Neurological Phenotypes and Brain-specific Expression Genes

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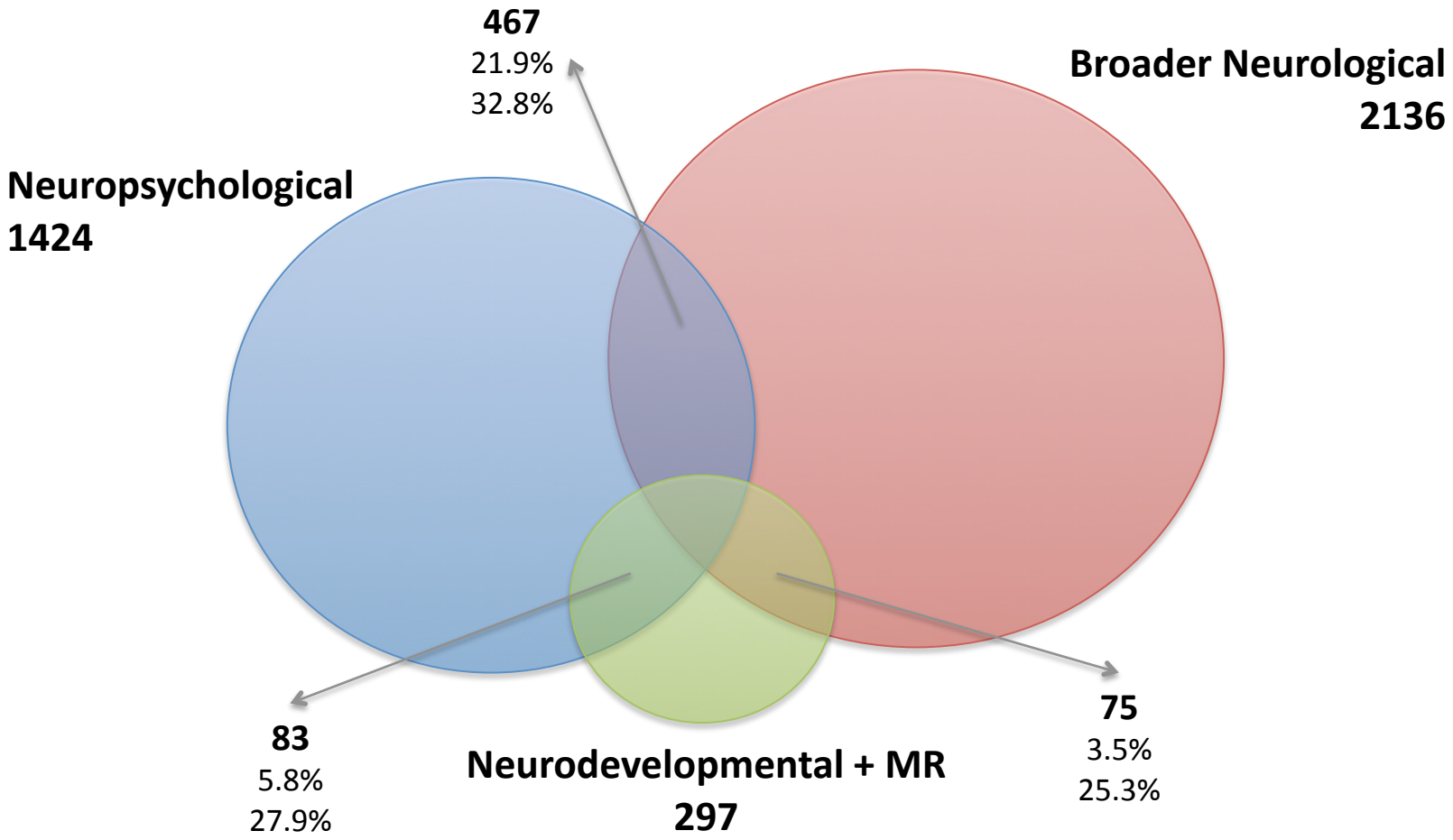
Sources

- **Neurological phenotypes**
  - Human
    - sources
      - » *GAD*: GWAS and candidate gene association studies
      - » *OMIM*: mostly (but not only) Mendelian (i.e. linkage analysis)
    - Domains:
      - » *Neuropsychological*
        Autism, Schizophrenia, Mood disorders, ADHD, Obsessive-compulsive, Anxiety, Alcoholism, Eating disorders, Antisocial/aggressive traits, Intelligence
      - » *Neurodevelopmental*
        Neural development abnormalities with mental retardation (e.g. Angelman, Prader-Willi, Rett, Williams-Beuren syndromes) [Note *]
      - » *Broader neurological*
        neuromotor, neurosensitive, neurodegenerative, neurometabolic (e.g. Alzheimer, Parkinson, neuropathies, ataxia); explicitly neurovascular usually excluded
  - Mouse
    - Sources:
      - » *MGI*: spontaneous, induced, and genetically engineered mutations
    - Domains:
      - » Neurological

        I assumed it is harder to identify "neuropsychological" phenotypes in mouse, especially if paralleling human diseases such as schizophrenia and autism

[* Note] Ideally, *Neurodevelopmental* should focus only on genes acting early in neural development, producing major anatomical abnormalities of the CNS, often with syndromic consequences and also mental capacity impairment (any superior function, not only cognition). However, this "purity" is hard to achieve, as genes are often annotated by the phenotype induced, so it's hard to quickly figure out the mechanism of action; also, being too stringent would further reduce the size of the set. For this reason, we also included mental retardation conditions where the involved mechanism includes activity-dependent regulation of neuron connectivity and synaptic structure (e.g. Fragile-X Mental Retardation, FMRS1 gene). The genes may have a larger overlap with the *Neuropsychological* class, especially genes associated to disorders that present some degree of cognitive impairment.

Overlap between human neurological phenotypes



Overlapping Term (in human)

Phenotypes (MeSH)
- Schizophrenia
- Bipolar Disorder
- Alcoholism
- Autism

Pathways
- Neuroactive ligand-receptors
- Calcium signaling
- Heterotrimeric G
- Glutamate Receptors
- Long term depression
- Long term potentiation

GO BP
- Synaptic transmission
- G protein signaling
- Nervous system development
- cAMP signaling

Phenotypes (MeSH)
- Mental retardation
- Huntington Disease

Pathways
- Neurodegenerative diseases

GO BP
- Nervous system development

Phenotypes (MeSH)
- Alzheimer
- Stroke
- Parkinson
- Schizophrenia
- Deafness
- Ataxia

Pathways
- Neurodegenerative diseases
- Adipocytokine
- Complement Cascade
- Neuroactive ligand-receptors
- Type-I Diabetes

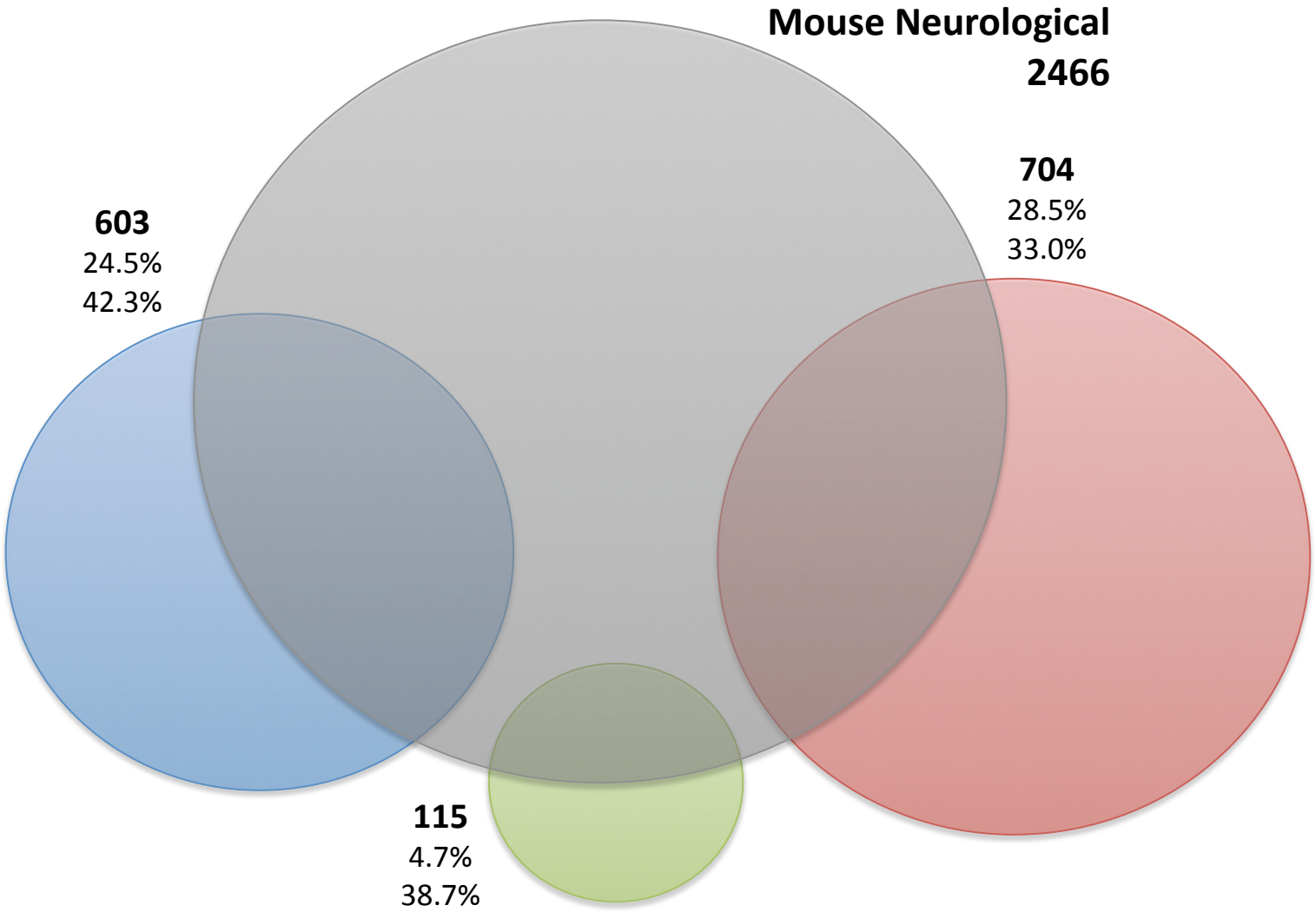
GO BP
- Sensory perception
- Synaptic transmission
- Nervous system development
- Response to wounding
- Cell death
- Electron transport chain / Oxidative metabolism
- Response to oxidative stress
- Inflammatory response

Enrichment in functional gene-sets and disease

MeSH: pubmed paper indexing system

GO BP: Biological Process

Overlap between human and mouse phenotypes



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GO BP
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- Stroke
- Parkinson
- Schizophrenia
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Pathways
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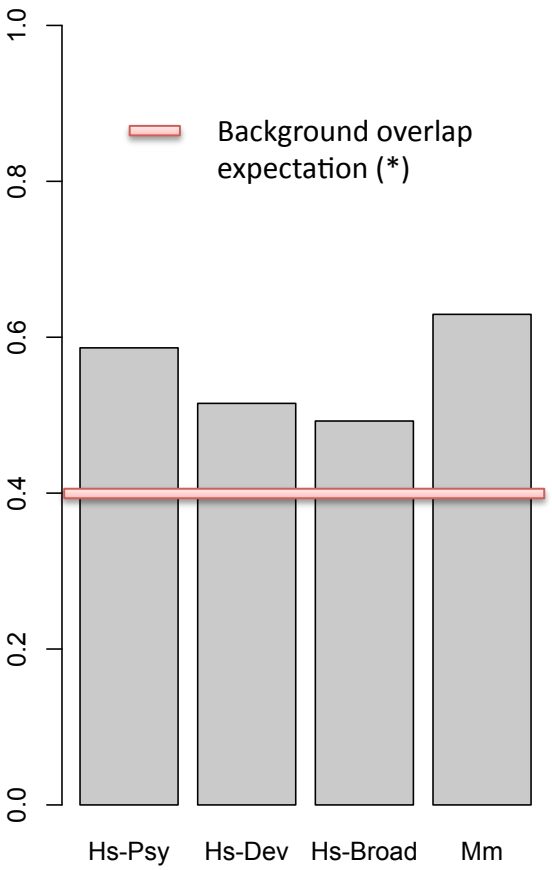
Overlapping Term (mouse to human)

Phenotypes (MeSH)
- Schizophrenia
- Alzheimer
- Neuroblastoma
- Retinitis pigmentosa
- Deafness
- ADHD

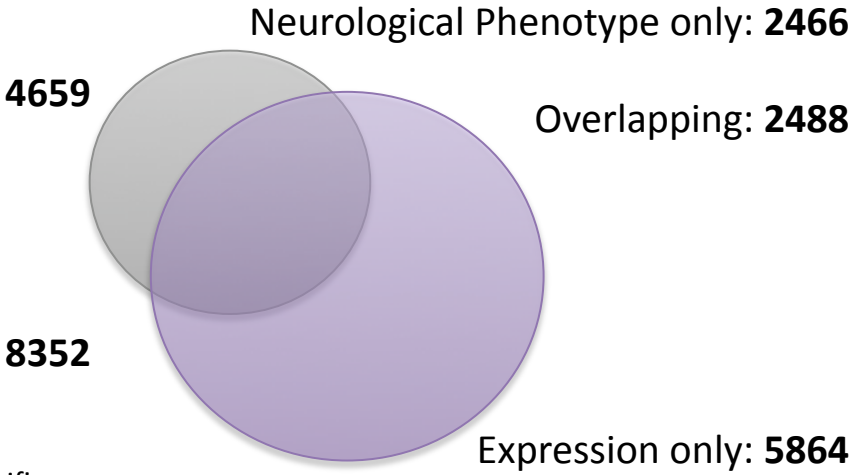
Pathways
- Axon guidance
- colorectal cancer
- MAPK
- Neuroactive ligand-receptors
- Neurodegenerative diseases

GO BP
- Nervous system development
- Synaptic transmission
- Embryonic development
- Cell projection organization and biogenesis
- Cell migration / Cell motility

Overlap between neurological phenotypes and brain-specific expression



- Usually larger than 50%
  - → cross-validates brain specificity set and neurological phenotype sets (p-value 10-5 – 10-144 *)
- Top:
  - Human Neuropsychological (Hs-Psy)
  - Mouse Neurological (Mm)



(*) These calculations assume a total of ~ 20500 genes and that brain-specific genes are not biased in favor of genes with any associated phenotype

Final Comments

- Good overall quality
  - Mutual overlap
  - Functional consistency
- Different sources overlap, but are also complementary
- Human phenotypes are distinct enough functionally, although there is some residual overlap (the curation process is imperfect)
- Mouse phenotypes are valuable, and cover functions not covered by human phenotypes