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An Atlas of Phenotype to Genotype Relationships of Patient-Derived Neurons and Oligodendrocytes: Implications for White Matter Disorders

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Molecular Biology and Cancer Genetic Program
The Ohio State University and the James Comprehensive Cancer Center

Disclosures: Editorial activity Journal Neuroimmunology, received Funds NIH, MS society

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Bradshaw/Elyaman Lab-HMS

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Acknowledgments

Modeling Immune-NSCs interactions

Insights Into the Molecular Pathogenesis of Progression in Multiple Sclerosis

Potential Implications for Future Therapies

Jaime Imitola, MD; Tanuja Chitnis, MD; Samia J. Khoury, MD

Imitola J, et al Arch Neurol 63:25-33, 2006

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Unmet Needs in MS: Regeneration and repair of organ damage

- Neurodegeneration
- Neural progenitor dysfunction
- Remyelination
- Alteration Local glial microenvironment
- Repair failure
- Lack of axonal regeneration
- Role of Microglia in repair

Imitola J, et al Arch Neurol 63:25-33, 2006

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Modeling Immune-NSCs interactions

Neural Stem/Progenitor Cells Express Costimulatory Molecules That Are Differentially Regulated by Inflammatory and Apoptotic Stimuli

Jaime Imitola,* Manuel Comabella,* ... for repair in neurodegenerative and demyelinating dis-

Cited 900 times.

Directed migration of neural stem cells to sites of CNS injury by the stromal cell-derived factor 1α/CXC chemokine receptor 4 pathway

Jaime Imitola*, Khadir Raddassi*, Kook In Park†¶§, Franz-Josef Mueller*§, Marta Nieto‖, Yang D. Teng§‖, Dan Frenkel*, Jianxue Li‖, Richard L. Sidman‖, Christopher A. Walsh‖, Evan Y. Snyder*§‖**, and Samia J. Khoury*,**

*Center for Neurologic Diseases and †Department of Neurosurgery, Brigham and Women's Hospital, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, M... Brain, Korea 21 Project for Medical Sciences, Yonsei University College of Medicine, Seoul 120-752, K...

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Modeling Immune-NSCs interactions

doi:10.1093/brain/awm219 Brain (2007), 130, 2816–2829

Persistent activation of microglia is associated with neuronal dysfunction of callosal projecting pathways and multiple sclerosis-like lesions in relapsing–remitting experimental autoimmune encephalomyelitis

doi:10.1093/brain/awn198 Brain (2008), 131, 2564–2578

Persistent inflammation alters the function of the endogenous brain stem cell compartment

Stefano Pluchino,[1,2] Luca Muzio,[1,2] Jaime Imitola,[3] Michela Deleidi,[1,2] Clara Alfaro-Cervello,[4] Giuliana Salani,[1,2] Cristina Porcheri,[1,2] Elena Brambilla,[1,2] Francesca C[illegible] Jose Manuel Garcia-Verdugo,[4,5] Giancarlo Comi,[2] Samia J. Khoury[3,6]

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Modeling Immune-NSCs interactions

Annals of Neurology, 2007

Paradoxical Dysregulation of the Neural Stem Cell Pathway Sonic Hedgehog-Gli1 in Autoimmune Encephalomyelitis and Multiple Sclerosis

Yue Wang, MD, PhD,[1] Jaime Imitola, MD,[1] Stine Rasmussen, PhD,[1,2] Kevin C. O'Connor, PhD,[1] [illegible]amia J. Khoury, MD[1]

Annals of Neurology, 2011

Reversible Neural Stem Cell Niche Dysfunction in a Model of Multiple Sclerosis

Stine Rasmussen, PhD,[1,2] Jaime Imitola, MD,[1] Ang[illegible]

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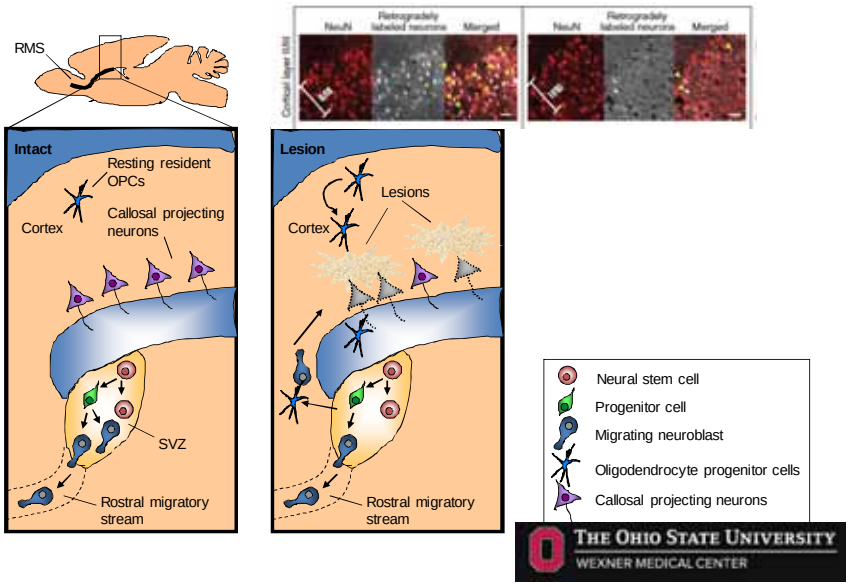
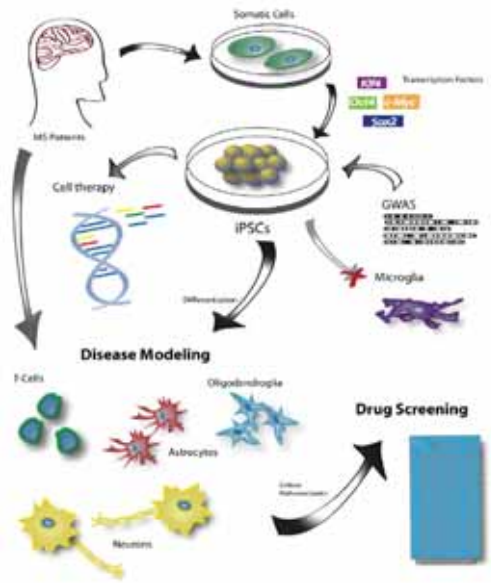
Repair Dysfunction in Multiple Sclerosis



Personalized Models of Progressive MS



1. Patient derived Neurons, OPCs.
2. Monocyte-derived microglia (MDMI).
3. T cell-NSCs interaction.
4. Live Cell Cell Arrays with stemness reporters
5. Organoids

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The (BIG) Problem with iPS Phenotypes

1. Overall *characteristics* of phenotypes is not known.
2. the degree of *interconnectivity*, their *reproducibility* is not known.
3. *Relationship* among phenotypes and genetic mutations have not been synthesized or catalogued.
4. Predictive models are not possible with current efforts.

The Phenogenetic model

$$p_i = f(g_i) + e_i$$

i : individual patient-derived cell

g_i : genotype of i

p_i : Quantitative phenotype of i cell: Cellular phenotypic trait (CPT)

e_i : Environmental contribution to p_i

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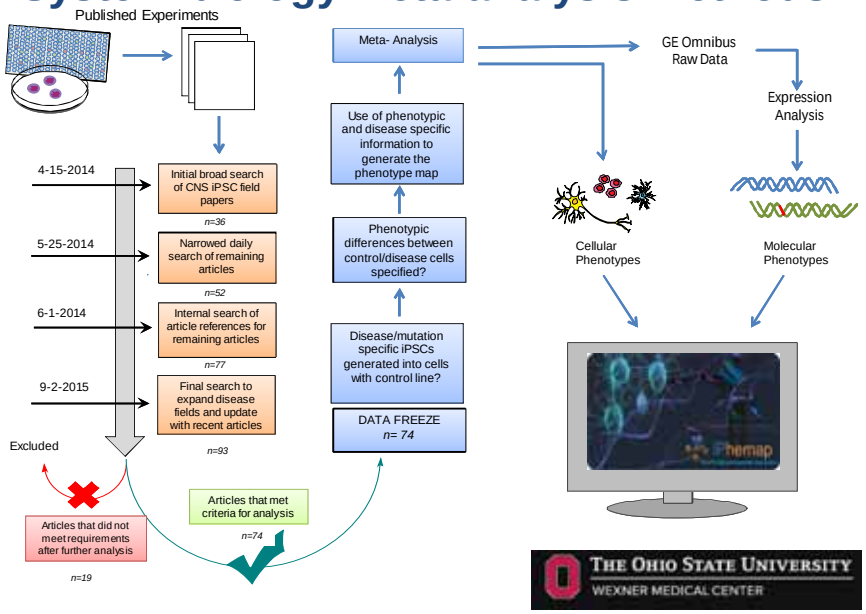
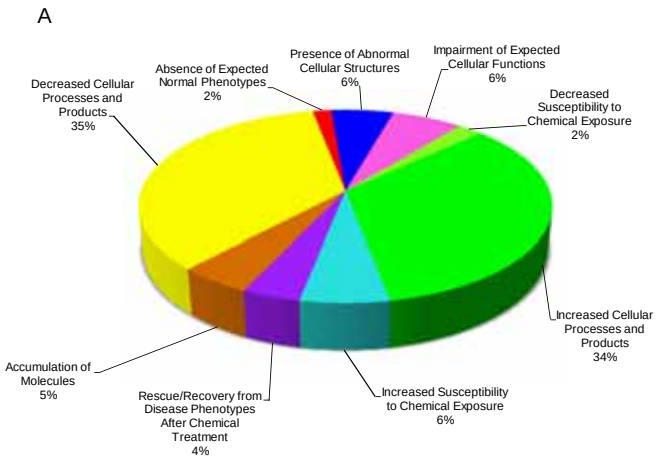
System biology meta-analysis methods



Distribution of iPSC-derived Phenotypes



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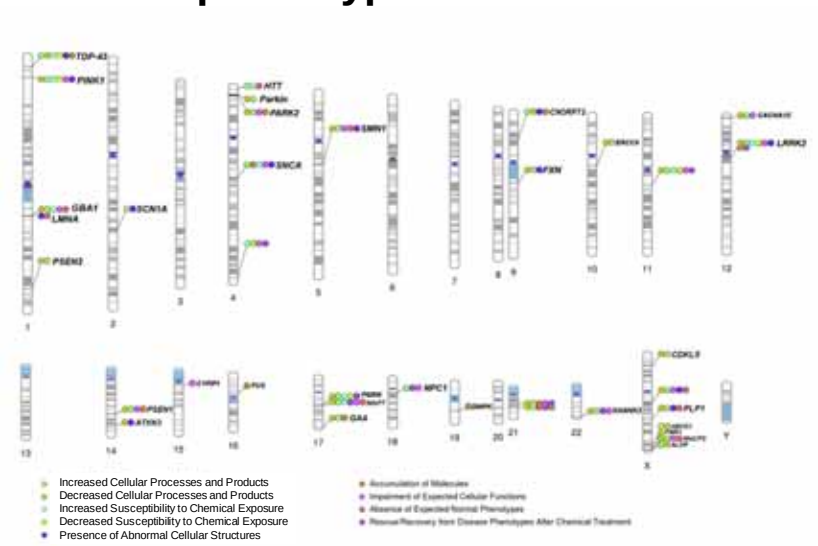
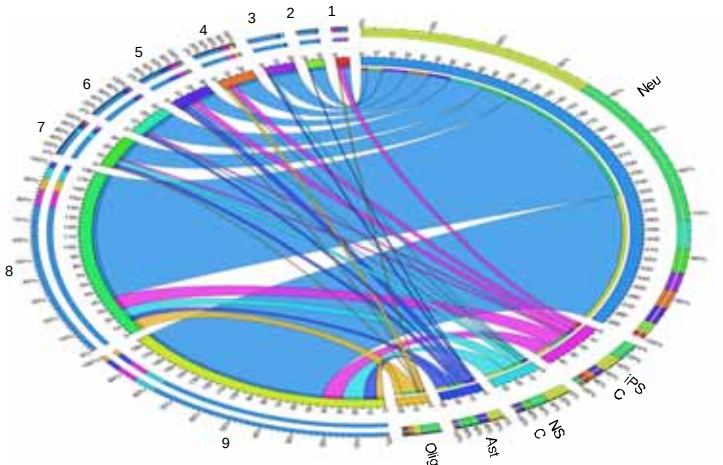
Genome wide distribution of iPSC phenotypes clusters



Phenotype class and patient-derived cell associations



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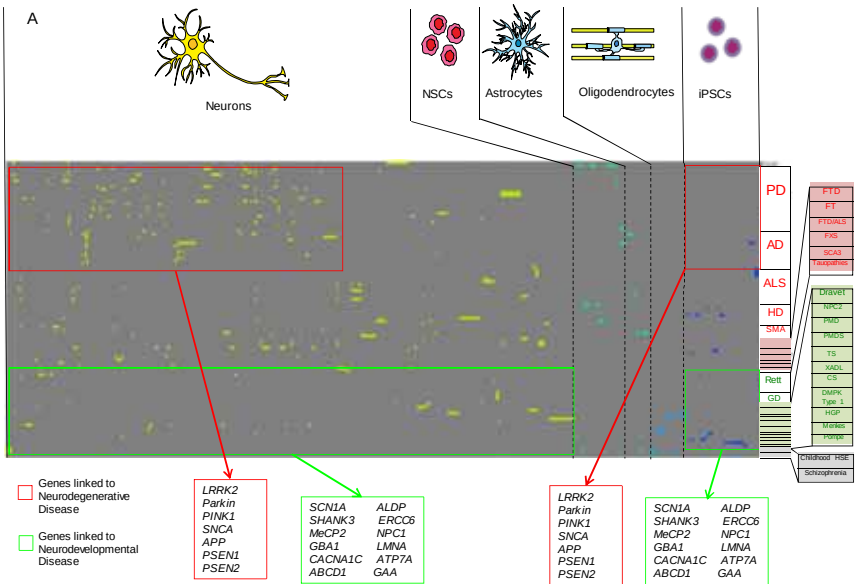
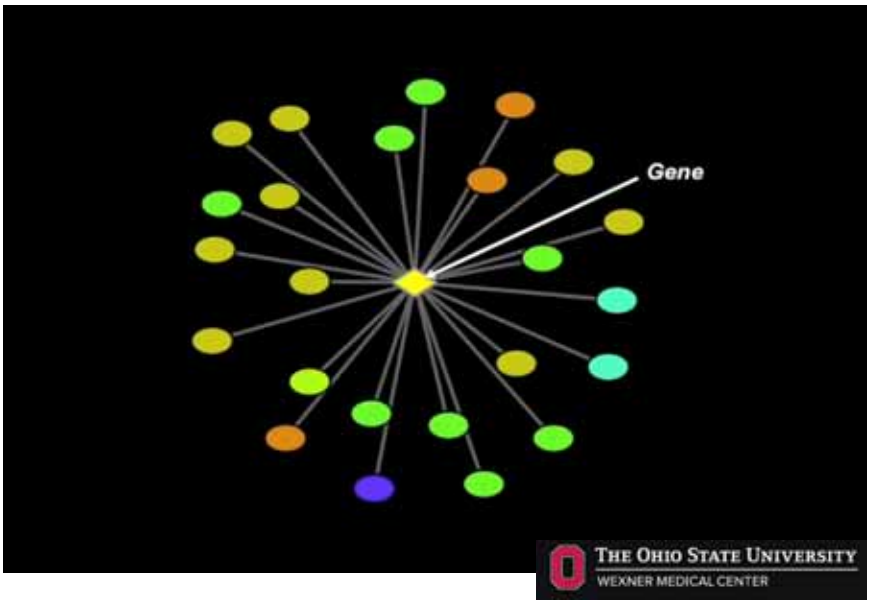
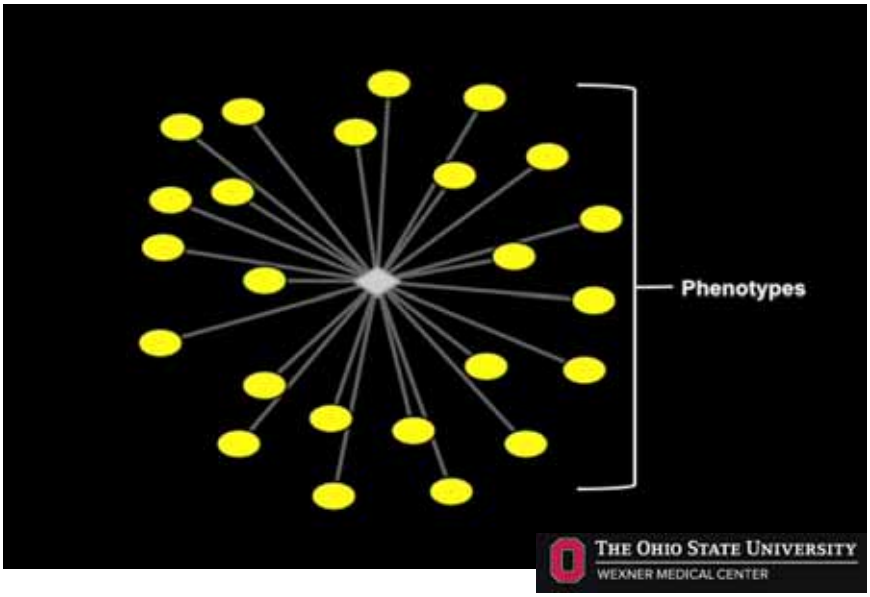
Map of phenotypes by developmental stages



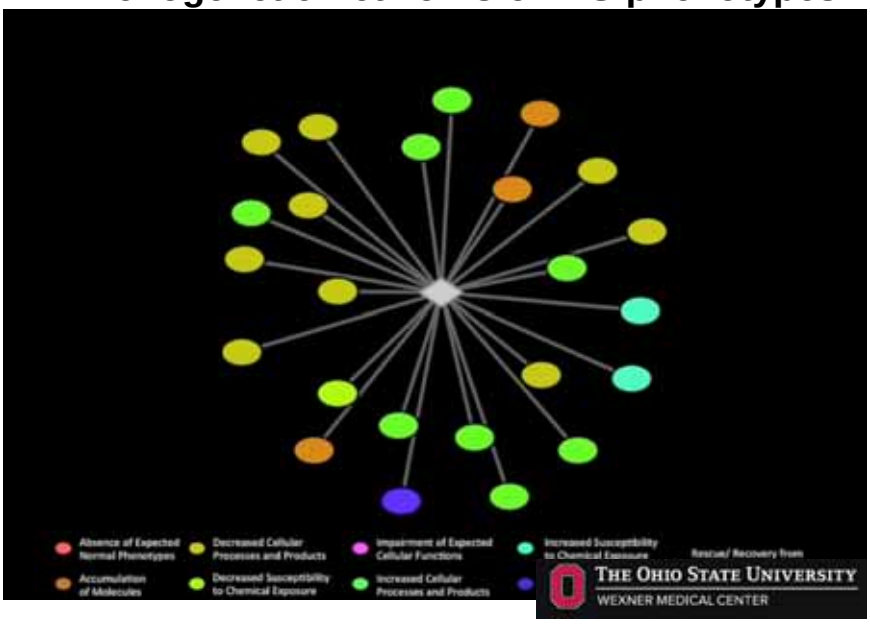
Phenogenetic networks of iPS phenotypes



Phenogenetic networks of iPS phenotypes

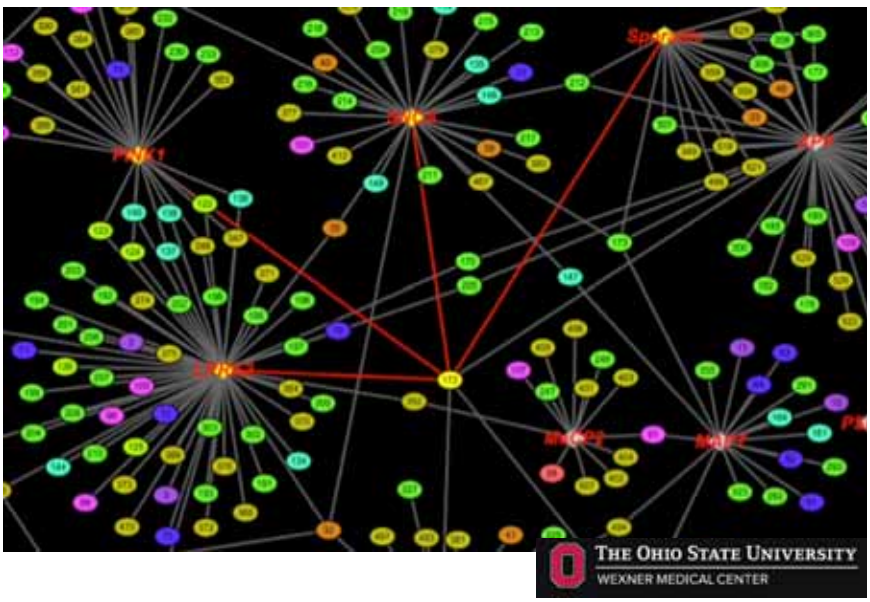


Phenogenetic networks of iPS phenotypes

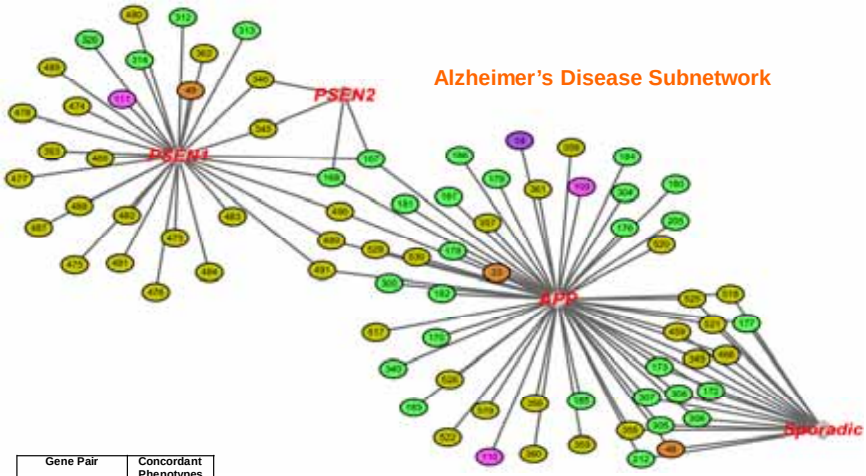


Phenogenetic networks of iPS phenotypes

Phenogenetic networks of iPS phenotypes



Phenogenetic networks of iPS phenotypes



Alzheimer's Disease Subnetwork

Gene Pair	Concordant Phenotypes
APP – Sporadic	16
PSEN1 – APP	5
PSEN2 – PSEN1	4
APP– PSEN2	2

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iPhemap www.iphemap.org

The iPS cells phenogenetic map project

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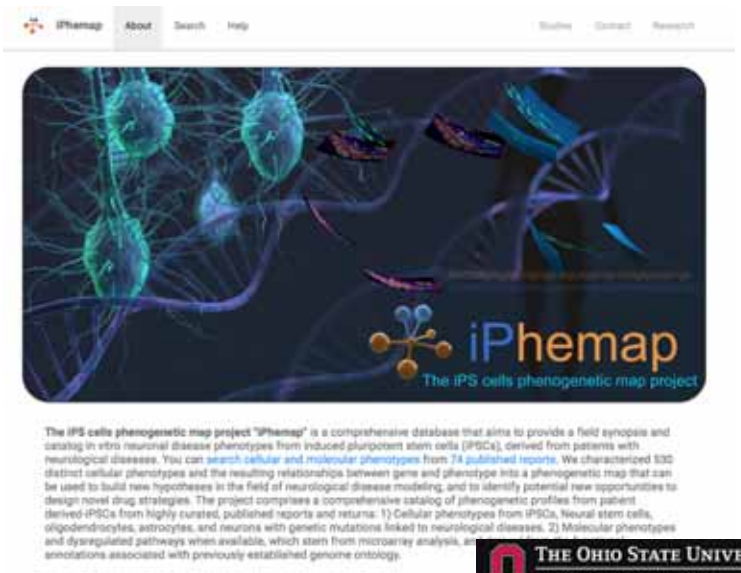
Webtool



Conclusions

1. Systematic analysis of the correlation of 530 neuronal phenotypes with genotypic data from 180 patients and 143 controls.
2. Creation of a public repository http://www.iPhemap.org.
3. Our analysis provides, for the first time, the **taxonomy** of phenotypes from patient-derived iPSC models of neurological diseases.

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Conclusions

4. The network shows overlapping phenotypes and the degree of association between cellular and molecular phenotypes.

5. Our web resource provides a tool for the mining of the phenogenetic correlation for human neurological diseases modeled by iPSCs

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Bedside-Bench-Bedside Roadmap of iPS Model in Neurology

Patient visit
Clinical diagnosis and Work-up
i.e Late onset Alzheimer Disease

↓

Disease Modeling Lab
Skin biopsy, iPS generation,
Confirmation of reprogramming
Functional i.e *in vitro analysis*
Genomic i.e *Cellnet*

↓

Genomic validation of defects using Central NIH-funded server
1.Gene expression array of patient neural cells
2.Data upload to "Central" NIH-funded server of iPS models containing submission of molecular profile from hundreds of controls neurons and diseased neurons from AD patients

→

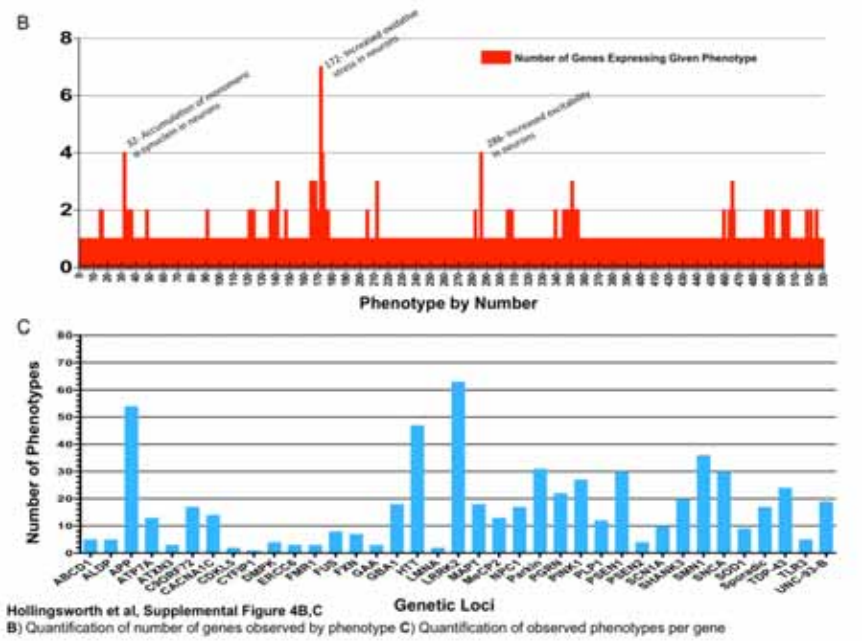
Phenogenetic Report
Disturbed networks in patient model (**molecular phenotypes**)
1. Genomic defects
2. Potential gene ontology and pathways to design future functional assay (**Cellular phenotypes**)
. Potential drugs target to screening FDA approved medications that can be repurposed

↓

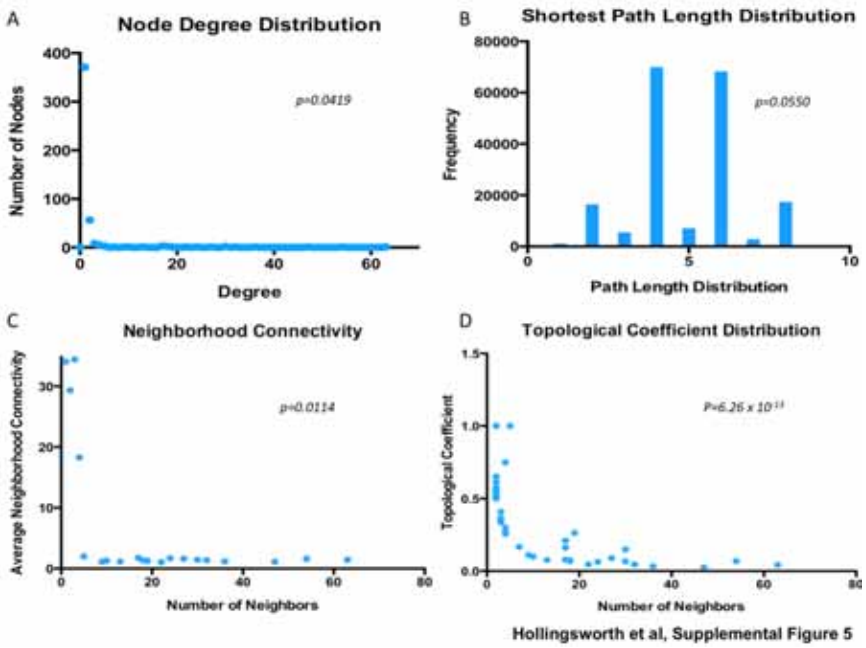
Back to Clinic:
Clinical Neurologist inform patient and discuss in next visit

↓

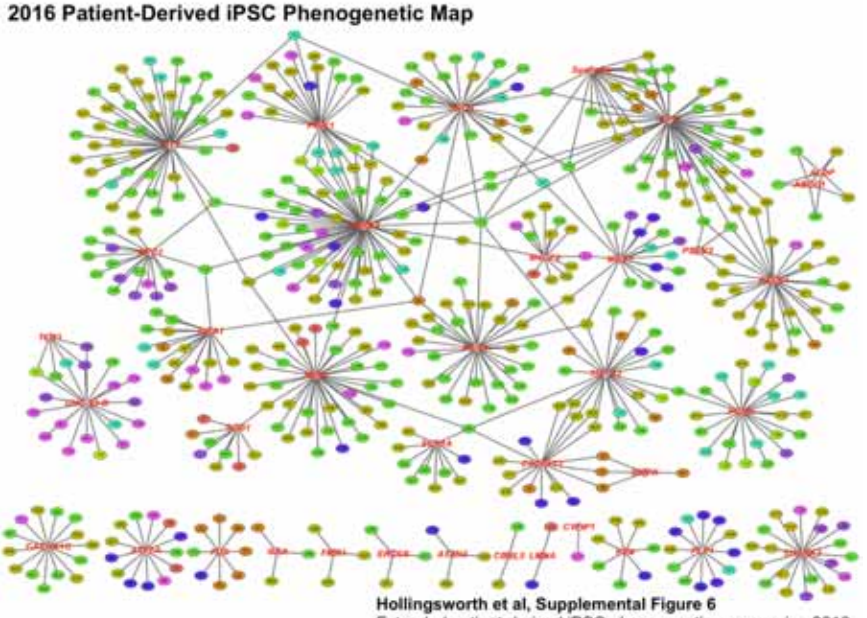
Potential Clinical trial n=1
Clinical trials or FDA approved based on prior interrogation of patient with similar molecular and cellular phenotypes.



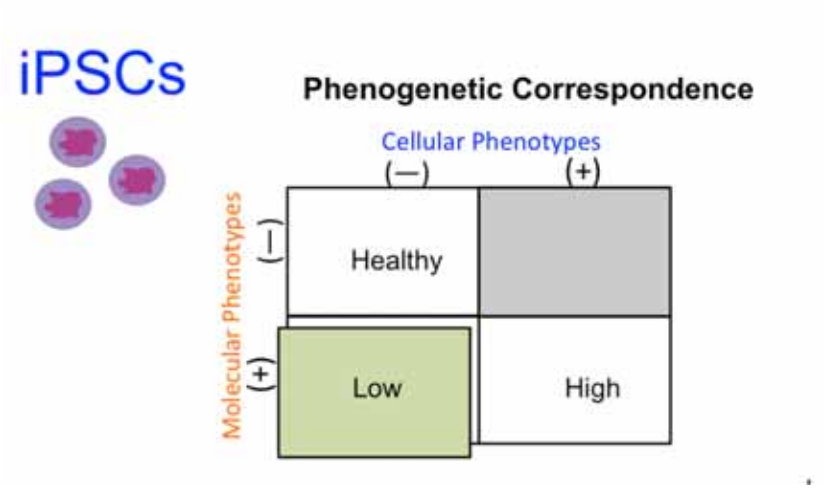
Hollingsworth et al, Supplemental Figure 4B,C
B) Quantification of number of genes observed by phenotype **C**) Quantification of observed phenotypes per gene

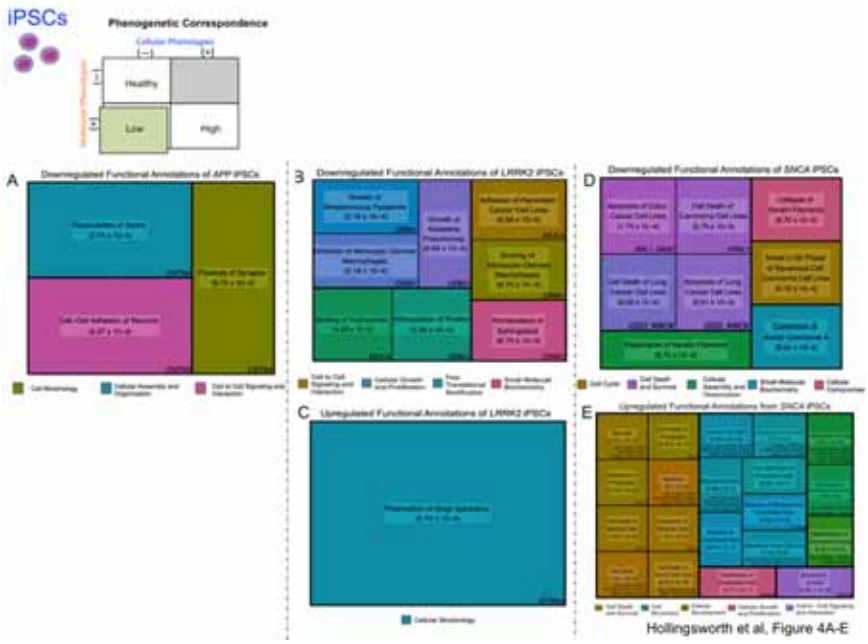


Hollingsworth et al, Supplemental Figure 5

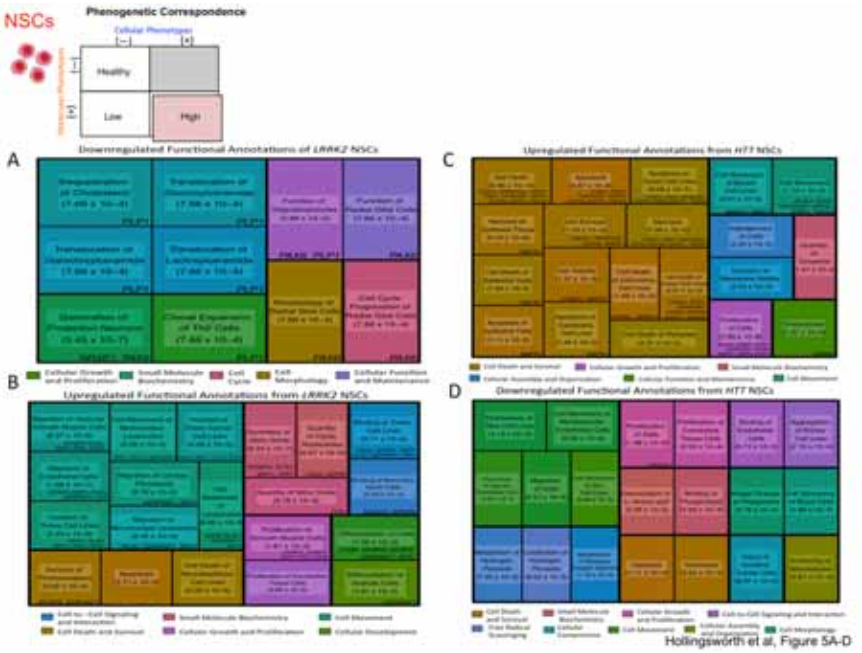


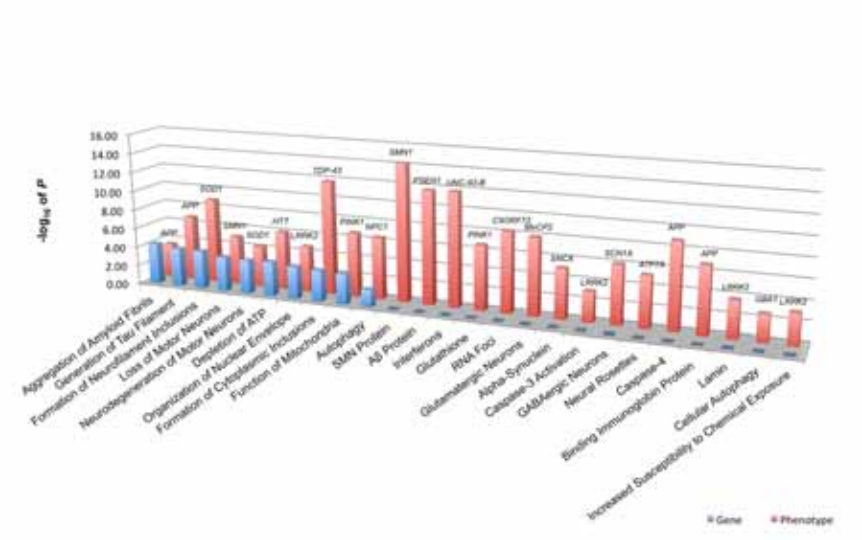
Hollingsworth et al, Supplemental Figure 6
Extended patient-derived iPSC phenogenetic map version 2016





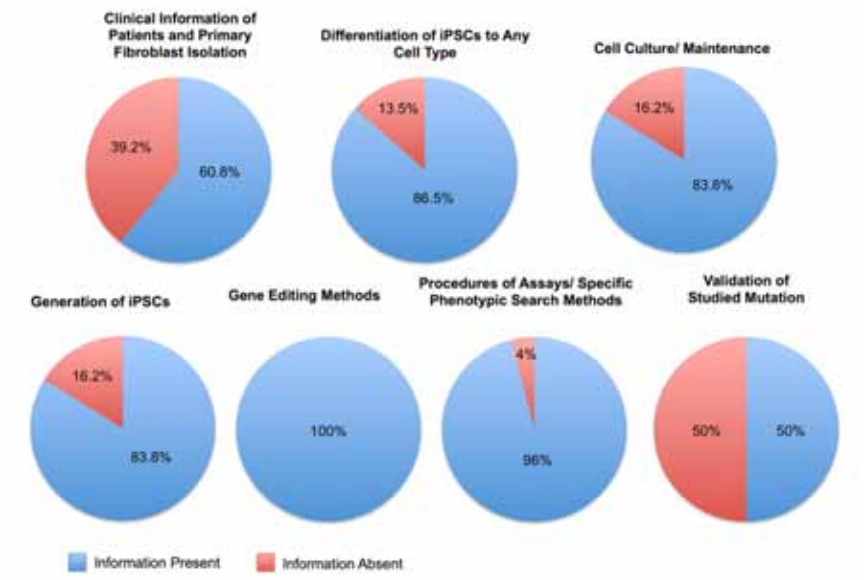
Hollingsworth et al, Figure 4A-E





Hollingsworth et al, Supplemental Figure 8

Comparison between phenotype and gene ontology. Pair-wise statistical comparison of functional annotations derived from well-established gene ontologies and phenotype ontology, which notably includes several novel phenotype ontology terms, *n=15*, that have yet to be reported in gene ontologies.



Hollingsworth et al, Supplemental Figure 12
MiPSC: Minimal information obtained from iPSC papers

Phenotype Ontology	Gene	*P* Value	Gene Ontology	*P* Value
TDP Inclusions	*TDP-43*	1.48×10^{-13}	Formation of Cytoplasmic Inclusions	6.02×10^{-4}
Aβ Protein	*PSEN1*	1.74×10^{-12}	Absent	Absent
SMN Protein	*SMN1*	5.98×10^{-10}	Absent	Absent
Neurofilaments	*SOD1*	1.38×10^{-8}	Formation of Neurofilament Inclusions	1.09×10^{-4}
Motor Neurons	*SMN1*	7.89×10^{-6}	Loss of Motor Neurons	2.74×10^{-4}
Interferons	*UNC-93-B*	1.48×10^{-13}	Absent	Absent
Motor Neurons	*SOD1*	4.86×10^{-6}	Neurodegeneration of Motor Neurons	Absent
Glutathione	*PINK1*	2.10×10^{-7}	Absent	Absent
RNA Foci	*C9ORF72*	1.81×10^{-8}	Absent	Absent
Aβ Protein	*APP*	2.77×10^{-4}	Aggregation of Amyloid Fibrils	5.47×10^{-5}
Tau Filaments	*APP*	1.59×10^{-7}	Generation of Tau Filament	1.09×10^{-4}
Mitochondrial Membrane	*PINK1*	2.03×10^{-7}	Function of Mitochondria	7.66×10^{-4}
ATP Levels	*HTT*	8.43×10^{-7}	Depletion of ATP	2.74×10^{-4}
Alpha-Synuclein	*SNCA*	7.76×10^{-6}	Absent	Absent
Glutamatergic Neurons	*MeCP2*	1.12×10^{-6}	Absent	Absent
Caspase-3 Activation	*LRRK2*	8.11×10^{-4}	Absent	Absent
GABAergic Neurons	*SCN1A*	8.43×10^{-7}	Absent	Absent
Neural Rosettes	*ATP7A*	5.48×10^{-6}	Absent	Absent
Nuclear Morphology	*LRRK2*	1.83×10^{-5}	Organization of Nuclear Envelope	4.38×10^{-4}
Cellular Autophagy	*NPC1*	3.56×10^{-7}	Autophagy	1.66×10^{-2}
Lamin	*LRRK2*	1.85×10^{-4}	Absent	Absent
Caspase-4	*APP*	1.38×10^{-5}	Absent	Absent
Binding Immunoglobin Protein	*APP*	1.59×10^{-7}	Absent	Absent
Cellular Autophagy	*GBA1*	2.13×10^{-5}	Absent	Absent
Increased Susceptibility to Chemical Exposure	*LRRK2*	8.11×10^{-4}	Absent	Absent

Hollingsworth et al, Table 1

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JAIME IMITOLA LABORATORY
Research in Molecular Genetics of CNS repair and Stem Cell Biology

Goal

Clinician: Care of Progressive MS patients

Scientist: Identify and validate genes that mediate the responses of neural stem cells to CNS injury in progressive multiple sclerosis.

Modeling Immune-NSCs interactions

Multimodal coherent anti-Stokes Raman scattering microscopy reveals microglia-associated myelin and axonal dysfunction in multiple sclerosis-like lesions in mice

Jaime Imitola,[a,*] Daniel Côté,[b,d,*] Stine Rasmussen,[a] X. Sunney Xie,[b] Yingru Liu,[a] Tanuja Chitnis,[a] Richard

Immunity
Article

Galectin-1 Deactivates Classically Activated Microglia and Protects from Inflammation-Induced Neurodegeneration

Sarah C. Starossom,[1,7] Ivan D. Mascanfroni,[2,7] Jaime Imitola,[1] Li

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Modeling human diseases with stem cells

Mutations in *ARFGEF2* implicate vesicle trafficking in neural progenitor proliferation and migration in the human cerebral cortex

Nature Genetics, 2004

Genomic and functional profiling of human Down syndrome neural progenitors implicates S100B and aquaporin 4 in cell injury

Giuseppe Esposito[1], Jaime Imitola[2], Jie Lu[5], Daniele De Filippis[6], Caterina Scuderi[1],

Human Molecular Genetics, 2008

A Novel 2q37 Microdeletion Containing Human Neural Progenitors Genes Including *STK25* Results in Severe Developmental Delay, Epilepsy, and Microcephaly

AJMG, 2015

Jaime Imitola,[1]* Divya S. Khurana,[2] Nadiya M. Teplyuk,[3] Mark Zucker,[1] Reena

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Phenogenetic networks of iPS phenotypes