Undiagnosed Pediatric Diseases

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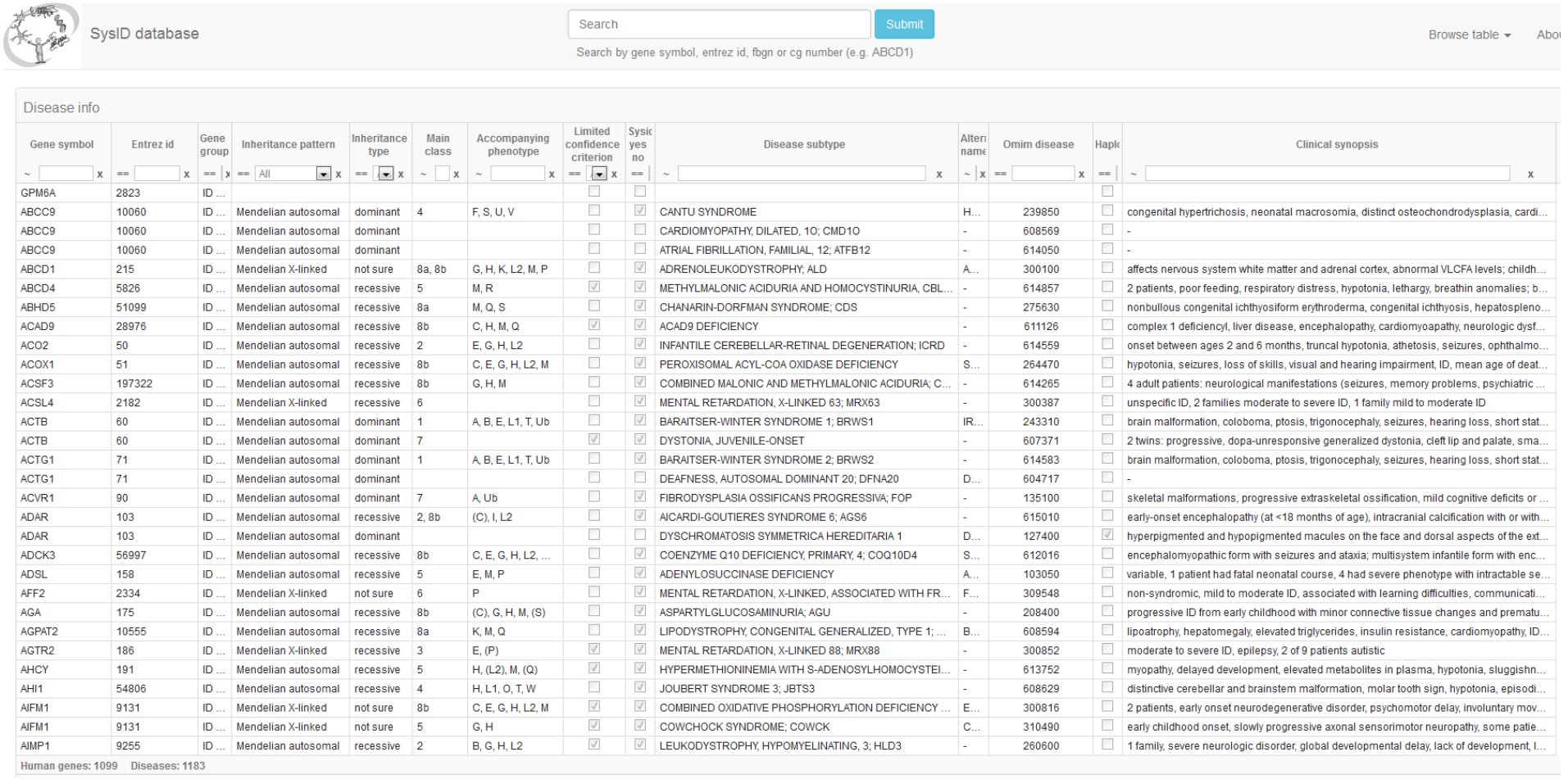
Neurodevelopmental Disorders

- 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/



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

Kochinke*, Zweier* et al., AJHG, 2016

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, padj<0.0001)

Kochinke*, Zweier* et al., AJHG, 2016

Phenotypes can predict gene functions

- 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

Kochinke*, Zweier* et al., AJHG, 2016

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**

Kochinke*, Zweier* et al., AJHG, 2016

What, if human phenotype data is limited?

- ……**try the fruitfly** !

- *Drosophila* can be used to generate custom-made phenotype data
- ID gene groups are associated with specific phenotypes in both humans and flies

Kochinke*, Zweier* et al., AJHG, 2016

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

Kochinke*, Zweier* et al., AJHG, 2016

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%

Popp et.al., EJHG, *in press*

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 hemizyguos, 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)

Popp et al., EJHG, *in press*

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

Straub et al., AJHG, *in press*

Increased protein levels of mutant RHOBTB2

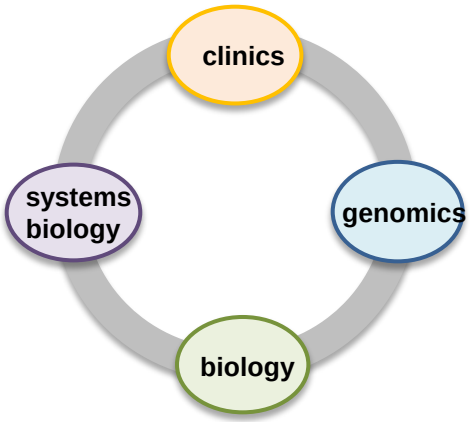
→ Impaired degradation of mutant RHOBTB2 in the proteasome, probably due to reduced auto-ubiquitination

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

Acknowledgement

AG Zweier

- Jonas Straub
- Enrico Konrad
- Laila Distel
- Johanna Grüner
- Anne Gregor
- Christine Suchy
- Anna Fliedner

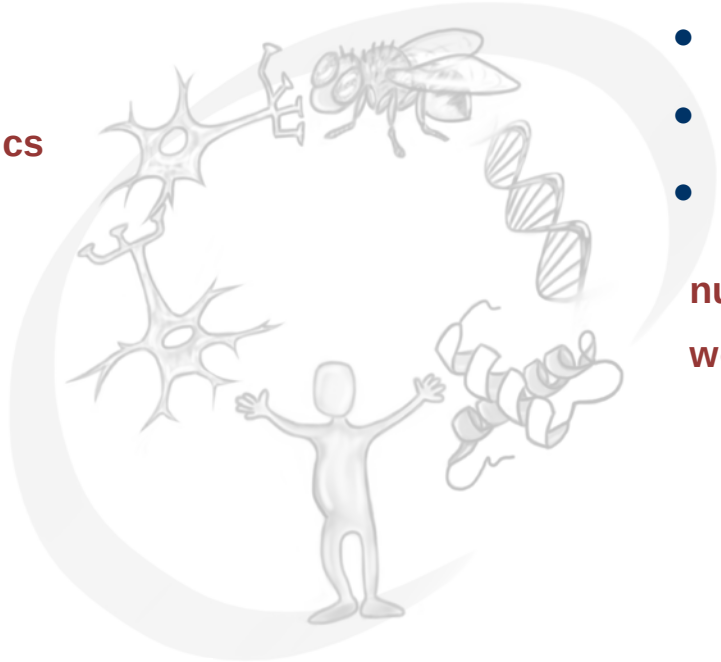
Institute of Human Genetics Erlangen

- Bernt Popp
- André Reis
- Arif Ekici
- Steffen Übe
- and many others

Radboud University Nijmegen

- Annette Schenck
- Korinna Kochinke
- Bonnie Nijhof
- Misa Fenckova
- Martijn Huynen
- Pavel Cizek
- Caleb Weber, Frank Honti
- and many others

numerous clinical colleagues world-wide



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