MEDICOVER
GENETICS

CATALOGUE
PEDIATRIC GLOBAL DELAY

Define&Decide

Physician Information

MEDICOVER GENETICS
ABOUT US

Medicover Genetics was developed as a strategic business area within Medicover, **a network of hospitals and diagnostic laboratories across 10 European markets**. Our purpose is to empower people to use comprehensive and meaningful genetic tests at the forefront of their diagnostic journey, fueled by our vision to place genetics at the core of medical decisions. We want to achieve this by leveraging advancements in genomics to develop relevant diagnostic solutions, supported by professional medical interpretation, to improve people's health and well-being.

Spanning cytogenetic analyses, molecular pathology solutions, the latest in next generation sequencing (NGS) technology and microbiome sequencing, Medicover Genetics offers a **complete in-house and tailor-made portfolio produced in our laboratories in Germany** and offered internationally. Medicover is the sole testing site in Europe for Bionano's Saphyr® technology: the third-generation optical mapping solution which resolves large-scale structural variations currently missed by NGS.

Using a robust diagnostics pipeline, we make **NGS testing and variant discovery efficient, scalable** and **accessible** by converting NGS data into customized clinical reports in a timely manner, **thereby decreasing turnaround times**.

Patient support through genetic counselling is integral to our patient journey and crucial to explain complex findings to them as well as assist physicians as they support their patients. With more than **20 certified genetic counsellors** across our markets, we are able to provide this locally and in the local language.

MEDICOVER GENETICS

PURPOSE

To empower people to use comprehensive and meaningful genetic tests at the forefront of their diagnostic journey

VISION

To place genetics at the core of medical decisions

MISSION

Leverage advancements in genomics to develop relevant diagnostic solutions, supported by professional medical interpretation, to improve people's health and well-being

VALUES

Humanity | Passion | Innovation | Medical Excellence | Integrity

MEDICOVER GENETICS
WHY US

- A network of laboratories and medical institutions makes Medicover Genetics **a leader in genetic testing** in Germany with foundations dating back to 1998

- A clinical team comprised of scientists, physicians and medical geneticists, several with **>20 years of experience** in genetic testing, assuring meaningful and comprehensive genetic tests

- **Up-to-date diagnostic algorithms** and gene panels based on current scientific literature and international guidelines

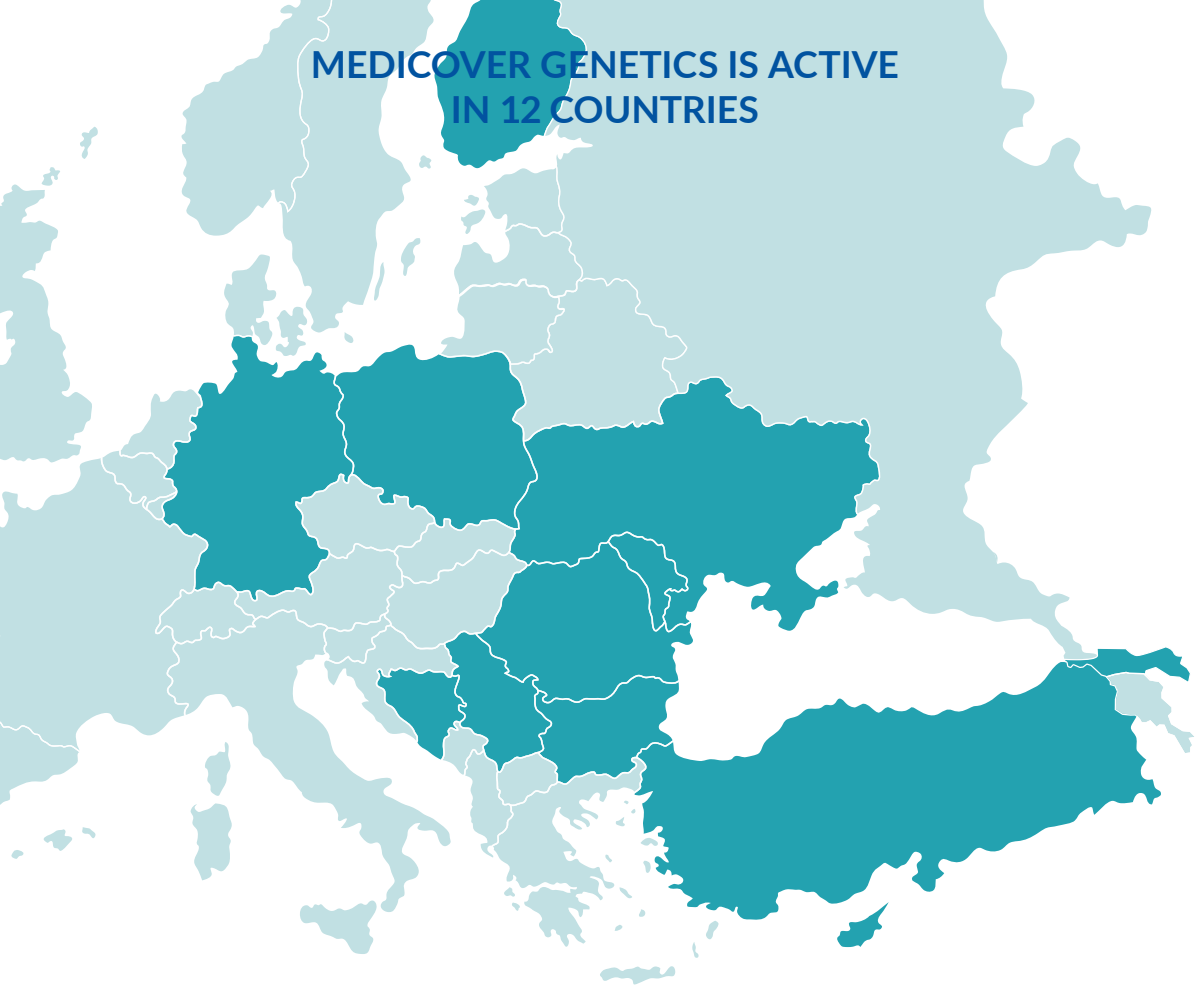
- Expertise in gene variant analysis ensuring **"no variant left behind"**

- Cutting-edge technology in sequencing and laboratory methods allows for **short turnaround times**

- **Quality** assessed by several certified bodies, including EFI, DIN EN ISO 9001, DIN EN ISO15189 accreditation for medical laboratories, DIN EN ISO/IEC 17025 accreditation for testing and calibration laboratories and a generally valid GMP (Good Medical Practice) certificate

- **Data privacy** is your right and our priority

MEDICOVER GENETICS IS ACTIVE IN 12 COUNTRIES



BOSNIA-HERZEGOVINA | BULGARIA | CYPRUS | FINLAND | GEORGIA
GERMANY | MOLDOVA | POLAND | ROMANIA | SERBIA | TURKEY | UKRAINE

MEDICOVER GENETICS
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TECHNICAL INFORMATION

MICROARRAY CGH

Technology	SurePrint G3 CGH ISCA v2 SNP-Microarray
Probes	4x180K
Functional resolution	50kb

NEXT GENERATION SEQUENCING

Technology	Illumina NovaSeq6000
Gene Coverage & Depth	>95% of the exome yields at least 20X sequence depth with 5bp into flanking introns
Single Nucleotide Variant (SNV) Sensitivity	99.93%
Insertions/Deletions (Indel) Detection	Up to 21bp
Indel Sensitivity	95.32%
Indel Precision	94.71%
Human Reference Genome	GRCh38
Pathogenic Variant Confirmation	Sanger sequencing (only if quality falls below our criteria) of pathogenic or likely pathogenic variants
Variant Classification	According to ACMG guidelines

HOW TO ORDER

STEP 1
TEST ORDERED
Patient visits specialist to find the right test

STEP 2
SAMPLE COLLECTED
Sample collected at nearest blood drawing point

STEP 3
SAMPLE PROCESSED
Molecular analysis is performed in our laboratories

STEP 4
RESULTS DELIVERED
Report is delivered to you and your patient

GENETIC COUNSELLING

Genetic counselling by our local Medicover counsellors is available upon request

MATERIAL REQUIRED

1 ml EDTA blood sample or 1 Medicover Genetics Buccal Swab Kit

TURNAROUND TIME

15-25 working days

For complete information about our panels, including technical information and gene list, please visit: https://www.medicover-genetics.com

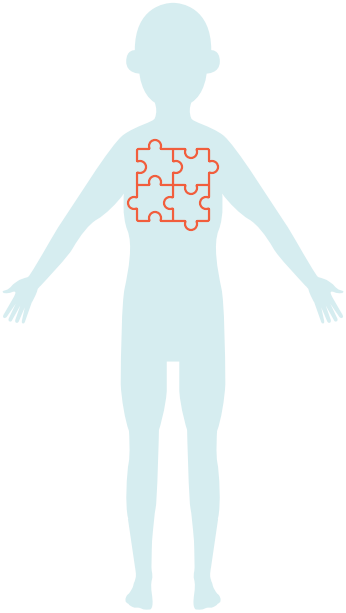
PEDIATRIC GLOBAL DELAY
OVERVIEW

BACKGROUND

Global developmental delay and intellectual disability (GDD/ID) affect up to 3% of children <5 years old and is defined as a delay in ≥2 developmental domains*. Up to 40% of GDD/ID cases are caused by genetic factors, including chromosomal abnormalities in 25% of cases, and monogenic disorders in up to 10% of cases. Up to two-thirds of children with GDD do not have a single group of symptoms that can point towards a specific diagnosis; therefore, several genetic tests are often required to define the cause of GDD/ID.

Our tests combine chromosomal analyses and (comprehensive) gene panels associated with many different disorders with overlapping features.

Having a diagnosis can help you decide on early rehabilitation (if possible) services and treatment options and identify associated medical risks, thereby improving the patient's clinical outcome and preventing further complications. Our genetic counselling can help guide management options and reproductive decisions based on recurrence risks.



*Developmental domains include physical, cognitive, speech/language, social and emotional

DEVELOPMENTAL DOMAIN SYMPTOMS

GROSS AND FINE MOTOR

• Delayed ability to sit, crawl or walk • Delayed ability to jump, run and climb • Inability to grasp objects • Inability to hold utensils, work with objects, and draw

SPEECH AND LANGUAGE

• Difficulty speaking or speaking late • Difficulty understanding language • Inability to express thoughts

COGNITION

• Lack of curiosity • Short attention span and easily distracted • Inability to remember things
• Inability to connect actions with consequences • Difficulty with problem-solving or logical thinking

PERSONAL AND SOCIAL DEVELOPMENT

• Difficulty communicating or socializing with others • Inability to express and control emotions
• Lower than average IQ test scores • Showing repetitive and restricted behavior • Showing extreme behavior (unusually fearful, aggressive, shy or sad)

ACTIVITIES OF DAILY LIVING

• Inability to do everyday tasks like getting dressed, eating, brushing teeth, washing hands or going to the bathroom without help

Please note that symptoms vary in type and severity between children and that not all symptoms are listed for each developmental domain. Children should be assessed by a physician and/or genetic counsellor. Adapted from https://www.cdc.gov/ncbddd/actearly/milestones

TARGET POPULATION

Children <5 years with a **significant delay in ≥2 developmental domains***

Children with an **autism spectrum disorder**

Children with **dysmorphic features**

DIAGNOSTIC PROCESS

STEP 1

Patient history, **physical examination** and **sensory evaluation** should be conducted for each child with suspected GDD/ID

STEP 2

Following a clinical evaluation, **genetic counselling** is recommended with one of our counsellors

STEP 3

Molecular genetic analysis of the patient's genome

WE OFFER TWO OPTIONS TO TEST FOR GDD/ID:

OPTION 1: Stepwise Analysis

First, a genome-wide screen for **deletions/duplications** is performed. If none are detected, another **genetic counselling session** is conducted and one of our **gene panels** will be recommended by our genetic counsellor.

OPTION 2: Simultaneous Analysis

Screening for **deletions/duplications** and **gene panel sequencing** are performed **at the same time**. Performing both steps simultaneously saves time and resources for the patient.

STEP 4

All cases are finalized with a **medical report** and **genetic counselling**

DELETIONS, DUPLICATIONS AND ANEUPLOIDIES

Microarray comparative genomic hybridization (microarray CGH) is used for genome-wide screening of deletions (loss of genetic material) and duplications (gain of genetic material) and does not require prior knowledge of precise genetic aberrations. This method will not detect chromosomal structural changes that do not result in deletions/duplications, such as translocations or inversions, ring chromosomes or low-level mosaicism.

GENE PANELS

- 63 genes — Autism Spectrum Disorders
- 43 genes — Brain Malformations, Comprehensive
- 9 genes — Brain Malformations, Lissencephaly
- 19 genes — Brain Malformations, Pontocerebellar Hypoplasia
- 8 genes — Brain Malformations, Tubulinopathies
- 10 genes — Coffin-Siris Syndrome
- 43 genes — Congenital Disorders Of Glycosylation
- 7 genes — Cornelia De Lange Syndrome
- 21 genes — GPI Anchor Deficiency
- 179 genes — Intellectual Disability
- 66 genes — Macrocephaly
- 30 genes — Microcephaly
- 11 genes — Overgrowth Syndromes
- 14 genes — Pediatric Neurotransmitter Disorders
- 20 genes — RASopathies, Comprehensive
- 3 genes — Rett Syndrome
- 22 genes — Rett Syndrome And Related Disorders

- Fragile X syndrome analysis is available upon request
- Interpretation of the molecular genetic results relies on having an accurate clinical picture of the patient

DELETIONS, DUPLICATIONS AND ANEUPLOIDIES

BACKGROUND

With the introduction of high-resolution techniques and fluorescence *in situ* hybridization (FISH), an increasing number of clinical syndromes have been found to be caused by microdeletions. Microdeletion syndromes usually lead to complex yet clinically distinguishable phenotypes and usually occur sporadically as an isolated case within a family. Most of the chromosomal microdeletion syndromes that are based on the loss of mainly submicroscopic chromosomal segments are associated with intellectual disability. However, other symptoms such as specific combinations of malformations and/or dysmorphic signs and characteristic "behavioral phenotypes" are almost always prominent. In these cases, there is usually a suspected clinical diagnosis that requires a specific examination.

Some of the microdeletion syndromes belong to the more common genetic disorders, especially the microdeletion 22q11.2 which causes DiGeorge syndrome and is observed with a frequency of at least 1:4,000. Most of the microdeletion syndromes are also called contiguous gene syndromes as the symptoms are most likely caused by the loss of several genes located in the deleted region. Some of the syndromes mentioned may also have other causes (single gene mutation, e.g., in Angelman syndrome (AS) and/or uniparental disomy, e.g., in Prader-Willi syndrome and AS).

Account for **25% of GDD/ID cases**

Mostly sporadic as an isolated case within a family

Syndromes with **complex** yet clinically **distinguishable phenotypes**

The use of chromosomal microarrays (CMA) has identified numerous new microdeletion and duplication syndromes which were unknown a few years ago and whose phenotype was only recognized as characteristic after repeated descriptions of the same imbalance.

The use of the microarray CGH in children with developmental delay/intellectual disability or malformation syndromes, has defined numerous new microdeletion and duplication syndromes that were completely unknown a few years ago. Through the use of array CGH in routine diagnostics, submicroscopic imbalances, which can be regarded as the cause of intellectual disability/developmental delay, and possibly other symptoms can now be found more frequently. In addition, autistic spectrum disorders, which often include intellectual disability, are frequently accompanied by certain copy number variants (CNV).

AUTISM SPECTRUM DISORDERS PANEL

BACKGROUND

Autism spectrum disorders (ASD) are among the neuropsychiatric diseases with the greatest heritability, as shown by high concordance rates of about 70% in monozygotic twins in early twin studies. Based on this, the empirical risk of recurrence for siblings of children with ASD is between 5 and 20%, i.e., significantly higher than for other multifactorial diseases. ASD are both clinically and genetically heterogeneous. The most common comorbidities are developmental disorders or reduced intelligence (about 70%), speech disorders (about 30%) or epilepsy.

It is now believed that modern genetic testing methods can find a genetic cause for about 20 to 25% of ASD. Approximately 20% carry *de novo* generated CNV, which are detected by chromosomal microarrays. Monogenic causes are found in 3-5%, mostly for syndromes caused by pathogenic variants in single genes that show ASD as a partial symptom.

GENE PANEL

63 genes

ALDH5A1, AP1S2, ARX, ATRX, AUTS2, BRAF, CACNA1C, CASK, CDKL5, CHD7, CHD8, CNOT3, CNTNAP2, DHCR7, DPP6, EHMT1, FGD1, FOXG1, FOXP1, FOXP2, GNAI1, GRIN2B, HPRT1, KDM5C, L1CAM, MBD5, MECP2, MED12, MEF2C, MID1, NHS, NIPBL, NLGN3, NLGN4X, NRXN1, NSD1, OPHN1, PCDH19, PHF6, PNKP, PQBP1, PTCHD1, PTEN, PTPN11, RAB39B, RAI1, RPL10, SCN1A, SHANK2, SHANK3, SLC9A6, SMARCB1, SMC1A, SMC3, TBR1, TCF4, TMLHE, TSC1, TSC2, UBE2A, UBE3A, VPS13B, ZEB2

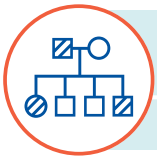
High risk of recurrence
for siblings of children
with an ASD

Up to 25% detected
by genetic testing

"Spectrum" refers to
wide range of symptoms, skills, and levels of disability

The American College of Medical Genetics recommends the use of a CMA for the genetic diagnosis of patients with ASD in whom clinical examination is inconclusive for a specific genetic syndrome. If the CMA analysis is not conclusive, the *MECP2* gene (Rett syndrome) should be examined in girls, the *FMR1* gene (Fragile X syndrome) in boys, or the *PTEN* gene (Bannayan-Riley-Ruvalcaba syndrome) if macrocephaly is present.

It is now assumed that numerous genes, probably more than 1,000, may be involved in the development of ASD, although it is not yet clear to what extent individual variants influence the expression in individual cases. Nevertheless, advanced diagnostics using NGS (gene panel diagnostics) can also lead to a diagnosis in individual cases and thus to more precise statements on the prognosis and the risk of recurrence.



PREVALENCE	INHERITANCE PATTERN
1:270 worldwide	Unknown, but highly heritable

BRAIN MALFORMATIONS, COMPREHENSIVE PANEL

BACKGROUND

The development of the human cerebral cortex involves complex developmental processes that eventually lead to the characteristic six-layer structure of the mature cerebral cortex. Central events in this process during fetal brain development are neuronal proliferation, migration and finally postmigratory cortical organization. Disorders in these developmental steps lead to the formation of various malformations, which can be subdivided and labeled either according to morphology (e.g., lissencephaly), anatomical structures (e.g., pontocerebellar hypoplasias), or functional criteria (e.g., tubulinopathies). When genetic causes are considered, there is clinical and genetic overlap. Meanwhile, more than 100 genes are known to control these complicated processes.

GENE PANEL

43 genes

AHI1, ARFGEF2, ARX, CASK, CC2D2A, CEP290, CEP41, DCX, EOMES, FKRP, FKTN, FLNA, GPR56, KIF7, LAMC3, LARGE, MKS1, NDE1, NPHP1, OCLN, OPHN1, PAFAH1B1, POMGNT1, POMT1, POMT2, PQBP1, RARS2, RELN, RPGRIP1L, SRPX2, TMEM138, TMEM216, TMEM237, TMEM67, TSEN2, TSEN34, TSEN54, TUBA1A, TUBA8, TUBB2B, TUBB3, VLDLR, VRK1

Major cause of **developmental disabilities**, **severe epilepsy**, and **reproductive disadvantage**

>100 genes associated with one or more types

Comprehensive analysis of clinical, imaging, and genetic data **needed to define disorder**

BRAIN MALFORMATIONS, LISSENCEPHALY PANEL

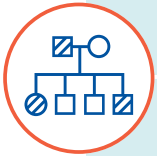
BACKGROUND

The term lissencephaly comes from the Greek and is derived from "lissos" = smooth and "enkephalos" = brain and refers to the main abnormality, the smooth brain surface. Lissencephaly is based on a disturbance of neuronal migration and consequently of the normal six-layer structure of the mature cerebral cortex in humans. Agyria, pachygyria and subcortical band heterotopia are also included under the umbrella term lissencephaly. There is both clinical and genetic overlap with other brain malformations, especially tubulinopathies.

The most common causes of lissencephaly are Miller-Dieker syndrome, which is caused by a contiguous gene syndrome due to microdeletion 17p13.3 or pathogenic variants in the *PAFAH1B1* gene (formerly *LIS1*) located in this chromosomal region, as well as variants in *DCX*, the causative gene for X-linked lissencephaly or X-linked subcortical laminar heterotopy.

GENE PANEL

9 genes ARX, DCX, KATNB1, MACF1, NDE1, PAFAH1B1, RELN, TMTC3, TUBA1A



PREVALENCE	INHERITANCE PATTERN
1.2:100,000 births	Autosomal dominant or recessive or X-linked

BRAIN MALFORMATIONS, PONTOCEREBELLAR HYPOPLASIA PANEL

BACKGROUND

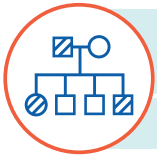
Pontocerebellar hypoplasia (PCH) is a clinically and genetically heterogeneous group of genetic, neurodegenerative diseases, most of which start prenatally and therefore usually cause early clinical symptoms. The leading symptoms are a severe motor and cognitive developmental disorder, often with muscle hypotonia, and a limited life expectancy. Neuroradiology shows a variable, but usually severe, hypoplasia or atrophy of the cerebellum.

To date, pathogenic variants of 18 genes are reported to cause various subtypes of PCH. As of 2019, 12 subtypes can be distinguished: PCH1 (PCH1 A to D), PCH2 (PCH2 A to F), PCH3 to 12. Clinically, the main symptom in patients with classic PCH1 is pronounced muscle hypotonia resulting in muscle atrophy comparable to other spinal muscular atrophies, as well as a severe global developmental disorder, a central visual impairment, swallowing and eating disorders, occasional seizures, and microcephaly in some patients. The other types show different neurological symptoms of varying degrees of severity, with and without progression, and possibly with associated brain malformations.

GENE PANEL

19 genes

AMPD2, CHMP1A, CLP1, COASY, EXOSC3, EXOSC8, EXOSC9, PCLO, RARS2, SEPSECS, SLC25A46, TBC1D23, TOE1, TSEN15, TSEN2, TSEN34, TSEN54, VPS53, VRK1



PREVALENCE	INHERITANCE PATTERN
Unknown, >100 cases reported	Autosomal recessive

BRAIN MALFORMATIONS, TUBULINOPATHIES PANEL

BACKGROUND

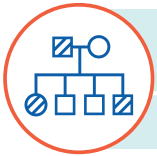
Tubulinopathies represent a broad, overlapping spectrum of congenital brain malformations. Brain malformations in the context of tubulinopathies can manifest themselves, among other things, in the form of lissencephaly, as classical lissencephaly, lissencephaly with cerebellar hypoplasia, lissencephaly with agenesia of the corpus callosum, or lissencephaly with pachygyria. Other common malformations are polymicrogyria-like cortical dysplasia, rarefied gyration, and microlissencephaly, often in combination with dysplastic basal ganglia and corpus callosum abnormalities, as well as hypoplasia or dysplasia of the brain stem and cerebellum.

Clinical symptoms can include a global developmental delay, epilepsy, primary microcephaly, and eye involvement of various degrees. The diagnosis is usually made on the basis of the specific brain malformation findings.

Molecular genetic confirmation of the suspected diagnosis can be made by examining genes that code for the different isotypes of tubulin. Most tubulinopathies follow an autosomal dominant inheritance pattern and are caused by *de novo* variants in the *TUBA1A*, *TUBB2A*, *TUBB2B*, *TUBB3*, *TUBB*, or *TUBG1* gene. Rarely, variants in the *TUBA8* and *TBCD* genes can be identified that follow autosomal recessive inheritance.

GENE PANEL

8 genes TBCD, TUBA1A, TUBA8, TUBB, TUBB2A, TUBB2B, TUBB3, TUBG1



PREVALENCE	INHERITANCE PATTERN
<1:1,000,000	Autosomal dominant or recessive, *de novo*

COFFIN-SIRIS SYNDROME PANEL

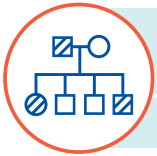
BACKGROUND

Coffin-Siris syndrome is a complex syndrome. The main symptoms are a developmental disorder of varying degree, muscular hypotonia and a characteristic appearance with full lips, a wide mouth, a broad nasal bridge and nose tip, thick eyebrows, long eyelashes, and hypertrichosis with sparse scalp hair. Hypoplasia/aplasia of the end phalanx of the 5th finger or fingernail is also characteristic. Nail hypoplasia may also be present on other fingers or toes. Failure to thrive is seen in most infants and toddlers, about half have seizures, almost half have hearing loss that is often due to frequent airway infections, and about half have strabismus or ptosis. Heart defects and malformations of the kidneys and the urinary tract occur in about one-third of cases.

Pathogenic heterozygous variants in 8 genes are causal: *ARID1A*, *ARID1B*, *ARID2*, *SMARCA4*, *SMARCB1*, *SMARCE1*, *SOX11*, and *DPF2*; pathogenic variants in *ARID1B* are most common at around 35-40%. In about 40% of patients with clinically suspected Coffin-Siris syndrome, no pathological variant can be detected in the above-mentioned genes. The disease is inherited autosomal dominantly, although a pathogenic *de novo* variant is usually present in affected individuals. Deletions (especially in *ARID1B*) have been reported rarely.

GENE PANEL

10 genes ARID1A, ARID1B, ARID2, DPF2, SMARCA4, SMARCB1, SMARCC2, SMARCE1, SOX11, SOX4



PREVALENCE	INHERITANCE PATTERN
Rare, <200 cases reported	Autosomal dominant or recessive, *de novo*

CONGENITAL DISORDERS OF GLYCOSYLATION PANEL

BACKGROUND

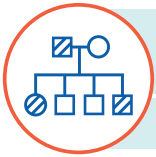
Congenital disorders of glycosylation (CDG syndrome) are genetic metabolic disorders due to hereditary defects in glycoprotein biosynthesis. These are usually severe multi-organ diseases with pronounced neurological disorders.

The most common is CDG syndrome type Ia, caused by a phosphomannomutase deficiency due to variants in the *PMM2* gene. A prominent developmental disorder is typical; brain malformations, skeletal anomalies, inverted nipples, coagulation defects, and other symptoms may also occur. The suspected diagnosis is usually assessed first using metabolic diagnosis to detect abnormal glycosylation of serum glycoproteins and then confirmed by molecular genetic examination. However, evidence of abnormal glycosylation of serum glycoproteins is not present in all types of CDG syndrome. Therefore, if the metabolic diagnosis is inconspicuous but a metabolic disorder is still suspected, NGS panel diagnostics may be indicated and may lead to a diagnosis in individual cases.

GENE PANEL

43 genes

ALG1, ALG11, ALG12, ALG13, ALG2, ALG3, ALG6, ALG8, ALG9, B4GALT1, CAD, CCDC115, COG1, COG4, COG5, COG6, COG7, COG8, DDOST, DOLK, DPAGT1, DPM1, DPM2, DPM3, MGAT2, MOGS, MPDU1, MPI, NGLY1, PGM1, PMM2, RFT1, SLC35A1, SLC35A2, SLC35C1, SLC39A8, SRD5A3, SSR4, STT3A, STT3B, TMEM165, TMEM199, TUSC3



PREVALENCE	INHERITANCE PATTERN
Unknown	Autosomal recessive

CORNELIA DE LANGE SYNDROME PANEL

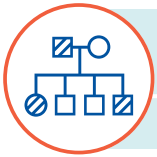
BACKGROUND

Cornelia de Lange syndrome (CdLS) is a malformation-retardation syndrome that typically presents with characteristic craniofacial dysmorphia, prenatal growth retardation, hypertrichosis, synophrys, reduction malformations of the upper extremities, and intelligence impairment (average IQ: 53). In addition, heart defects and gastrointestinal disturbances are frequently found. In milder forms, which probably affect the majority of patients, the facial dysmorphia is milder than in the classic form; the cognitive impairment and limb defects are also less severe.

So far, pathogenic variants in 6 genes are known, whereby the largest proportion of variants are in the *NIPBL* gene (60%). In about 15-20% of patients with classic CdLS, *NIPBL* variants cannot be detected in peripheral lymphocytes because they are present in mosaic form in other tissues. In addition, variants are described in mosaic form in rare cases in the genes *SMC3*, *RAD21*, and *SMC1A*.

GENE PANEL

7 genes ANKRD11, BRD4, HDAC8, NIPBL, RAD21, SMC1A, SMC3



PREVALENCE	INHERITANCE PATTERN
1:10,000-100,000	Autosomal dominant or X-linked, 99% *de novo*

GPI ANCHOR DEFICIENCY PANEL

BACKGROUND

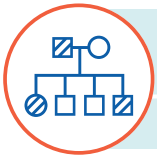
Glycosylphosphatidylinositol anchors (GPI anchors) are protein complexes of the plasma membrane that anchor glycoproteins to the cell surface. GPI anchor defects represent a subgroup of glycosylation disorders (CDG syndrome).

Hyperphosphatasia is one of the leading symptoms of this group of severe developmental disorders. Depending on the type and location of the various GPI anchor defects, such pathological changes in serum parameters may be present, but if the underlying disturbance is in other locations, these may be completely absent, thus making diagnosis more difficult in these cases. Typical symptoms of many GPI anchor defects are severe developmental disorders, epilepsy, partly congenital organ malformations, and facial dysmorphia. In recent years, various genes have been identified which lead to a disruption of the mechanism of GPI anchor synthesis or function.

GENE PANEL

21 genes

GPAA1, PGAP1, PGAP2, PGAP3, PIGA, PIGB, PIGC, PIGG, PIGH, PIGL, PIGM, PIGN, PIGO, PIGP, PIGQ, PIGS, PIGT, PIGU, PIGV, PIGW, PIGY



PREVALENCE	INHERITANCE PATTERN
Unknown, rare	Autosomal recessive

INTELLECTUAL DISABILITY PANEL

BACKGROUND

Intellectual disability, defined as an IQ <70, has a prevalence of 1.5% to 2%. More severe forms with an IQ <50 have a prevalence of 0.3% to 0.4%. Males are more commonly affected due to X-linked genes. The causes of intellectual disability are diverse; however, genetic factors are involved in at least 50% of cases. Comorbidities such as behavioral disorders and/or epilepsies are common. If the cause of an intellectual disability is not clear, an empirical risk of recurrence of approximately 8% must be assumed for further pregnancies. Despite increasing numbers of new genetic syndromes associated with intellectual disability in recent years, the cause of intellectual disability still remains unexplained in some patients.

In syndromic forms of intellectual disability, a characteristic combination of malformations, minor external abnormalities, or characteristic behaviors may suggest a tentative diagnosis, which can be clarified with targeted diagnostics (e.g., fragile X, Rett or Angelman syndromes). However, many patients present with non-characteristic symptoms making the diagnosis impossible even for an experienced pediatrician or clinical geneticist. Studies have shown that CNV are responsible for approximately 10 to 15% of cases of intellectual disability with inconspicuous chromosomal analysis.

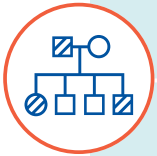
About 60% of the causes of developmental disorders remain unexplained. Since developmental disorders often occur sporadically, i.e., as an isolated case within a family, it has been assumed that new mutations occur, for example, in genes that are important for the development and interconnection of neurons, especially since humans have a high rate of new mutations.

In recent years, several studies have confirmed that dominant new mutations seem to contribute to a large extent to the cause of severe (IQ <50) intellectual disability. The rate of dominant new mutations increases with paternal age. Studies suggest that up to 50% of severe non-syndromic developmental disorders are caused by *de novo* point mutations and small indels with a large degree of genetic heterogeneity. It is thought that NGS can determine the underlying cause of approximately 30% of previously unexplained developmental disorders.

GENE PANEL

179 genes

ABCD1, ACSL4, AFF2, AGTR2, AIFM1, ALG13, AMER1, AP1S2, AP4B1, AP4E1, AP4M1, AP4S1, ARHGEF6, ARHGEF9, ARX, ATP6AP2, ATP7A, ATRX, BCAP31, BCOR, BRWD3, CA8, CASK, CC2D1A, CCDC22, CDH15, CDKL5, CLCN4, CLIC2, CNKSR2, CNTNAP2, CRBN, CREBBP, CUL4B, DCX, DDX3X, DKC1, DLG3, DMD, EBP, EIF2S3, EP300, ERLIN2, FAAH2, FANCB, FGD1, FLNA, FMR1, FOXG1, FOXP1, FRMPD4, FTSJ1, GDI1, GJB1, GK, GPC3, GPKOW, GRIA3, GRIK2, GRIN2B, GSPT2, HCCS, HCFC1, HDAC6, HDAC8, HMGB3, HNRNPH2, HPRT1, HSD17B10, HUWE1, IDS, IGBP1, IKBKG, IL1RAPL1, IQSEC2, KDM5C, KDM6A, KIAA2022, KIF4A, KIRREL3, KLF8, KLHL15, L1CAM, LAMP2, LAS1L, MAGT1, MAN1B1, MAOA, MBTPS2, MECP2, MED12, MEF2C, MID1, MID2, MSL3, MTM1, NAA10, NDP, NDUFA1, NEXMIF, NHS, NLGN3, NLGN4X, NONO, NRXN1, NSDHL, NXF5, OCRL, OFD1, OGT, OPHN1, OTC, PAK3, PCDH19, PDHA1, PGK1, PHF6, PHF8, PIGA, PLP1, PORCN, PQBP1, PRPS1, PRSS12, PTCHD1, RAB39B, RAB40AL, RAI1, RBM10, RBMX, RLIM, RNF113A, RPL10, RPS6KA3, SHROOM4, SLC16A2, SLC25A5, SLC6A8, SLC9A6, SMC1A, SMS, SOBP, SOX3, SRPX2, SSR4, ST3GAL3, STAG2, STXBP1, SYN1, SYNGAP1, SYP, TAF1, TCF4, THOC2, TIMM8A, TMLHE, TRAPPC9, TSPAN7, TUSC3, UBE2A, UBE3A, UPF3B, USP27X, USP9X, VLDLR, WDR13, WDR45, ZC3H14, ZC4H2, ZCCHC12, ZDHHC15, ZDHHC9, ZEB2, ZMYM3, ZNF41, ZNF526, ZNF674, ZNF711, ZNF81



PREVALENCE	INHERITANCE PATTERN
2.5-5:1,000 (severe), 2-30:1,000 (mild)	Autosomal dominant, X-linked, *de novo*

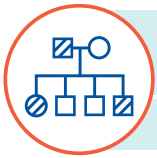
INTELLECTUAL DISABILITY
ANGELMAN SYNDROME

BACKGROUND

Angelman syndrome (AS) presents with severe developmental delay, with language more affected than motor skills. Early symptoms include insecure grasping, muscle hypotonia followed by gait ataxia, increased salivation, increased exploration of objects with the mouth, hand automatisms, and epilepsy. External features can include microcephaly, midface hypoplasia with mandibular prognathism, and a wide oral cleft. Many patients only know a few words and can better communicate using gestures or sign language. Patients with AS are described as well-balanced and friendly.

Causative genes are located in 15q11.2-q13 which is affected by genomic imprinting. This parent-specific imprinting causes genes to differ in the degree of DNA methylation, chromatin structure, and thus expression, depending on which parent they derive from. Hence, AS may have other causes that lead to loss of gene expression aside from microdeletions. To date, the only gene associated with AS is the *UBE3A* gene, which is expressed in the brain exclusively by maternal chromosome 15.

Causes of AS include: maternal microdeletions involving chromosome 15q11.2-q13 (70%), a paternal uniparental disomy 15 (UPD, 1%), imprinting defects (4%), and variants in the *UBE3A* gene (5-10%). In 20% of AS patients, the cause remains unexplained with current testing methods. Microdeletion and UPD have a low risk of recurrence, while imprinting defects and *UBE3A* variants have a risk of recurrence up to 50%.



PREVALENCE	INHERITANCE PATTERN
1:10,000-20,000	Autosomal dominant

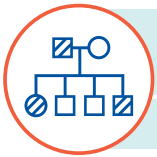
Also included in: Rett Syndrome And Related Disorders Panel

INTELLECTUAL DISABILITY
COFFIN-LOWRY SYNDROME

BACKGROUND

Coffin-Lowry syndrome (CLS) is an X-linked dominant inherited syndrome with an incidence between 1:50,000 and 1:100,000. The leading symptoms in males are intellectual disability (IQ 15-60) and a characteristic appearance. The external features are a prominent forehead, wide-set eyes, downward slanting eyelid folds, broad nose with everted nasal base, full lips with everted lower lip, hyperextensible hand and finger joints, and broad tapering fingers. In infancy and childhood, muscle hypotonia is also a prominent feature. The final height is usually below the third percentile. 80% of affected individuals develop progressive kyphoscoliosis, sometimes with cardiovascular complications, and many have a funnel (sunken) or pigeon chest. In addition, about 15% show mitral regurgitation, and about 30% have sensorineural hearing loss. Seizures occur in about 5%, and drop attacks, a sudden loss of tone without loss of awareness to auditory or tactile stimuli, occur in about 20%. Females are usually more mildly affected, and the spectrum of symptoms can range from mild symptoms with normal intelligence to complete penetrance as seen in the male sex, depending on X inactivation.

CLS is caused by variants in the *RPS6KA3* gene on the X chromosome. The gene encodes a serine-threonine kinase. Germ cell mosaics have been described.



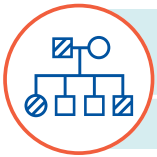
PREVALENCE	INHERITANCE PATTERN
1:50,000-100,000	X-linked dominant

INTELLECTUAL DISABILITY
LUJAN-FRYNS SYNDROME

BACKGROUND

Patients with Lujan-Fryns syndrome (LFS), also known as X-linked intellectual disability with marfanoid habitus or X-linked syndromic intellectual developmental disorder, present with marfanoid habitus, certain craniofacial features, generalized muscle hypotonia, developmental delay, behavioral problems, and nasal speech. Thus, there is clinical overlap with other connective tissue disorders such as Marfan syndrome, Loeys-Dietz syndrome, and Shprintzen-Goldberg syndrome. Inheritance is X-linked recessive, resulting in predominantly male patients, while female carriers are usually clinically inconspicuous.

Hemizygous variants in the *MED12* gene, which encodes mediator complex subunit 12, are the genetic cause. Allelic disorders with *MED12* variants include FG syndrome type 1 and X-linked Ohdo syndrome. Variants in the *UPF3B* and *ZDHHC9* genes have also been described in patients with intellectual disability and marfanoid habitus. However, these patients only partially exhibited the characteristic facial abnormalities of LFS, such as a long narrow face, prominent forehead, broad nasal root, short philtrum, micrognathia, and high palate.



PREVALENCE	INHERITANCE PATTERN
Unknown, predominantly in males	X-linked recessive

Also included in: Macrocephaly Panel

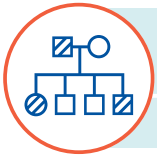
INTELLECTUAL DISABILITY
PITT-HOPKINS SYNDROME

BACKGROUND

Pitt-Hopkins syndrome (PTHS) is characterized by deep-set eyes, with eyelid axes rising slightly outwards, prominent nasal root, slightly curved nasal bridge and flattened nasal tip, flared nostrils, short philtrum, and a prominent chin. Fetal fingertip pads are often present.

Muscle hypotonia is seen in the first year of life and most children are described as quiet during this period. A severe global developmental disorder is usually present. On average, affected children learn to walk between the ages of 3 and 4. Speech development is severely impaired or absent with many affected individuals knowing only a few words. Their mood is usually described as cheerful. Repetitive hand movements such as waving or clapping are frequently observed. About 60% have episodes of hyperventilation and/or apnea while awake that are not related to epileptic activity, and almost half of the patients have epilepsy. Severe congenital malformations are rare, and chronic constipation is often present. Growth is usually unaffected, and about one-third develop microcephaly. MRI may reveal a corpus callosum deficiency and ventricular dilation. Half of the children have myopia or strabismus.

PTHS is caused by haploinsufficiency of the *TCF4* gene due to pathogenic variants (~70%) and deletions (~30%). As pathogenic variants and deletions in *TCF4* usually occur *de novo*, the recurrence risk for siblings is low unless a somatic or germ cell mosaic has been detected in one parent. Differential diagnoses include Angelman, Mowat-Wilson, Rett and Joubert syndromes.



PREVALENCE	INHERITANCE PATTERN
1:11,000	Autosomal dominant

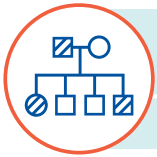
Also included in: Rett Syndrome And Related Disorders Panel

INTELLECTUAL DISABILITY
RUBINSTEIN-TAYBI SYNDROME

BACKGROUND

Rubinstein-Taybi syndrome (RTS) is characterized by symptoms of low intelligence, postnatal growth delay with reduced final height, and microcephaly. Distinctive facial features are seen, such as a deep hairline, broad, arched eyebrows, outwards and downward sloping eyes, base of the columella below the nostrils when seen in profile, retrognathia, and dental anomalies. Additionally, broad, often radially angled thumbs and broad big toes are seen. When laughing, there is a characteristic facial expression with almost closed eyes. Seizures occur frequently. RTS usually occurs sporadically.

Pathogenic variants in the *CREBBP* gene are a known cause of RTS (approximately 50-70%). In addition, pathogenic variants have been described in the *EP300* gene (approximately 5%), which codes for the E1A binding protein p300. These two proteins are transcriptional co-activators involved in many signaling pathways within the cell (e.g., DNA repair, growth, differentiation and apoptosis).



PREVALENCE	INHERITANCE PATTERN
1:100,000-125,000	Autosomal dominant (rare), *de novo*

MACROCEPHALY PANEL

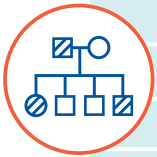
BACKGROUND

Macrocephaly, defined as a frontooccipital head circumference above the 97th percentile, can have a variety of causes. It can be differentiated into asymptomatic familial forms (so-called benign macrocephaly) and secondary forms resulting from hydrocephalus or other space-occupying intracranial processes, such as tumors, hygroma or hematomas. Isolated thickening of the calvarium is rare. In most other cases, megalencephaly of varying degree may be the cause, which in turn may also have various causes. After exclusion of the above-mentioned secondary causes, rare genetic diseases can be considered, such as lysosomal storage diseases; leukodystrophies, such as Alexander's disease; metabolic disorders of organic or amino acids, such as glutaraciduria or Canavan disease; as well as other syndromic diseases, such as overgrowth syndromes.

GENE PANEL

66 genes

ABCC9, AKT3, AMER1, ASPA, BRWD3, CCDC22, CCND2, CDKN1C, CHD8, CUL4B, DIS3L2, DNMT3A, DVL1, DVL3, EZH2, FOXP1, GCDH, GFAP, GLI3, GPC3, GRIA3, HEPACAM, HERC1, HRAS, HUWE1, KIF7, KPTN, KRAS, LZTR1, MED12, MLC1, MTOR, NDUFA1, NFIB, NFIX, NONO, NRAS, NSD1, NXN, OFD1, PIGA, PIGN, PIGT, PIGV, PIK3R2, PPP1CB, PPP2R5D, PTCH1, PTCH2, PTEN, RAB39B, RAF1, RHEB, RIT1, RNF135, ROR2, SETD2, SHOC2, SOS1, SUFU, TBC1D7, TMCO1, UPF3B, WASHC5, WNT5A, ZDHHC9



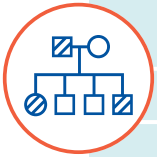
	PREVALENCE	INHERITANCE PATTERN
Alexander disease	1:1,000,000 births	Autosomal dominant
Canavan disease	Unknown	Autosomal recessive
Lysosomal storage diseases	1:5,000 live births	Autosomal recessive

MACROCEPHALY
ROBINOW SYNDROME

BACKGROUND

Robinow syndrome is a rare genetic syndrome, the main symptoms of which are characteristic craniofacial features (prominent forehead and flat midface, short nose with everted nasal floor, wide interocular distance), diminutive growth with mesomelic shortening especially of the upper extremities, brachydactyly-clinodactyly V, and hypoplastic genitals, especially in males. Cognitive abilities are normal for 80 to 90% of cases. In 10 to 20% a developmental disorder is described.

The first report of a family with affected persons in six generations suggested an autosomal dominant pattern of inheritance. Affected siblings with healthy parents, especially where there is consanguinity, showed that there is also an autosomal recessive inherited form. Pathogenic variants in the *ROR2* gene were found to be the cause of this form as well as the cause of an autosomal dominant form of brachydactyly type B. Pathogenic variants in the *WNT5A* gene were found to be the genetic cause of the autosomal dominantly inherited form in the original family, and in 2015 pathogenic variants in *DVL1* and *DVL3* were found to be a further cause. Clinically, the dominant forms are similar, while the recessive form seems to be associated with more pronounced short stature and additional skeletal malformations of the ribs and vertebrae.

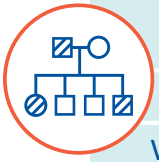


PREVALENCE	INHERITANCE PATTERN
<50 cases	Autosomal dominant
<200 cases	Autosomal recessive

MACROCEPHALY
SOTOS AND WEAVER SYNDROMES

BACKGROUND

Sotos syndrome is an overgrowth syndrome of childhood that is characterized by macrocephaly, distinctive craniofacial features, mild intellectual disability (IQ average 76), advanced bone age, and normal height in adulthood. The head is narrow and long, the forehead high and broad with a laterally receding frontal hairline, and the is chin accentuated and pointed. The distance between the eyes seems widened, and the eyelids slope downwards. The palate is pointed and high. Hands and feet are large and the joints are often hyperextensible. Feeding problems are common in infancy. About 50% of the children have seizures, and about half of them occur with fever. Congenital malformations such as heart defects are rare. A slightly increased tumor rate has been reported involving various tissues. Increased anxiety, hyperactivity, and aggressiveness are often described. In 75-90% of cases, Sotos syndrome is caused by nucleotide alterations or deletions in the *NSD1* gene. The recurrence risk for siblings is low because the nucleotide changes or deletions are mostly new.
Weaver syndrome is characterized by tall stature, variable intellectual disability, and characteristic facial dysmorphia. It is a potential differential diagnosis to Sotos syndrome. Pathogenic variants in the *EZH2* gene have been found to be causative for a large number of Weaver syndrome cases. However, genetic heterogeneity cannot be excluded.



	PREVALENCE	INHERITANCE PATTERN
Sotos	1:10,000-50,000	Autosomal dominant, *de novo*
Weaver	Unknown, 50 cases reported	Autosomal dominant

Both included in: Overgrowth Syndromes Panel

MICROCEPHALY PANEL

BACKGROUND

Autosomal recessive primary microcephalies (MCPH) are very rare disorders. In the Central European population, the frequency is about 1:1 million, and in Pakistan it is about 1:10,000. The disorders are characterized by a head circumference at birth or in the last trimester of pregnancy that is at least two standard deviations (SD) below the median value. At the age of 6 months, the deviation can be -3 SD or more.

It is a heterogeneous group of diseases whose genes are partially known. The diagnostic criteria are: small head circumference, impaired cognitive development, minimally impaired motor development with language development delay and attention deficit; no serious neurological symptoms other than seizures in about 10%; no serious malformations, only discrete signs of dysmorphia due to microcephaly, such as a narrow receding forehead and occasional dwarfism with body measurements also between the 2nd and 3rd SD below the median; reduction in brain volume, which affects both the white and grey matter, whereby the cerebral cortex can present a simplified gyration. In addition, signs of neuronal migration disturbances, such as periventricular heterotopias, cortical dysplasia or polymicrogyria, can also be found.

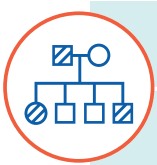
The proteins encoded by the microcephaly genes are centrosomal proteins whose alterations cause an imbalance between the cell proliferation of neuronal progenitor cells and cell death, ultimately leading to a reduced number of neurons and a smaller brain volume. Pathogenic variants in *CENPJ* and *CEP152* cause MCPH6 and MCPH9, respectively; loss-of-function variants in these genes also cause Seckel syndrome 4 and 5, respectively. Clinical overlaps exist with microcephalic osteodysplastic primordial dwarfism (MOPD2), which differs from Seckel syndrome through its more pronounced short stature, less pronounced developmental delay, and radiological abnormalities. MOPD2 is caused by loss-of-function variants in the pericentrin gene. Pericentrin is also a centrosomal protein that plays an essential role in the organization of the mitotic spindles and thus in cell division.

Since there is little difference clinically between the individual forms of autosomal recessive primary microcephalies, molecular genetic diagnostics using NGS (gene panel diagnostics) can be used to identify a causative pathogenic variant and facilitate diagnosis.

GENE PANEL

30 genes

ANKLE2, ASPM, CDK5RAP2, CDK6, CENPE, CENPF, CENPJ, CEP135, CEP152, CIT, COPB2, DONSON, KDM6A, KIF14, KMT2D, KNL1, MCPH1, MFSD2A, NCAPD2, NCAPD3, NCAPH, NUP37, PCNT, PHC1, SASS6, STIL, WDFY3, WDR62, ZEB1, ZNF335



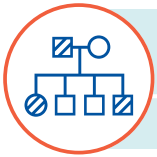
PREVALENCE	INHERITANCE PATTERN
1:1,000,000 (Central European population)	Autosomal dominant or recessive

MICROCEPHALY
KABUKI SYNDROME

BACKGROUND

Kabuki syndrome is a characteristic combination of small physical features, malformations and a developmental disorder; failure to thrive is often also seen in infancy and toddlerhood. The characteristic craniofacial features are: laterally elongated eyelid crevices with eversion of the lateral lower lid; arched, laterally sparse eyebrows, often with a hairless narrow area in the middle; a short columella and a flat-looking tip of the nose; poorly shaped, large earlobes; fetal fingertip pads on the hands; brachydactyly V; and occasionally cleft palate or lip-jaw-palate cleft. Initially, there is muscle hypotonia, extreme failure to thrive that requires tube feeding, and a heart defect; later a moderate developmental delay, increased otitis media and infections are seen, as well as seizures in some patients.

Kabuki syndrome is caused by heterozygous pathogenic variants in the *KMT2D* gene in about 60% of cases, and rarely by pathogenic changes in *KDM6A* on the X chromosome. No cause has been found in some cases, so that genetic heterogeneity is suspected.



PREVALENCE	INHERITANCE PATTERN
1:32,000-86,000	Autosomal dominant or X-linked dominant

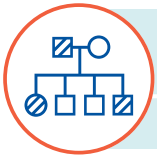
MICROCEPHALY
MOWAT-WILSON SYNDROME

BACKGROUND

Characteristic features of Mowat-Wilson syndrome (MWS), some of which become more pronounced with age, include high forehead with frontal bossing; uplifted earlobes with a central depression; diffuse, medially sparse eyebrows; widely-spaced, deep-set eyes; a broad nasal root; rounded nasal tip with prominent columella; M-shaped upper lip; a prominent, pointed chin; excess soft tissue of the neck; and long, slender fingers. Most of the affected individuals develop microcephaly and half of them have a final height below the 3rd percentile. About 80% have epilepsy which usually starts at the age of 2. Malformations include hypoplasia or agenesis of the corpus callosum, heart defects, and genitourinary malformations, especially hypospadias. About half of the patients have proven Hirschsprung disease, and a further portion have chronic constipation.

In most cases, there is a severe global developmental disorder. On average, the affected children learn to walk between the ages of 4 and 6. The gait pattern often remains wide-based with raised, bent arms. Speech development is severely impaired or absent with many affected individuals knowing only a few words. The children are often described as cheerful and laughing frequently.

The disease is caused by haploinsufficiency of the *ZEB2* gene due to pathogenic variants. Since pathogenic variants usually occur *de novo*, the recurrence risk for siblings is low unless a somatic or germ cell mosaic has been detected in one parent. Differential diagnoses include Angelman and Pitt-Hopkins syndromes.



PREVALENCE	INHERITANCE PATTERN
1:50,000-70,000 live births	Autosomal dominant

OVERGROWTH SYNDROMES PANEL

BACKGROUND

Overgrowth syndromes are a heterogeneous group of diseases with above average growth in childhood in common. There is currently no formal definition of overgrowth. It can be generalized (concerning the whole body) or segmental (concerning a part of the body). A suggested definition would be: dysmorphic features plus size and head circumference greater than +2 SD, target size (calculated based on the mean size of the parents) greater than +2 SD.

The pediatric overgrowth syndromes include Beckwith-Wiedemann (BWS), Sotos, Weaver, Simpson-Golabi-Behmel, Perlman, and Tatton-Brown-Rahman syndromes. The main characteristics are increased pre- and postnatal linear growth, facial abnormalities and partial psychomotor retardation. There are phenotypic overlaps between some syndromes that make clinical differentiation difficult, but there are also characteristic symptoms that suggest a certain diagnosis, such as the combination of large stature, omphalocele and macroglossia in BWS.

Generalized (involving whole body) **or localized to one body part** (segmental)

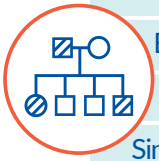
Diagnosis important for possible **cancer surveillance and prognosis**

Intellectual disability is a key feature

Changes in various genes, such as *NSD1* (Sotos syndrome 1), *NFIX* (Sotos syndrome 2) and *EZH2* (Weaver syndrome) form the molecular basis of the syndromes, and the investigation of these can help to clarify the differential diagnosis. Tatton-Brown-Rahman syndrome also known as DNMT3A overgrowth syndrome, is caused by pathogenic variants of the *DNMT3A* gene, which is one of the genes that code for DNA methyltransferase enzymes. BWS is caused by pathogenic variants in *CDKN1C* as well as more frequently by epigenetic alterations on the short arm of chromosome 11. In some syndromes, there is an increased risk of embryonic tumors, for example, a Wilms tumor in BWS and Perlman syndrome for which specific screening measures are recommended.

GENE PANEL

11 genes CDKN1C, DIS3L2, DNMT3A, EED, EZH2, GPC3, HERC1, HIST1H1E, NFIX, NSD1, OFD1



	PREVALENCE	INHERITANCE PATTERN
Beckwith-Wiedeman	1:13,700 births	Autosomal dominant
Perlman	30 cases reported	Autosomal recessive
Simpson-Golabi-Behmel	250 cases reported	X-linked recessive
Tatton-Brown-Rahman	80 cases reported	Autosomal dominant

PEDIATRIC NEUROTRANSMITTER DISORDERS PANEL

BACKGROUND

Neurotransmitters are chemical messengers tasked with the transmissions of signals from one nerve cell to another across the synaptic cleft. Congenital disorders of synthesis, transport, or degradation of neurotransmitters cause rare metabolic disorders. Examples of these disorders are listed on the following page. Leading symptoms of a neurotransmitter disorder are muscle hypotonia, (progressive) psychomotor retardation, epilepsy, ocular symptoms, and extrapyramidal movement disorders. Among the most important neurotransmitters are the biogenic amines: dopamine, adrenaline, and noradrenaline, as well as serotonin. Tetrahydrobiopterin is an essential co-factor in the synthesis of biogenic amines. A number of defects in the metabolism of biogenic amines and pterins — the corresponding clinical manifestations include Segawa syndrome — can be elucidated by molecular genetics. The diagnosis of a defect in dopaminergic/serotonergic neurotransmission may be relevant to therapy: starting treatment early can have a significant effect on the prognosis.

GENE PANEL

14 genes

DBH, DDC, DNAJC12, GCH1, MAOA, PCBD1, PTS, QDPR, SLC18A2, SLC6A3, SPR, TH, TPH1, TPH2

All deficiencies result in a **lack of monoamine neurotransmitters**

Symptoms may already occur in the **neonatal period**

Treatment based on supplementing **missing neurotransmitter precursors** or restoring **deficient cofactors** for enzymatic synthesis

	PREVALENCE	INHERITANCE PATTERN
Co-chaperone defects	20 cases reported	Autosomal recessive
Monoamine catabolism disorders	~20 cases worldwide, Unknown	Autosomal recessive or X-linked
Monoamine transportopathies	Unknown	Autosomal recessive
Primary neurotransmitter synthesis defects	Unknown	Autosomal recessive
Segawa syndrome	0.5:100,000	Autosomal dominant
Sepiapterin reductase deficiency	~50 cases reported	Autosomal recessive

RASOPATHIES, COMPREHENSIVE PANEL

BACKGROUND

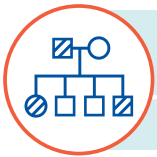
The term RASopathies refers to a clinically and genetically heterogeneous group of diseases caused by germline variants in genes coding for proteins of the RAS/mitogen-activated protein kinase signaling pathway. The clinical symptoms affect several organ systems (integument, cardiovascular system, skeleton, muscles, gastrointestinal tract, CNS, eyes). Some syndromes have characteristic craniofacial features and some have an increased risk of tumors. Clinically, there is a large overlap between the individual syndromes, which can make a reliable clinical diagnosis and targeted diagnostics more difficult. In addition, since several of these diseases can be caused by pathogenic changes in various genes of the RAS/MAPK signaling pathway, stepwise diagnostics using NGS may be useful for clarification.

Syndromes include: Cardiofaciocutaneous syndrome, Costello syndrome, Legius syndrome, LEOPARD syndrome, Neurofibromatosis type1, and Noonan syndrome.

GENE PANEL

20 genes

BRAF, CBL, HRAS, KRAS, LZTR1, MAP2K1, MAP2K2, MRAS, NF1, NRAS, PPP1CB, PTPN11, RAF1, RASA2, RIT1, RRAS, SHOC2, SOS1, SOS2, SPRED1



PREVALENCE	INHERITANCE PATTERN
1:1,000 live births (cumulative)	Autosomal dominant or recessive

RETT SYNDROME PANEL

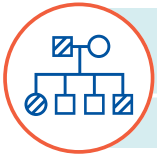
BACKGROUND

Rett syndrome is an X-linked dominant neurodegenerative disorder that occurs predominantly in females. In the classic course, children lose previously acquired abilities, including meaningful hand movements, speech, and social interaction, between 6 and 18 months of age after initially inconspicuous development. A main symptom is the development of stereotypical hand movements. Other symptoms include delayed growth, microcephaly, gait ataxia, episodes of apnea or hyperpnea, sleep disturbances, progressive scoliosis, and seizures. The few affected males predominantly present with severe neonatal encephalopathy.

The disorder is caused by pathogenic variants in the *MECP2* gene. The severity of the disorder is influenced by the pattern of X inactivation and the type of variant. Most pathogenic variants arise *de novo* resulting in a low risk of recurrence. In rare cases, the pathogenic variant is already present in combination with a non-random X-inactivation in the clinically inconspicuous mother, so that a diagnosis can be made in the mother of an affected child. Since germ cell mosaics have been observed in isolated cases, prenatal diagnosis may also be appropriate in the absence of maternal variant detection. Pathogenic variants in the *CDKL5* gene have been found in a few patients with a non-classical form of Rett syndrome with early-onset seizures.

GENE PANEL

3 genes — CDKL5, FOXG1, MECP2



PREVALENCE	INHERITANCE PATTERN
1:10,000 females	X-linked dominant

RETT SYNDROME AND RELATED DISORDERS PANEL

BACKGROUND

Atypical Rett syndrome was first described in a girl with benign neonatal seizures (BNS) followed by a disease with a very similar clinical course to classical Rett syndrome. To date, patients have been mainly characterized by an early-onset, therapy-resistant epilepsy and, in later stages, by severe psychomotor developmental delay. In addition to BNS, other seizure types may occur. The EEG is not typical but depends on age and the seizure type. Unlike Rett syndrome, there is no initial phase of seemingly normal development.

The diagnostic criteria are: inconspicuous prenatal development; irritability, vigilance disturbances and sucking difficulties in the postnatal period before the onset of the first epileptic seizures; early childhood epilepsy with onset between the 1st week and the 5th month of life; stereotypical hand movements; severe psychomotor developmental delay; and severe hypotonia.

Variants in the *CDKL5* gene are causative for this X-linked dominant atypical Rett syndrome. Pathogenic variants in the *CDKL5* gene lead to misregulation of gene expression in several genes. Furthermore, pathogenic variants in the *FOXG1* gene have also been identified in female and male patients with a congenital variant of Rett syndrome as well as in patients with symptoms of classical Rett syndrome (without a pathogenic *MECP2* variant).

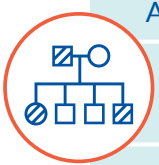
The clinical presentation in patients with pathogenic *FOXG1* variants is variable and associated with severe developmental delay. Genotype-phenotype studies have shown that severe microcephaly (-4 to -6 SD) is always present in this group of patients. Based on data collected to date, it can be predicted that *FOXG1* haploinsufficiency leads to microcephaly and a thin cortex with abnormal cortical architecture resulting in cognitive and developmental deficits.

In recent years, several other genes have been discovered in which pathogenic variants have been described that can lead to Rett syndrome-like clinical pictures or disease courses. In patients with Rett syndrome-like diseases, NGS panel diagnostics may therefore be recommended. In individual cases, this can lead to a diagnosis and thus to more precise statements on the prognosis and the risk of recurrence.

GENE PANEL

22 genes

ALDH5A1, ARX, BDNF, CDKL5, CNTNAP2, FOXG1, FOXP2, IQSEC2, KCNA2, KCNQ2, KIF1A, MECP2, MEF2C, NRXN1, NTNG1, PLP1, SCN2A, SCN8A, STXBP1, TCF4, UBE3A, ZEB2



	PREVALENCE	INHERITANCE PATTERN
Angelman syndrome	1:12,000-24,000	Autosomal dominant
Atypical Rett syndrome	~1:40,000-60,000 live births	X-linked
Congenital Rett syndrome	1:10,000-15,000 females	Autosomal dominant

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