Neurogenetics

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Connecting the Dots in Neurogenetics

Gene → Disorder
Connecting the Dots in Neurogenetics

Gene

Association Studies
Linkage Studies
Post-mortem gene expression studies
Model organism genetics

Disorder
Variations between genomes

SNPs:
Single or Simple Nucleotide Polymorphisms
- Small
- Extremely common.
- We all have millions.

CNVs:
Copy Number Variations
Large 10’s to 100’s of KBs (kilobases)
- We all have hundreds to thousands
- Inherited and de novo

Repeat Polymorphisms
- Fragile X
- Huntington's

Cytogenetic Abnormalities
- Large deletions or duplications of (microscopically) visible fragments of genomes
- Rare
- Severe phenotypes
  - Downs (3x chr 21)

Somatic vs Germline
Diseases of the nervous system

The Neurological Perspective:

Arose largely from studies of end-of-life disease, stroke, and brain lesion data

A larger focus on simpler behaviors – motor output, reflexes, specific classes of memory or knowledge

Disease: Alzheimers, ALS, Parkinsons...

The Psychiatric Perspective:

Initially study of the mind, rather than the brain

Arose largely from studies of behavior, and aggregation of symptoms and patients by similar behaviors

More complex behaviors -Social interaction, hallucination, mood

Diseases: Autism, Tourette’s, Depression, Anxiety, Addiction...

In current era, clear that the mind is embodied in the brain, and these are no longer as distinct
Neurological diseases of the nervous system

Final diagnosis may require post mortem pathology, but there is usually a ‘gold standard’ test.
Psychiatric diseases of the nervous system

Diagnostic and Statistical Manual of Mental Disorders: DSM IV

- Largely Categorical

- Socially constructed
Examples – new DSM V has ‘hoarding disorder’
- DSM I–II (1973): homosexuality no longer a disorder (Sexual orientation disturbance), and mention removed entirely by DSM III (1987)

- Overlapping qualitative groups of symptoms define disorder
Autism Spectrum Disorder 299.00 (F84.0)

Diagnostic Criteria (DSM V)

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive, see text):

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.

3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).

3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).

4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.
Connecting the Dots
Cellular heterogeneity.
Connecting the Dots

Gene → Disorder

Gene → Cell Types → Symptom(s) → Disorder

Gene Expression
How genetic are disorders of the CNS?

Heritability (h)
\[ H^2 = \frac{V_g}{V_p} \]
Ranges from 0-1.
Calculated by family, adoption and twin studies traditionally, and now GWAS.
Concordance between monozygotic twins often used as a shorthand for it
\[ h^2 = 2(r_{mz} - r_{dz}) \]
Up to \(~.25\) (depression) to \(.9\) (autism)
Genetic patterns in neurogenetics

- Mendelian (Dom/Rec)
- Risk Alleles
- Rare *de novo* events
- Somatic mutations

Specific examples in next few slides
Huntington’s Disease

• Prevalence: ~5 per 100,000
• Onset: Anytime possible
• Pre-Symptoms
  – Restlessness and fidgeting
  – Personality changes (irritable, disinhibited)
  – Forgetfulness
• Symptoms
  – Chorea (http://www.youtube.com/watch?v=QORlwMeWOeU)
  – Incoordination
  – Motor impersistence (milkmaid grip)
  – Slowed saccadic eye movements
  – Cognitive impairments: planning, checking or adapting to alternatives. Motor learning.
  – Suicidal ideation? (25% attempt at some point)
• Latency from diagnosis to death ~20 years.

Genetics of Huntington’s Disorder

*Autosomal Dominant
Genetics of Huntington’s Disorder

*Autosomal Dominant

Trinucleotide repeat in Huntington Gene:
Genetics of Huntington’s Disorder

Normal ~ 20 copies CAG
Incomplete penetrance ~36-41 copies
>41 copies, disease
Easily genotyped in at risk individuals. But less than 5% choose to do so. (No treatments)

“Anticipation” Disease gets worse in progressive generations (earlier onset).
Why? >28 copies, instability of repeats

8% of patients have no family history
Mechanism of Repeat Expansion?

Figure 5. Hypothetical mechanistic models of somatic trimucleotide repeat expansion and deletion. (A) The figure shows a proposed model for how expansion mutations might arise in non-dividing somatic cells by a process of inappropriate DNA MMR. If normal duplex DNA (a) in the region of the repeat is disassociated (b), then the repeats may re-anneal out of register to yield an S-DNA structure with complementary small loop-outs (c). The small loop-outs thus generated may act as targets for repair by the MMR machinery (d). In long repeated arrays loop-outs on complimentary strands are likely to be processed as independent events. Moreover, in the absence of any strand-specific signals to identify the 'correct' template strand, the MMR machinery may be conservatively biased toward incorporating the loop-out and introducing single stranded nicks on the strand opposite the loop-out that would act as initiation points for exonuclease mediated gap extension (e). These single stranded gaps could be filled by DNA polymerase and the free ends joined with DNA ligase to generate a mutant product expanded by the size of the original loop-outs (f). Multiple rounds of mutation could generate large expansions in non-dividing cells. Strands of unique sequence flanking DNA are indicated by thick lines, CTG-CAG repeat as thin lines, newly synthesized DNA as dashed lines and enzymes from the MMR machinery as shaded circles. (B) In the absence of DNA MMR small loopouts (a) may accumulate (b) to form large hairpin structures (c). Large hairpins may be detected by an alternative DNA-repair pathway that results in the excision (c) and large deletions in the repeat tract (d).
Huntington’s Disease Pathogenesis

- Primarily Loss of Medium Spiney Neurons of the Striatum (Caudate and Putamen) – loss of D2+ / Enk+ positive cells of indirect pathway, specifically

Similar phenotype can be caused by injury
http://www.youtube.com/watch?v=7u0AGXY1IPw

Principles of Neuroscience, Kandel et al.
Connecting the Dots

Gene → Cell Types → Circuits → Symptom(s) → Disorder

Gene Expression
Huntington’s Disease Pathogenesis

- Primarily Loss of D2+/Enk+ Medium Spiney Neurons of the Striatum (Caudate and Putamen)
- Other neurons also die
- Nuc and Cytoplasmic inclusions of huntington protein (PolyQ). (cause neuron death?)
- Probably Gain of Function.
- Why Selective vulnerability of these neurons?
Spinocerebellar Ataxias

- SCA1,2,3,6,7,12,17 also PolyQ expansions, but in different genes.
- Cell death, but in different cells
Risk Allelle’s Introduction

- Not all genetically influenced disorders display simple mendelian inheritance patterns
- Sometimes common variants can contribute substantial genetic risk
Dementias & Alzheimer’s Disease

• Memory Disturbances (episodic)
  – Aphasia, Apraxia, Agnosia

• Alterations in mood and behavior
  – Alz: Hallucinations, Delusions, agitation, depression, anxiety
  – FTD: Euphoria, Anxiety, Disinhibition. Language dysfunction. Memory later.

• 1.5% of individuals at 65
• 24-35% at 85
• Survival – 8 years from diagnosis
• Some treatments available, with modest benefits
Alzheimer’s Disease Pathogenesis

- Presence of Plaques and Neurofibrillary tangles, especially in cortex, medial temporal lobe structures.
- Plaques: made of Abeta (APP protein) aggregates
- Tangles: hyperphosphorylated Tau

Loss of cholinergic neurons?

Inflammation and gliosis?

Cerebrovascular disease?

Blennow, de Leon, Zetterberg, Lancet, 2006
Frontotemporal Dementia Pathogenesis

• Onset 50-60’s
• 60% TDP43 inclusions (and in ALS disease). Gnrn mutations.
• 40% Tau aggregates
Genetics of Alzheimer’s Disease

• Both Familial and ‘Sporadic’ variants
  • Familial: Autosomal Dominant, age <65
    – Prevalence below 0.1%
    – Mutations in APP, PSEN1 (inc. CNV deletions), PSEN2
    – CNV Duplications in APP (also Down’s syndrome)

• Sporadic Alzheimers still has a heritability of ~80%.
  – (identical twins still 83% concordant, vs 46% for fraternal twins)
  – Association to APOE4 allele
  – Hets, 3X risk, Homo, 15X risk of Alzheimer’s
  – And earlier age of onset
  – Why?
Genetics of Frontotemporal Dementia

- MAPT, GRN mutations explain 10-25% of familial forms, 5-10% of all FTD. Also Rare variants in CHMP2B, VCP, TDP43.
- GRN (Haploinsufficiency). ~ 200 families with various mutations.
- Rare individuals with TDP43 mutations (also develop ALS)
Amyotrophic Lateral Sclerosis

• ‘Lou Gehrig’s Disease’
• 6 per 100,000
• Slightly more males than females 1.6:1
• 50% mortality within 30 months of diagnosis.
Amyotrophic Lateral Sclerosis Pathogenesis

• Upper motor Neuron disease
  – Spasticity, weakness, brisk deep tendon reflexes

• Lower Motor Neuron disease
  – Fasciculations (involuntary muscle twitches)
  – wasting, weakness

• Bulbar UMN
  – Spastic dysarthria (slow labored distorted speech)
  – Dysphagia (can’t swallow)
  – Gag and jaw jerk reflex pathologically brisk

• TDP43 inclusions!
Amyotrophic Lateral Sclerosis Genetics

- 5-10% Familial, Mendelian, mostly dominant
  - SOD1 (20%), TDP43(5%-10%), FUS(5%), ANG(1%), OPTN
- 90% Sporadic
  - Risk factors, but with low Odds ratio (<2)
  - Some familial overlap with FTD
  - 60% heritability, based on very small number of twins
ALS

46% of familial
~20% sporadic in Finland
Percentage ALS explained by genetic mutation since 1992

Familial ALS
- FUS
- TARDBP
- C9ORF72
- OPTN, VCP, SQSTM1, PFN1, UBQLN2
- Unknown

Sporadic ALS
- FUS
- TARDBP
- C9ORF72
- OPTN, VCP, SQSTM1, PFN1, UBQLN2
- Unknown
SOD1: Super Oxide Dismutase: Removes free radicals. Ubiquitously expressed.
Parkinson’s disease

• Lifetime risk, 1.5%
• Median onset at 60. Life Expectancy of 15 years.
• Symptoms
  – Involuntary movement
  – Hand Deformity
  – Stooped Posture
  – Odd gait
  – Trouble Turning
  – Hand Banging/Pill rolling
  – Tremor
  – Rigidity
  – Akinesia
  – Postural Instability

https://www.youtube.com/watch?v=sf1N0Zf5IqA
https://www.youtube.com/watch?v=j86omOwx0Hk
Parkinson’s Disease Pathogenesis

• Loss of dopaminergic neurons of Substantia Nigra Pars Compacta
  – (and Locus Coeruleus, Dorsal Raphe, and other catecholaminergic nuclei)
• Usually with ‘Lewy bodies’ in 3-4% of nigral neurons
• Lewy bodies are composed of SCNA protein
• Can also be found in cortex
• 10% of normal postmortem brains of people >60 have some
Parkinson’s Disease Pathogenesis

- Treatable, but not curable
  - L-Dopa
  - Fetal transplant
  - Deep brain stimulation

Principles of Neuroscience, Kandel et al.
Genetics of Parkinson’s disease

• About 5% are due to rare mendelian genetic causes.
• Most cases sporadic
• Clear environmental risk factors (Paraquat)
• ..And protective effects (Coffee)
• As well as gene by environment interactions:
  – Among heavy coffee-drinkers, rs4998386_T carriers have lower PD risk than rs4998386_CC carriers (Hamza, Plos genetics, PMID:21876681)
# Genetics of Parkinson’s disease

**Table 1**

Mendelian Genes that Lead to Parkinsonism and Their Pathology

<table>
<thead>
<tr>
<th>Locus</th>
<th>Genes</th>
<th>Clinical Features</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dominant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARK1/4</td>
<td>α-Synuclein</td>
<td>Typical PD but can sometimes have a dementia presentation</td>
<td>Lewy bodies</td>
</tr>
<tr>
<td>PARK2</td>
<td>LRRK2</td>
<td>Typical PD</td>
<td>Usually Lewy bodies: sometime tangles, sometimes neither</td>
</tr>
<tr>
<td>FTDP-17</td>
<td>MAPT</td>
<td>Most mutations have a dementia phenotype but some have a typical PD presentation</td>
<td>Tau/tangle pathology</td>
</tr>
<tr>
<td>SCA3</td>
<td>Ataxin3</td>
<td>Usually ataxia in Europeans, but often Parkinsonian especially in Africans</td>
<td>Probably not Lewy bodies. Probably polyglutamine inclusions</td>
</tr>
<tr>
<td>SCA2</td>
<td>Ataxin2</td>
<td>Usually ataxia in Europeans, but often Parkinsonian especially in Asians</td>
<td>Probably not Lewy bodies. Probably polyglutamine inclusions</td>
</tr>
<tr>
<td><strong>Recessive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARK2</td>
<td>Parkin</td>
<td>Very slowly progressive early onset disease usually with sleep benefit</td>
<td>Usually not Lewy bodies</td>
</tr>
<tr>
<td>PARK6</td>
<td>PINK1</td>
<td>Usually very slowly progressive early onset disease usually with sleep benefit</td>
<td>One case with Lewy bodies</td>
</tr>
<tr>
<td>PARK7</td>
<td>DJ-1</td>
<td>Little data, but seems similar to parkin</td>
<td>Not known</td>
</tr>
<tr>
<td>PARK9</td>
<td>ATP13A2</td>
<td>Aggressive and complex parkinsonism with many additional features</td>
<td>Not known</td>
</tr>
<tr>
<td>PARK14</td>
<td>PLA2G6</td>
<td>Aggressive and complex parkinsonism with many additional features</td>
<td>Lewy bodies</td>
</tr>
<tr>
<td>SPG11</td>
<td>Spatacsin</td>
<td>Usually spastic paraplegia but sometimes aggressive and complex parkinsonism with additional features</td>
<td>Not known</td>
</tr>
<tr>
<td><strong>High-Risk Locus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gaucher’s (1) locus</td>
<td>GBA</td>
<td>Typical PD</td>
<td>Lewy bodies</td>
</tr>
<tr>
<td><strong>Low-Risk Loci</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNCA</td>
<td>Typical PD</td>
<td>Lewy bodies</td>
<td></td>
</tr>
<tr>
<td>MAPT</td>
<td>Typical PD</td>
<td>Lewy bodies (though tau pathology not systematically assessed</td>
<td></td>
</tr>
<tr>
<td>LRRK2</td>
<td>Typical PD</td>
<td>Lewy bodies</td>
<td></td>
</tr>
<tr>
<td>HLA</td>
<td>Typical PD</td>
<td>Lewy bodies</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Locus</th>
<th>Gene</th>
<th>Protein</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park1</td>
<td>SNCA</td>
<td>α-synuclein</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Park2</td>
<td>PARK2</td>
<td>Parkin</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Park3</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Park4</td>
<td>SNCA</td>
<td>α-synuclein</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Park5</td>
<td>UCHL1</td>
<td>Ubiquitin C terminal hydrolase</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Park6</td>
<td>PINK1</td>
<td>Pten-induced putative kinase 1</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Park7</td>
<td>PARK7</td>
<td>Dj-1</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Park8</td>
<td>LRRK2</td>
<td>Leucine-rich repeat kinase 2</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Park9</td>
<td>ATP13A2</td>
<td>Lysosomal type 5 ATPase</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Park10</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Risk locus</td>
</tr>
<tr>
<td>Park11</td>
<td>GIGYF2</td>
<td>GRB interacting GYF protein 2</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Park12</td>
<td>Unknown</td>
<td>Unknown</td>
<td>X-linked</td>
</tr>
<tr>
<td>Park13</td>
<td>HTRA2</td>
<td>HTRA serine peptidase 2</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Park14</td>
<td>PLA2G6</td>
<td>Phospholipase A2</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Park15</td>
<td>FBXO7</td>
<td>F-box only protein 7</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Park17</td>
<td>VPS35</td>
<td>Vacuolar protein sorting 35</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Park18</td>
<td>EIF4G1</td>
<td>Eukaryotic translation initiation factor 4 gamma 1</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Park19</td>
<td>DNAJC6</td>
<td>DNAJ/HSP40 homolog subfamily C member 6</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td></td>
<td>SNCA</td>
<td>α-synuclein</td>
<td>Risk locus</td>
</tr>
<tr>
<td></td>
<td>LRRK2</td>
<td>Leucine-rich repeat kinase 2</td>
<td>Risk locus</td>
</tr>
<tr>
<td></td>
<td>GBA</td>
<td>Glucocerebrosidase</td>
<td>Risk locus</td>
</tr>
</tbody>
</table>
SCNA expression (mouse)
Multiple Sclerosis

• Lesions in white matter visible in MRI
• Presentation can vary widely depending on location of lesions.
• Episodic and progressive in nature (one episode: clinically isolated syndrome)
• Progression starts around 40
• Death usually around 30 years after onset
• Must attack more than on region, and on more than one occasion
• Classically Unique Symptoms
  — Lhermitte’s symptom (electrical sensation down back and limbs)
  — Uhthoff phenomenon (symptoms worsen with heat)
Multiple Sclerosis Pathogenesis

MRI Lesions (Sclerotic plaques) in white matter
Auto-immune attack of myelin
Oligoclonal bands in CSF
Demyelination, axon damage and degeneration, neuronal loss
Genetics of Multiple Sclerosis

- Strong familial contribution.
- Mz twins 25% concordant
- Strongly linked to certain MHC Haplotypes
- DRB1*1501, DRB5*0101, DQA1*0102, DQB2*0602 confer risk.
- As of 2013 smaller but significant effect of 100 SNPs, some near interleukins, etc. (Top OR, 1.2)
Psychiatric disorders: Autism, Schizophrenia

- Few well replicated common risk alleles for autism
- 107 now found for Schizophrenia!
- But many rare variants in ASD (99), and CNVs
- Some common cytogenetic abnormalities
- And very strong genetic component? 60-90% Mz concordance for autism.
- No clearly replicated brain pathogenesis
- Some shared risk variants across the two disorders
- Shared risk between various psych diseases (Variable Expressivity)
Other examples include 16p11.2 (CNVs) duplications and deletions which are associated with both autism and schizophrenia, as well as small and large head size.
Psychiatric disorders, progress at last?

1980’s-now Linkage
1990’s-2005 Candidate Gene Association Studies
2003-2010 Genome Wide Association Studies
2005-2011 Copy Number Variation studies
2010-Now Exome Sequencing
Now- Future : Genome sequencing
Now – Future : Giant GWAS
Psychiatric disorders, progress at last?

1980’s-now Linkage [Still a useful tool]
1990’s-2005 Severely underpowered association studies (candidate genes) [Mostly Ignore]
2003-2010 Genome Wide Association Studies [SNPS – only alleles with very small effect]
2005-2011 Copy Number Variation studies [some rare events replicated]
2010-Currently Exome Sequencing [estimates ~ 1000 genes contributing to autism]
- Future – Genome sequencing
GWAS for common variants are now massive.

https://doi.org/10.1016/j.cell.2018.05.046
The Manhattan Plot
Zoom in on one locus
The dirty secret: the odds ratio
Autism ~35K exomes

Satterstrom, BioRxiv
B

\[
\log_{10}(Q) \geq 16
\]

\[
\log_{10}(Q) = 12
\]

\[
\log_{10}(Q) = 8
\]

\[
\log_{10}(Q) = 4
\]

\[
\log_{10}(Q) = 0
\]

Chromosome

FWER \leq 0.05

FDR \leq 0.05

FDR \leq 0.1

SCN2A  SYNGAP1  CHD8

ADNP

FOXP1

POGZ  SLC6A1  ARID1B  KMT5B  DYRK1A  SHANK3

PTEN  GRIN2B  MED13L

GIGYF1  DEAF1  DSCAM

ANK2

ASH1L  CTNNB1  ANK2

DNMT3A  NRXN1  SETD5  TBL1XR1

KCNQ3  WAC  SRPRA  SHANK3

GABRB3  SPTA1  SHANK2

PRPS1A  TPX2

ANKRD11  TLK2
Many of the mutations being discovered already implicated in other diseases

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Known Disease Association</th>
<th>Family</th>
<th>Structure</th>
<th>Consanguinity</th>
<th># Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>MECP2 p.E483X</td>
<td>Rett syndrome, ASD</td>
<td>AU-5400</td>
<td>Multiplex</td>
<td>No</td>
<td>2 (2M)</td>
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<tr>
<td>NLGN4X p.Q329X</td>
<td>Nonsyndromic X-linked ID and/or ASD</td>
<td>AU-5700</td>
<td>Simplex</td>
<td>Yes</td>
<td>1 (M)</td>
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<tr>
<td>PAH p.198_205 del</td>
<td>Phenylketonuria</td>
<td>AU-13100</td>
<td>Simplex</td>
<td>Yes</td>
<td>1 (M)</td>
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<tr>
<td>PAH p.Q235X</td>
<td>Phenylketonuria</td>
<td>AU-4100</td>
<td>Multiplex</td>
<td>Yes</td>
<td>2 (2F)</td>
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<tr>
<td>VPS13B p.A3943fs</td>
<td>Cohen syndrome</td>
<td>AU-21100</td>
<td>Simplex</td>
<td>Yes</td>
<td>1 (M)</td>
</tr>
<tr>
<td>(B) Hypomorphic Mutations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>Known Disease Association</td>
<td>Family</td>
<td>Structure</td>
<td>Consanguinity</td>
<td># Affected</td>
</tr>
<tr>
<td>AMT p.I308F</td>
<td>Nonketotic hyperglycinemia</td>
<td>AU-1700</td>
<td>Multiplex</td>
<td>Yes</td>
<td>3 (2M&lt;comma&gt; 1F)</td>
</tr>
<tr>
<td>AMT p.D198G</td>
<td>Nonketotic hyperglycinemia</td>
<td>AU-11800</td>
<td>Simplex</td>
<td>Yes</td>
<td>1 (M)</td>
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<tr>
<td>PEX7 p.W75C</td>
<td>Rhizomelic chondrodysplasia punctata</td>
<td>AU-3500</td>
<td>Multiplex</td>
<td>Yes</td>
<td>3 (2M&lt;comma&gt; 1F)</td>
</tr>
<tr>
<td>POMGNT1 p.R367H</td>
<td>Muscle eye &amp; brain disease</td>
<td>AU-13300</td>
<td>Simplex</td>
<td>Yes</td>
<td>1 (M)</td>
</tr>
<tr>
<td>SYNE1 p.L3206M</td>
<td>Autosomal recessive cerebellar ataxia type 1, arthrogryposis congenita, ASD, bipolar disease</td>
<td>AU-1600</td>
<td>Multiplex</td>
<td>Yes</td>
<td>4 (1M&lt;comma&gt; 3F)</td>
</tr>
<tr>
<td>VPS13B p.S824A</td>
<td>Cohen syndrome</td>
<td>AU-17800</td>
<td>Simplex</td>
<td>Yes</td>
<td>1 (M)</td>
</tr>
</tbody>
</table>
C

99 ASD-associated genes
Family-based: *De novo*

- pLI ≥ 0.995
- pLI 0.5-0.995: insufficient data
- pLI 0-0.5: insufficient data

99 ASD-associated genes
Family-based: Transmission

- pLI ≥ 0.995
- pLI 0.5-0.995: insufficient data
- pLI 0-0.5: insufficient data

99 ASD-associated genes
Case-Control

- pLI ≥ 0.995
- pLI 0.5-0.995: insufficient data
- pLI 0-0.5: insufficient data

Variant liability (z-score)

95% CI, Mean
- Males
- Females
- Both sexes
- ** p < 0.01
- *** p < 0.001
Other Psychiatric Disorders

- Tourette’s Syndrome
- OCD
- MDD
- Bipolar
- Addiction

Still large genetic component, but not as large in other cases

Largely following the same pattern of gene discovery as autism and schizophrenia

Sample sizes drive discovery even when genetic contribution lower (e.g. 1.5 M person GWAS for MDD to get 100 loci)
Neurogenetic Syndromes

• Largely *de novo*, and recognized early
• Reproducible yet diverse collections of symptoms across individuals.
• Not as variant as psychiatric disorder
• Initially identified by clinical insight. Beginning to be more post-hoc.
• Usually a single genetic cause (or several genes in related pathways), but gene not always known in case of larger lesions
• Best case scenario for association studies
Clinical whole-exome sequencing for the diagnosis of mendelian disorders.


Author information

Abstract

BACKGROUND: Whole-exome sequencing is a diagnostic approach for the identification of molecular defects in patients with suspected genetic disorders.

METHODS: We developed technical, bioinformatic, interpretive, and validation pipelines for whole-exome sequencing in a certified clinical laboratory to identify sequence variants underlying disease phenotypes in patients.

RESULTS: We present data on the first 250 probands for whom referring physicians ordered whole-exome sequencing. Patients presented with a range of phenotypes suggesting potential genetic causes. Approximately 80% were children with neurologic phenotypes. Insurance coverage was similar to that for established genetic tests. We identified 86 mutated alleles that were highly likely to be causative in 62 of the 250 patients, achieving a 25% molecular diagnostic rate (95% confidence interval, 20 to 31). Among the 62 patients, 33 had autosomal dominant disease, 16 had autosomal recessive disease, and 9 had X-linked disease. A total of 4 probands received two nonoverlapping molecular diagnoses, which potentially challenged the clinical diagnosis that had been made on the basis of history and physical examination. A total of 83% of the autosomal dominant mutant alleles and 40% of the X-linked mutant alleles occurred de novo. Recurrent clinical phenotypes occurred in patients with mutations that were highly likely to be causative in the same genes and in different genes responsible for genetically heterogeneous disorders.

CONCLUSIONS: Whole-exome sequencing identified the underlying genetic defect in 25% of consecutive patients referred for evaluation of a possible genetic condition. (Funded by the National Human Genome Research Institute.)
Single gene: Rett’s Syndrome

- Point mutations in the MeCP2 gene
- Mostly effects females (on X)

Symptoms:
- Normal development to 6-18 months, then regression (complete loss of language...)
- Autism like features
- Hand-wringing
- Ataxia
- Breathing abnormalities

Other ‘common’ syndromes that can lead to autism like features – Fragile X disorder, and Tuberous sclerosis
Many of the rare variants from ASD studies will soon be thought of as single gene syndromes.

Eg: Chd8
Polygenic (contiguous): Williams Syndrome

- Deletion of ~30 gene region on 7q11.23

Symptoms:
- Cardiac defects
- Unusual facial feature (elfin appearance)
- M.R. (very poor visual-spatial abilities)
- Unusually hyper-social personality
- Elastin gene causes cardiac defects. Others not known.
- Anxiety

* Reciprocal duplication causes autism
Mapping strategies

1. Identification of fortuitous microdeletions

2. Work in animal models
Williams Deletions summary

conflicting reports with LIMK1 deletions: cardiac defects but upper cases were diagnosed with WBS, lower cases were diagnosed as not presenting with WBS phenotypes

cardiac defects, some or no facial dysmorphia, better visuospatial reasoning than average WBS patients. Some patients with increased sociability reported

cardiac defects alone

Michael Rieger
Strategies in Model Organisms

Strategies in Model Organisms

Polygenic: Bardet-Biedl syndrome

- Frequent developmental delay
- Rod-cone dystrophy
- Polydactyly
- Renal dysfunction
- Anosmia

14 different genes give similar symptoms – all are components of cilia
Angleman’s and Prader-Willi Syndrome

Disorders of imprinting

Angleman’s – Deletion of maternal copy of 15q11-13
- Developmental delay
- Speech impairment
- Ataxia
- Frequent laughing/smilng, happy, hand-flapping
- Frequent: microcephaly, seizures, (ab EEG), large mouth, fascination with water
- Loss of function of Ube3a gene

Prader-Willi – Deletion of the paternal copy of 15q11-13
- Low muscle tone
- Short stature
- Incomplete sexual development
- Cognitive disabilities
- Behavioral problems
- Hyperphagia
- Frequent: hallucination, paranoia, depression...
- Loss of function of Necdin and snoRNA clusters (SnorD116 most likely candidate)
Syndromic and monogenetic forms give us the opportunity to try and move up the chain to the next dot.
Connecting the Dots

Gene $\rightarrow$ Cell Types $\rightarrow$ Circuits $\rightarrow$ Symptom(s) $\rightarrow$ Disorder

How?

I) Gene Expression
II) Brain Imaging
III) Model Organisms
I) Gene Expression

1) Selective Expression: Narcolepsy and Hypocretin

Symptoms

Sleep Onset REM Periods

Excessive daytime sleepiness

Sleep attacks

May include

Cataplexy – loss of muscle tone

Sleep Paralysis

Hypnagogic Hallucinations

Prevalence

1:2000
I) Gene Expression

1) Selective Expression: Narcolepsy and Hypocretin

http://www.youtube.com/watch?feature=player_detailpage&v=XOh2nleWTwI#t=13s

http://www.youtube.com/watch?feature=player_detailpage&v=70jFzlxCnZA#t=40s

http://www.youtube.com/watch?feature=player_detailpage&v=I2x14qETS7E#t=43s
I) Gene Expression

1) Selective Expression: Narcolepsy and Hypocretin

Causes (with Cataplexy)

**Dogs** – Mutations of Hcrt Receptor 2 (Linkage)

**Mice** (mutants) – Hcrt Peptide, Receptors (Knockouts)
I) Gene Expression

1) Selective Expression: Narcolepsy and Hypocretin

**Causes (with Cataplexy)**

- **Dogs** – Mutations of Hcrt Receptor 2
- **Mice** (mutants) – Hcrt Peptide, Receptors
- **People** – Loss of Hcrt neurons (80-90%)/Peptide

**Human Genetics:** Usually not mutations in Hcrt genes.
– Association to certain HLA Haplotypes

(Redrawn from Thannickal et al. 2000)
I) Gene Expression

2) Enriched Expression?

Candidates from human genetics studies

Genes enriched in a certain cell type
**TRAP: Translating Ribosome Affinity Purification**

- **5HT Neurons** will stick to affinity matrix and yield enriched mRNA (IP).
- **All other cells** will not stick to affinity column and yield background mRNA (UB).

*Also working techniques for miRNA, liNC RNA, Synaptic RNA...*

qPCR, Microarrays or RNA-seq
I) Gene Expression

2) Enriched Expression?

A cell type where overlap is greater than expected by chance?
Can the approach work?

Yes. Thanks to Corbo Lab for retinal array data

~120 Genes That cause Dom or Rec. Retinopathies

http://www.sph.uth.tmc.edu/RetNet/

Does the approach work?

AutDB (328 genes)
II) Brain Imaging

- Williams Syndrome & Amygdala Activation

III) Model Organisms

- Cre/Lox experiments (Rett’s Syndrome, FMRP, Tsc)

Caveat:
III) Model Organisms

- Cre/Lox experiments (Rett's Syndrome)

Conclusions, Common Themes and Puzzles

• Familial and sporadic variations of these disorders: multiple genetic routes to some of these diseases.

• Can we treat the gene?

• Broad expression of mutated genes, but selective vulnerability of distinct neuronal populations?

• Plaques, Tangles, Inclusions: Cause or correlate, or consequence of neuropathology?

• What is the clinical utility of risk alleles?
  – Polygenic risk beginning to perhaps be useful