

Undiagnosed Pediatric Diseases

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Neurodevelopmental Disorders

- Intellectual Disability
 - Cognitive and adaptive impairment (>18y, IQ<70)
 - Prevalence 2-3%; limited therapeutic options
- Extreme clinical heterogeneity
 - Variable severity of intellectual disability
 - Variable manifestation, e.g. syndromic, non-syndromic
- Extreme genetic heterogeneity
 - ca. 20% chromosomal (micro)aberrations
 - ca. 40-50% monogenic causes (>1000 ID genes, various inheritance pattern: **de novo**, aut-dom, aut-rec, X-linked)
 - Others (e.g. mosaicism, imprinting, oligogenic)??
- Large biological/functional heterogeneity
 - Various mutational mechanisms (e.g. LOF, GOF, dominant negative)
 - Various biological processes

SysID database: <http://sysid.cmbi.umcn.nl/>



SysID database

Search by gene symbol, entrez id, fbgm or cg number (e.g. ABCD1)

Browse table ▾

Disease info

Gene symbol	Entrez id	Gene group	Inheritance pattern	Inheritance type	Main class	Accompanying phenotype	Limited confidence criterion	Sysic yes no	Disease subtype	Alter name	Omim disease	Haplo	Clinical synopsis
~ [] x	== [] x	== [] x	== [All] x	[] x	~ [] x	~ [] x	== [] x	== [] x	~ [] x	~ [] x	== [] x	== [] x	~ [] x
GPM6A	2823	ID ...					<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>	
ABCC9	10060	ID ...	Mendelian autosomal	dominant	4	F, S, U, V	<input type="checkbox"/>	<input type="checkbox"/>	CANTU SYNDROME	H...	239850	<input type="checkbox"/>	congenital hypertrichosis, neonatal macrosomia, distinct osteochondrodysplasia, cardi...
ABCC9	10060	ID ...	Mendelian autosomal	dominant			<input type="checkbox"/>	<input type="checkbox"/>	CARDIOMYOPATHY, DILATED, 10; CMD10	-	608569	<input type="checkbox"/>	-
ABCC9	10060	ID ...	Mendelian autosomal	dominant			<input type="checkbox"/>	<input type="checkbox"/>	ATRIAL FIBRILLATION, FAMILIAL, 12; ATRF12	-	614050	<input type="checkbox"/>	-
ABCD1	215	ID ...	Mendelian X-linked	not sure	8a, 8b	G, H, K, L2, M, P	<input type="checkbox"/>	<input type="checkbox"/>	ADRENOLEUKODYSTROPHY; ALD	A...	300100	<input type="checkbox"/>	affects nervous system white matter and adrenal cortex, abnormal VLCFA levels; childh...
ABCD4	5826	ID ...	Mendelian autosomal	recessive	5	M, R	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, CBL...	-	614857	<input type="checkbox"/>	2 patients, poor feeding, respiratory distress, hypotonia, lethargy, breathin anomalies; b...
ABHD5	51099	ID ...	Mendelian autosomal	recessive	8a	M, Q, S	<input type="checkbox"/>	<input checked="" type="checkbox"/>	CHANARIN-DORFMAN SYNDROME; CDS	-	275630	<input type="checkbox"/>	nonbullous congenital ichthyosiform erythroderma, congenital ichthyosis, hepatospleno...
ACAD9	28976	ID ...	Mendelian autosomal	recessive	8b	C, H, M, Q	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	ACAD9 DEFICIENCY	-	611126	<input type="checkbox"/>	complex 1 deficiency, liver disease, encephalopathy, cardiomyopathy, neurologic dysf...
ACO2	50	ID ...	Mendelian autosomal	recessive	2	E, G, H, L2	<input type="checkbox"/>	<input checked="" type="checkbox"/>	INFANTILE CEREBELLAR-RETINAL DEGENERATION; ICRD	-	614559	<input type="checkbox"/>	4 adult patients: neurological manifestations (seizures, memory problems, psychiatric ...
ACOX1	51	ID ...	Mendelian autosomal	recessive	8b	C, E, G, H, L2, M	<input type="checkbox"/>	<input checked="" type="checkbox"/>	PEROXISOMAL ACYL-COA OXIDASE DEFICIENCY	S...	264470	<input type="checkbox"/>	hypotonia, seizures, loss of skills, visual and hearing impairment, ID, mean age of deat...
ACSF3	197322	ID ...	Mendelian autosomal	recessive	8b	G, H, M	<input type="checkbox"/>	<input checked="" type="checkbox"/>	COMBINED MALONIC AND METHYLMALONIC ACIDURIA; C...	-	614265	<input type="checkbox"/>	4 adult patients: neurological manifestations (seizures, memory problems, psychiatric ...
ACSL4	2182	ID ...	Mendelian X-linked	recessive	6		<input type="checkbox"/>	<input checked="" type="checkbox"/>	MENTAL RETARDATION, X-LINKED 63; MRX63	-	300387	<input type="checkbox"/>	unspecific ID, 2 families moderate to severe ID, 1 family mild to moderate ID
ACTB	60	ID ...	Mendelian autosomal	dominant	1	A, B, E, L1, T, Ub	<input type="checkbox"/>	<input checked="" type="checkbox"/>	BARAITSER-WINTER SYNDROME 1; BRWS1	IR...	243310	<input type="checkbox"/>	brain malformation, coloboma, ptosis, trigonocephaly, seizures, hearing loss, short stat...
ACTB	60	ID ...	Mendelian autosomal	dominant	7		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	DYSTONIA, JUVENILE-ONSET	-	607371	<input type="checkbox"/>	2 twins: progressive, dopa-unresponsive generalized dystonia, cleft lip and palate, sma...
ACTG1	71	ID ...	Mendelian autosomal	dominant	1	A, B, E, L1, T, Ub	<input type="checkbox"/>	<input checked="" type="checkbox"/>	BARAITSER-WINTER SYNDROME 2; BRWS2	-	614583	<input type="checkbox"/>	brain malformation, coloboma, ptosis, trigonocephaly, seizures, hearing loss, short stat...
ACTG1	71	ID ...	Mendelian autosomal	dominant			<input type="checkbox"/>	<input checked="" type="checkbox"/>	DEAFNESS, AUTOSOMAL DOMINANT 20; DFNA20	D...	604717	<input type="checkbox"/>	-
ACVR1	90	ID ...	Mendelian autosomal	dominant	7	A, Ub	<input type="checkbox"/>	<input checked="" type="checkbox"/>	FIBRODYSPLASIA OSSIFICANS PROGRESSIVA; FOP	-	135100	<input type="checkbox"/>	skeletal malformations, progressive extraskeletal ossification, mild cognitive deficits or ...
ADAR	103	ID ...	Mendelian autosomal	recessive	2, 8b	(C), I, L2	<input type="checkbox"/>	<input checked="" type="checkbox"/>	ACARDI-GOUTIERES SYNDROME 6; AGS6	-	615010	<input type="checkbox"/>	early-onset encephalopathy (at <18 months of age), intracranial calcification with or with...
ADAR	103	ID ...	Mendelian autosomal	dominant			<input type="checkbox"/>	<input type="checkbox"/>	DYSCHROMATOSIS SYMMETRICA HEREDITARIA 1	D...	127400	<input checked="" type="checkbox"/>	hyperpigmented and hypopigmented macules on the face and dorsal aspects of the ext...
ADCK3	56997	ID ...	Mendelian autosomal	recessive	8b	C, E, G, H, L2, ...	<input type="checkbox"/>	<input type="checkbox"/>	COENZYME Q10 DEFICIENCY, PRIMARY, 4; COQ10D4	S...	612016	<input type="checkbox"/>	encephalomyopathic form with seizures and ataxia; multisystem infantile form with enc...
ADSL	158	ID ...	Mendelian autosomal	recessive	5	E, M, P	<input type="checkbox"/>	<input checked="" type="checkbox"/>	ADENYLOSUCCINASE DEFICIENCY	A...	103050	<input type="checkbox"/>	variable, 1 patient had fatal neonatal course, 4 had severe phenotype with intractable se...
AFF2	2334	ID ...	Mendelian X-linked	not sure	6	P	<input type="checkbox"/>	<input checked="" type="checkbox"/>	MENTAL RETARDATION, X-LINKED, ASSOCIATED WITH FR...	F...	309548	<input type="checkbox"/>	non-syndromic, mild to moderate ID, associated with learning difficulties, communicati...
AGA	175	ID ...	Mendelian autosomal	recessive	8b	(C), G, H, M, (S)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	ASPARTYLGLUCOSAMINURIA; AGU	-	208400	<input type="checkbox"/>	progressive ID from early childhood with minor connective tissue changes and prematu...
AGPAT2	10555	ID ...	Mendelian autosomal	recessive	8a	K, M, Q	<input type="checkbox"/>	<input type="checkbox"/>	LIPODYSTROPHY, CONGENITAL GENERALIZED, TYPE 1; ...	B...	608594	<input type="checkbox"/>	lipoatrophy, hepatomegaly, elevated triglycerides, insulin resistance, cardiomyopathy, ID...
AGTR2	186	ID ...	Mendelian X-linked	recessive	3	E, (P)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	MENTAL RETARDATION, X-LINKED 88; MRX88	-	300852	<input type="checkbox"/>	moderate to severe ID, epilepsy, 2 of 9 patients autistic
AHCY	191	ID ...	Mendelian autosomal	recessive	5	H, (L2), M, (Q)	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	HYPERMETHIONINEMIA WITH S-ADENOSYLHOMOCYSTEI...	-	613752	<input type="checkbox"/>	myopathy, delayed development, elevated metabolites in plasma, hypotonia, sluggishn...
AHI1	54806	ID ...	Mendelian autosomal	recessive	4	H, L1, O, T, W	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	JOUBERT SYNDROME 3; JBTS3	-	608829	<input type="checkbox"/>	distinctive cerebellar and brainstem malformation, molar tooth sign, hypotonia, episod...
AIFM1	9131	ID ...	Mendelian X-linked	not sure	8b	C, E, G, H, L2, M	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY ...	E...	300816	<input type="checkbox"/>	2 patients, early onset neurodegenerative disorder, psychomotor delay, involuntary mov...
AIFM1	9131	ID ...	Mendelian X-linked	not sure	5	G, H	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	COWCHOCK SYNDROME; COWCK	C...	310490	<input type="checkbox"/>	early childhood onset, slowly progressive axonal sensorimotor neuropathy, some patie...
AIMP1	9255	ID ...	Mendelian autosomal	recessive	2	B, G, H, L2	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	LEUKODYSTROPHY, HYPOMYELINATING, 3; HLD3	-	260600	<input type="checkbox"/>	1 family, severe neurologic disorder, global developmental delay, lack of development, l...

Human genes: 1099 Diseases: 1183

Dec 2017: 1069 confirmed ID genes and 711 published candidate genes

ID genes: Highly heterogeneous, yet still convergent

- 47% of ID proteins physically interact with other ID proteins
- 30% increase in connectivity compared to genome wide background
- Significant co-expression in **body-wide** expression data (GTEx; $E=1.1$, $p<0.0001$) and in **brain** (BrainSpan: $E=1.04$, $p=0.001$)
- highest co-expression in the hippocampus (BrainSpan: $E=1.21$, $p_{adj}<0.0001$)

Phenotypes can predict gene functions

↓
ID genes
↓
accompany.
phenotypes

function ↓

- Mapping of ID genes associated with similar phenotypes and identification of co-occurring phenotypes
- Identifies gene – phenotype – molecular function relationships
- Phenotypes can predict novel gene functions

Phenoprofiles of biological processes

- Enrichment of ID accompanying phenotypes among Gene Ontology-defined groups of ID genes relative to their occurrence among all ID genes

→ **Phenotype delineation of IDopathies**

ID gene properties have the power to be predictive

- Functional similarity=closer proximity within a phenotypic linkage network compared to random genes (Honti et al., Plos Comp Biol, 2014)
- ID genes can predict other ID genes by their functional coherence
- Several clinical classes and accompanying phenotypes show additive predictive power

Approach to neurodevelopmental disorders

- Systematic and detailed phenotype data
- Extensive functional data
- Molecular data (disease genes and causative variants)

(Diagnostic) testing strategies in NDDs

- Karyotyping, chromosomal microaberration analysis
 - → ca. 20%
- Targeted sequencing of individual genes
 - → <5%
- NGS Panel Sequencing
 - 25 kb panels: 5 most frequently mutated ID genes
- (Trio) Exome Sequencing
 - → detection rate >40% (DDD study, Nature, 2017; own experience)
 - Trio (inheritance filter, mainly *de novo*)
 - Affected only (gene or variant list)
- Genome Sequencing

Screening by Exome Pool-Seq

- capture based exome + DNA-sample pooling = **exome Pool-Seq**
- Pilot-study: 96 patients with NDDs → 8 Pools with 12 samples each
- cost reduction up to 85%

Exome Pool-Seq: detection rate 28%

- **13** loss-of-function variants in 398 AD/XL confirmed ID genes
(11 *de novo*, 1 not maternal, 1 also affected father)
- **11** missense variants in 398 AD/XL confirmed ID genes
(7 *de novo*, 1 not maternal, 2 hemizygous, 1 X-linked maternal)
- **1** homozygous variant in 569 autosomal-recessive confirmed ID genes
- **3** *de novo* loss-of-function variants in ID candidate genes
(543 published; 1.649 haploinsufficiency intolerant)

From candidate variant/gene to a new disease gene

- Variant segregates with suspected inheritance
 - e.g. *de novo* variant in sporadic ID
 - e.g. homozygous variant in consanguineous families
- Loss-of-function variant
- Missense variant??
 - *In silico* prediction
 - ExAC constraint scores
- Functional/experimental evidence
- **Additional patients with similar phenotype and/or similar mutations**

International Matchmaking platforms

- Single patient with severe ID and epilepsy and a *de novo* missense variant in *RHOBTB2*
- Genematcher + Decipher + emails
 - 10 patients with developmental and epileptic encephalopathy, microcephaly and movement disorders

Increased protein levels of mutant RHOBTB2

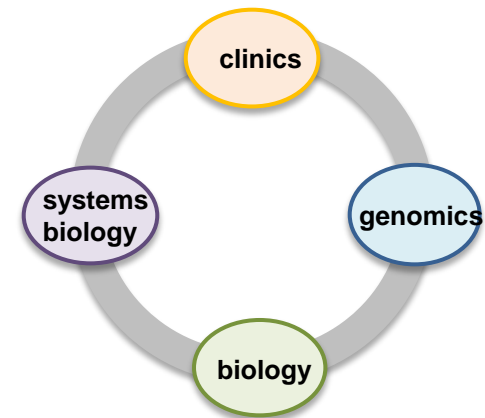
→ Impaired degradation of mutant RHOBTB2 in the proteasome, probably due to reduced auto-ubiquitination

Epilepsy in RhoBTB overexpressing flies

Bang sensitivity

What do we need to diagnose pediatric diseases?

- State of the art sequencing (exome, genome)
- National and international collaborations (matchmaking platforms)
- Variant databases (e.g. ClinVar, LOVD)
- Interdisciplinary collaborations



- **What do we need to treat pediatric diseases?**
 - a cause
 - a better understanding of the underlying mechanisms and pathomechanisms

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