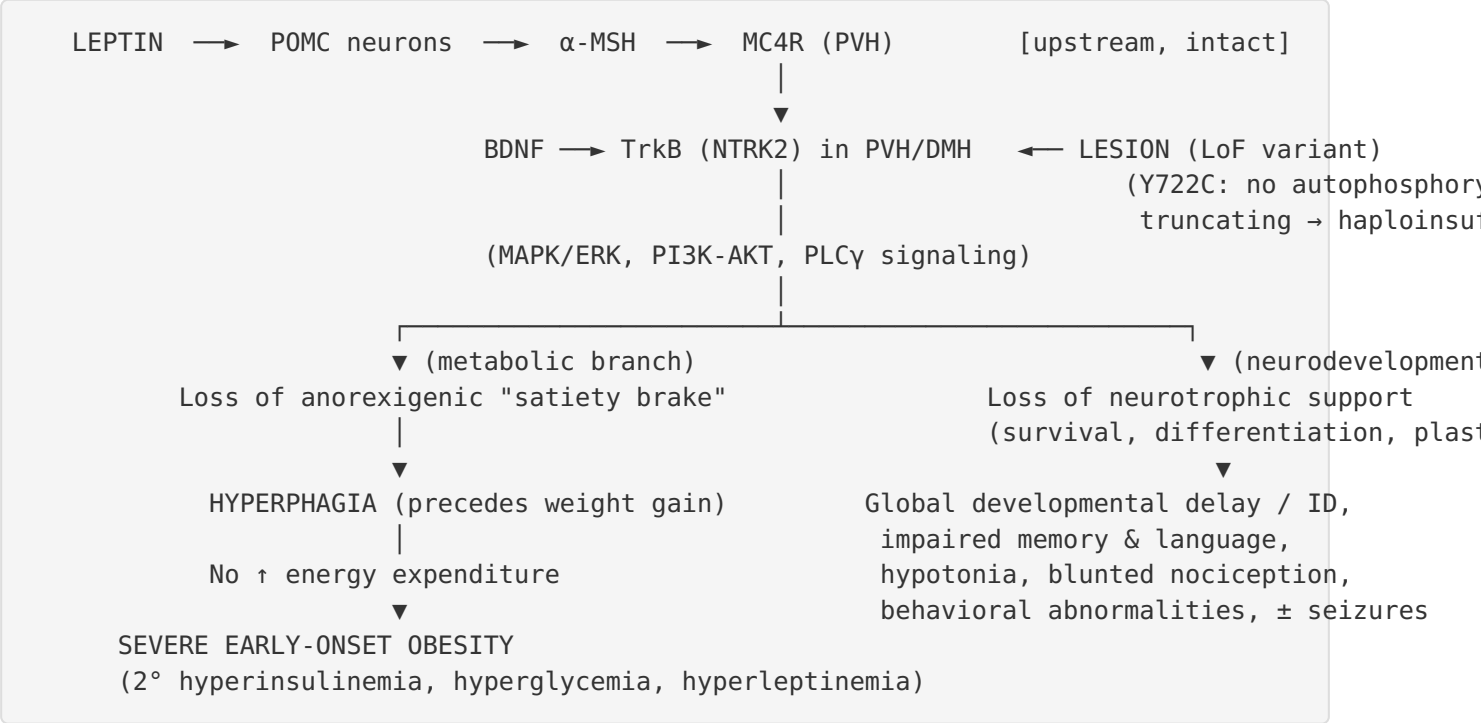
15. Model Organisms

Mouse (*Mus musculus*) is the primary model.

Model	Manipulation	Key phenotype	PMID
PVH-specific *Ntrk2* deletion	Conditional KO	Severe hyperphagic obesity; chemogenetic TrkB-PVH neurons bidirectionally control feeding	32265438
DMH TrkB neuron manipulation	Circuit genetics	TrkB-DMH neurons necessary & sufficient to suppress homeostatic feeding	30718415
Nkx2.1-Ntrk2$^{-/-}$ (hypothalamic)	Conditional KO	Increased body weight/adiposity; hyperphagia precedes weight gain; hyperglycemia, hyperinsulinemia, hyperleptinemia	26629410
Adipocyte/neuron-specific BDNF/TrkB CKO	Conditional KO	Feeding/obesity effects, sex-dependent (female-predominant adipose axis)	28721258
Sim1$^{+/-}$ / conditional *Sim1* (shared circuit)	KO	Hyperphagic obesity; ~80% reduced oxytocin; reduced PVN *Mc4r*/*Oxt*; oxytocin rescues feeding	18451093, 20220015, 24773343
Patient iPSC line (CUIMCi003-A)	ARNT2 variant (SIM1 partner)	iPSC resource for modeling PVH neurodevelopment	34214899

Phenotype recapitulation. Mouse TrkB/Ntrk2 models reproduce the **hyperphagia and obesity** core and localize the effect to hypothalamic PVH/DMH — excellent recapitulation of the metabolic phenotype. **Limitations:** rodent models less fully capture the human **cognitive/developmental delay, memory, language, and nociception** phenotypes; sex-dependence in mice is not clearly mirrored in humans. **Resources:** MGI (*Ntrk2*), IMPC/KOMP for knockout alleles; patient-derived iPSCs for human neuronal modeling.

Mechanistic Model (synthesis)



Key point for therapy: the TrkB defect is **downstream of MC4R**, so MC4R agonists (setmelanotide) may not rescue satiety — unlike in POMC/LEPR deficiency or acquired hypothalamic obesity, where MC4R signaling is intact.

SIM1 vs NTRK2 — same circuit, distinct genes

Feature	*NTRK2*/TrkB (MONDO:0013483, this disease)	*SIM1* / 6q16 deletion (Prader–Willi-like, differential)
Gene / locus	*NTRK2*, 9q21.33	*SIM1*, 6q16.3 (often contiguous deletion)
Molecular role	BDNF receptor; satiety signal downstream of MC4R	bHLH-PAS TF; builds PVH, sustains MC4R/oxytocin
Inheritance	AD, de novo; high penetrance	Haploinsufficiency; **incomplete penetrance** (8/13 obese)
Core triad	Obesity, hyperphagia, DD	Obesity, hyperphagia, DD, hypotonia (PWS-like)
Energy expenditure	Unchanged (hyperphagia-driven)	Unchanged (hyperphagia-driven)
Distinguishing test	NGS/CMA at 9q21	CMA detects 6q16 deletion; oxytocin ↓80% in mice

Evidence Base

PMID	Title (abbrev.)	Role in this report
15494731	*De novo TrkB mutation in severe obesity & developmental delay*	**Index case**; defines NTRK2/TrkB causation; Y722C impairs autophosphorylation/MAPK
39540377	*Upregulation vs loss of NTRK2 in 44 individuals → 2 disorders*	**Allelic series**; LoF→obesity/hyperphagia/DD vs GoF→epilepsy/blindness
32265438	*TrkB PVH neurons suppress appetite*	Localizes satiety action to PVH; circuit mechanism
30718415	*TrkB DMH neurons suppress feeding*	DMH TrkB necessary & sufficient for satiety
26629410	*Hypothalamic TrkB ablation & energy balance*	Hyperphagia precedes weight gain; metabolic sequelae
18753648	*BDNF & obesity in WAGR*	Human ligand-side evidence (BDNF haploinsufficiency → ↑BMI)
38672441	*BDNF/TrkB in energy & glucose balance (review)*	Conserved circuitry; mechanistic synthesis
28721258	*CNS & adipose BDNF/TrkB axes*	Peripheral axis; sex-dependence
18451093	*Oxytocin deficiency in Sim1 mice*	Shared-circuit (SIM1) mechanism
20220015	*Postnatal Sim1 deficiency*	SIM1→↓Mc4r/Oxt; differential context
24773343	*Inducible Sim1 inactivation*	SIM1 ongoing role; no ΔEE
25351778	*Incomplete penetrance of 6q16/ SIM1*	Differential; penetrance contrast
23778136	*LoF SIM1 mutations & obesity/ PWL*	Differential; SIM1 LOF severity
42761221	*Leptin-melanocortin variants in Greek cohort*	Diagnostic approach; panel testing; VUS caution
42114845	*MC4R agonist in ROHHAD*	Setmelanotide context (MC4R-intact disease)
42878773	*Acquired HO as α-MSH deficiency*	Why MC4R agonism works when signaling is intact
42496807		Treatment landscape

PMID	Title (abbrev.)	Role in this report
	Hypothalamic obesity interventions (review)	
42821228	*Hunger severity in MC4R-pathway diseases*	QoL/hyperphagia burden
34214899	*iPSC line, ARNT2 variant*	Model resource; SIM1 partner
34571524	*CMT2Q with NTRK2 variant*	Phenotypic breadth; NTRK2-obesity link noted

Limitations and Knowledge Gaps

1. **Rarity limits epidemiology.** Prevalence, incidence, sex ratio, and penetrance for *NTRK2*-OBHD are not quantitatively established; the HPO frequencies are anchored largely to the index proband.
2. **Mid-course gene correction.** Early iterations pursued *SIM1*/6q16; the authoritative MONDO definition anchors MONDO:0013483 to *NTRK2*. SIM1 material is retained as shared-circuit/differential context, not as the cause of this entity. Readers should not conflate the two.
3. **Human neurodevelopmental mechanism is partly inferred.** The feeding mechanism is strongly demonstrated in mice; the cognitive/memory/nociception phenotypes are inferred from TrkB's general neurobiology and single-patient observations rather than mechanistic human studies.
4. **Therapeutics unproven.** No controlled trials in *NTRK2*-OBHD. The downstream-of-MC4R position makes setmelanotide's benefit uncertain; TrkB-agonist therapy is conceptual.
5. **Variant interpretation.** Many obesity-panel variants are VUS; functional validation (as done for Y722C) is needed to classify novel *NTRK2* variants and to assign them to the LoF vs GoF axis.
6. **Signaling branches partly inferred.** MAPK defect is demonstrated; PI3K-AKT and PLCγ contributions are inferred from canonical TrkB biology.

Proposed Follow-up Experiments / Actions

1. **Functional variant classification pipeline.** Systematically assay novel *NTRK2* variants (autophosphorylation, MAPK/ERK, PI3K-AKT, PLCγ readouts) to assign LoF vs GoF — critical because the two define opposite disorders and opposite therapeutic logic.
2. **Patient-derived iPSC hypothalamic organoids/neurons.** Model TrkB LoF in human PVH/DMH-like neurons to test satiety-signaling defects and candidate TrkB-agonist rescue in a human system.
3. **Natural-history registry.** Aggregate *NTRK2*-OBHD cases (via GeneMatcher/Orphanet) to define penetrance, sex ratio, progression, seizure frequency, and long-term outcomes.
4. **Therapeutic test of downstream vs upstream logic.** Preclinically compare MC4R agonism (setmelanotide) vs small-molecule TrkB agonists in hypothalamic *Ntrk2*-LoF models to determine whether rescuing *below* the lesion is required.
5. **Deep phenotyping of cognition/nociception.** Standardized neurocognitive and sensory testing across the LoF cohort to characterize the neurodevelopmental branch quantitatively.
6. **Biomarker discovery.** Explore circulating BDNF, leptin, and insulin trajectories as potential monitoring biomarkers in affected children.

Evidence source types are indicated throughout: human clinical (index case, cohorts, WAGR), model organism (mouse Ntrk2/Sim1 genetics), in vitro (luciferase/autophosphorylation assays), and computational (gnomAD constraint, ClinVar burden). Ontology suggestions (HPO, GO, CL, UBERON, NCIT, MONDO) are embedded in the relevant sections.
