Multi-omics Approach Identifies Pathological Phosphorylation Events Driving Synapse Loss in Schizophrenia

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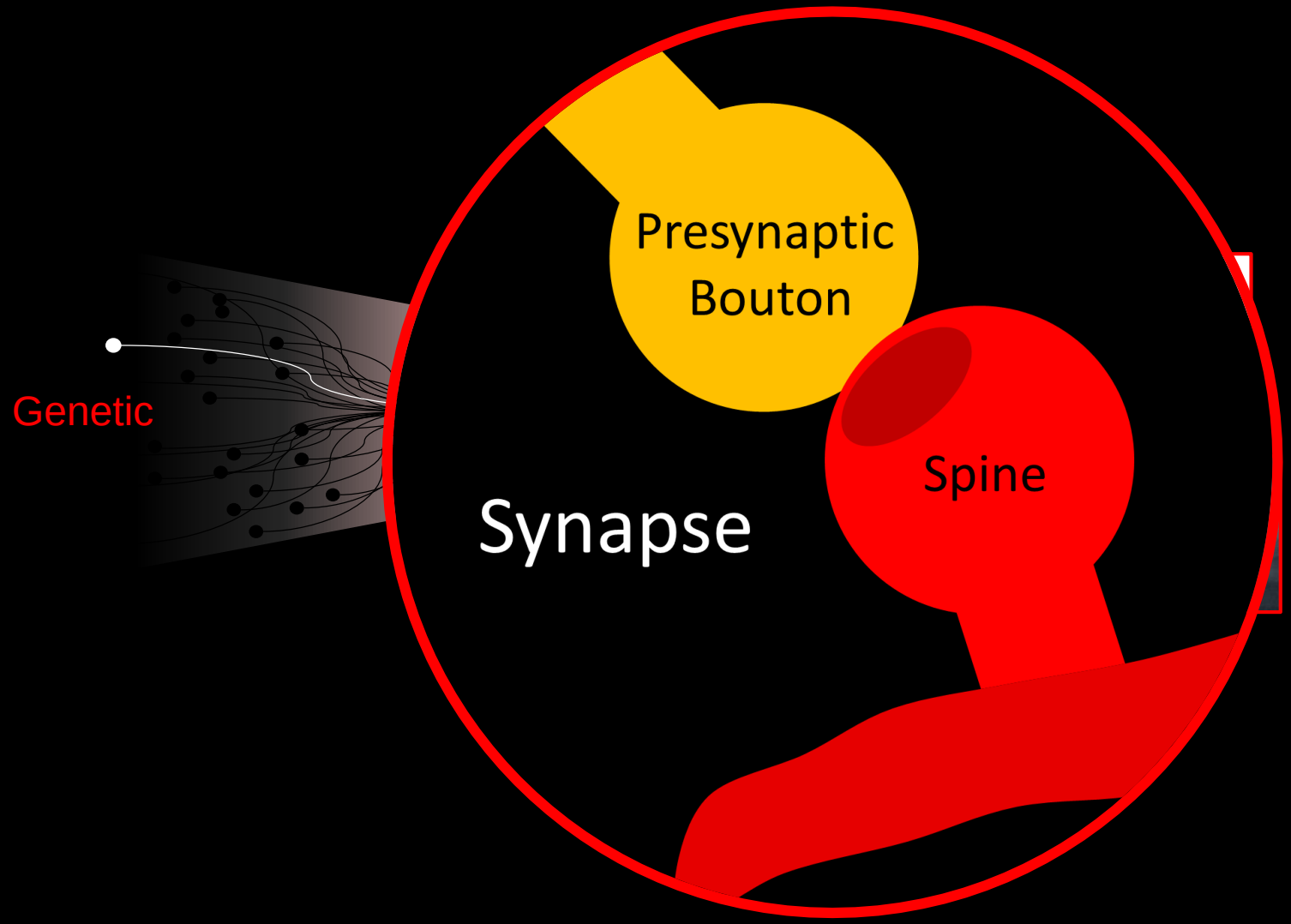
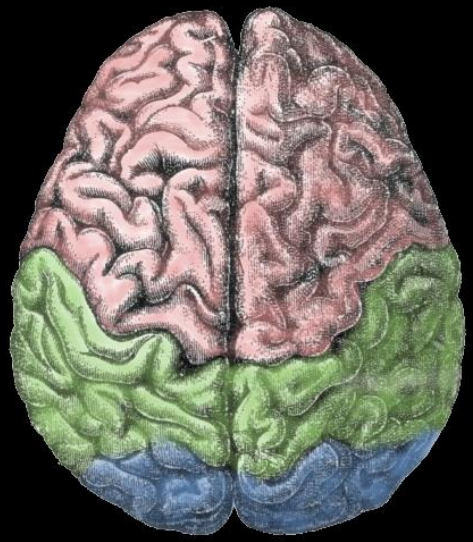
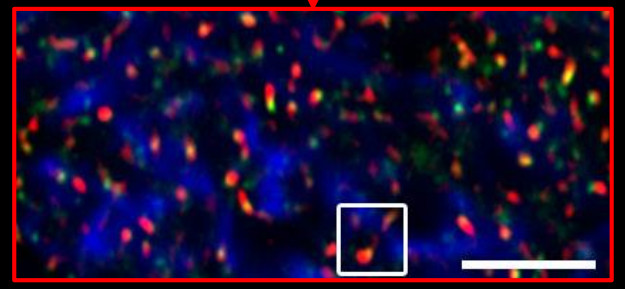

Genetic
Presynaptic
Bouton
Spine
Synapse

Parallel Approaches to Investigate Spine Pathology

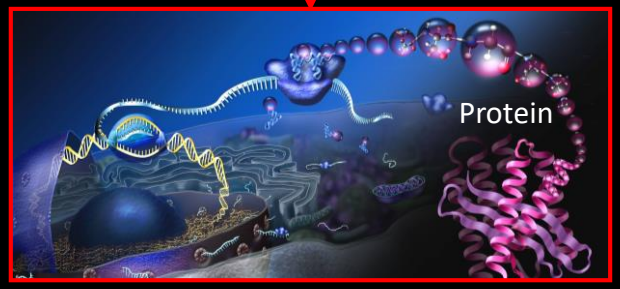


Fixed



Microscopy
→ Spine Number

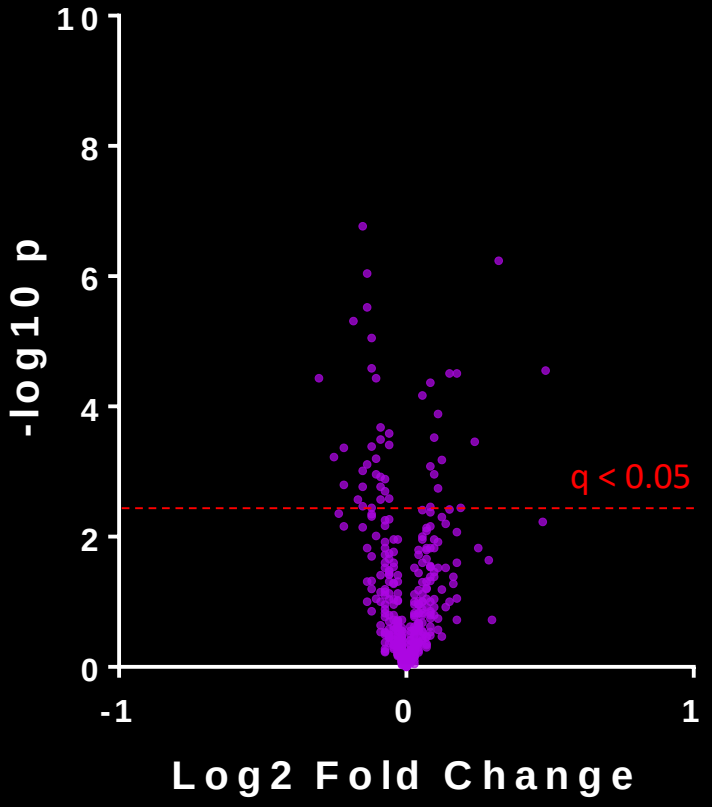
Frozen



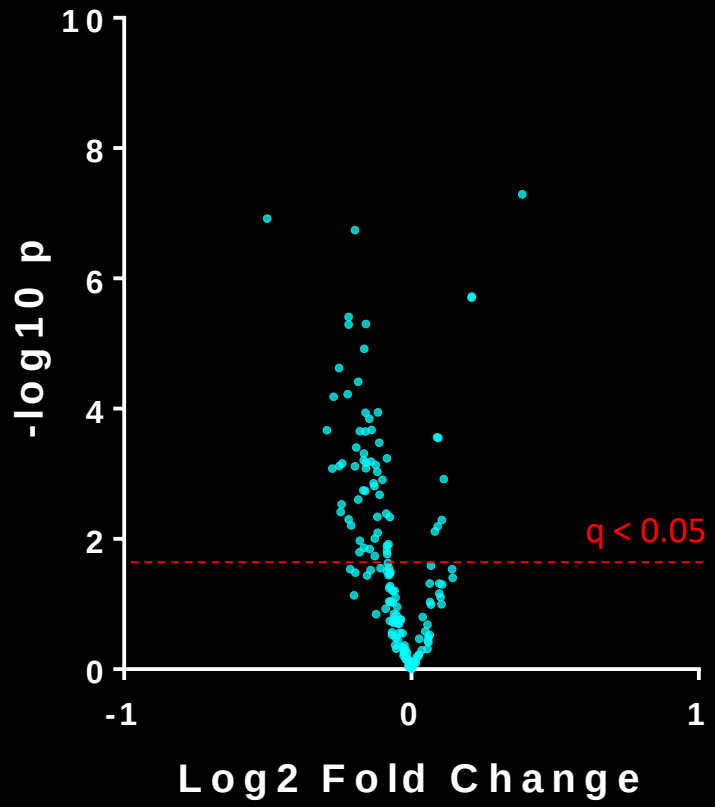
Mass Spectrometry
→ Protein Expression
→ Synaptic Protein Levels
→ Protein Phosphorylation

Sz v Control

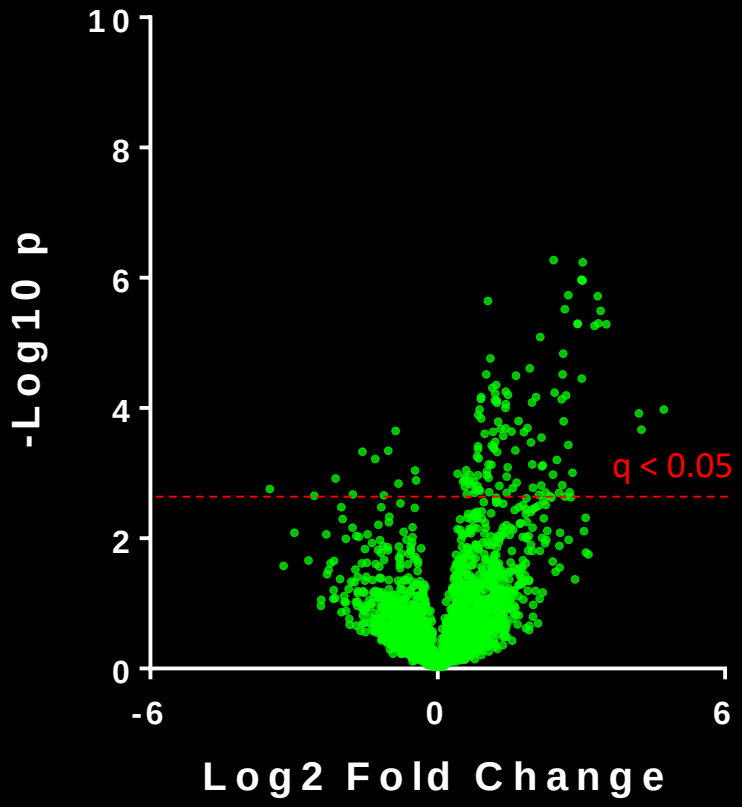
Protein Expression



Synaptic Protein Levels

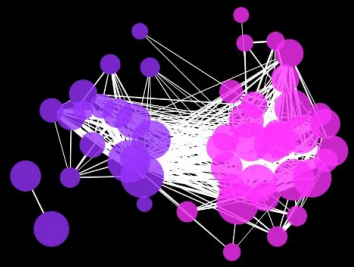


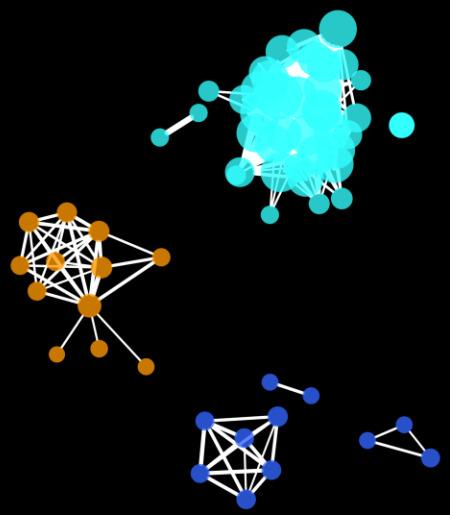
Protein Phosphorylation

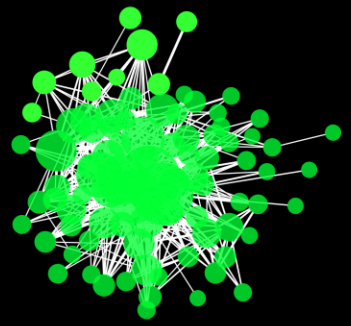


Networking Altered Proteins & Phosphorylations To Gain Biological Insight

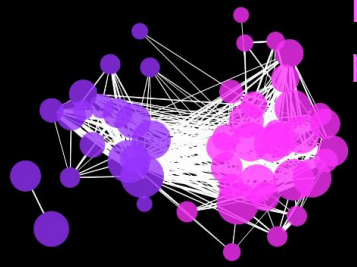
[Schizophrenia & Control] + [Differentially Regulated Proteins] ⇨







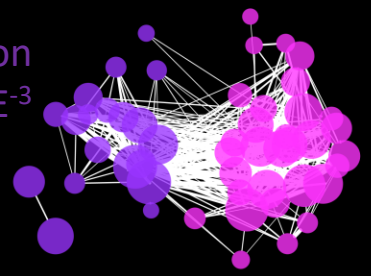
Cytoskeleton
$p = 4.9E^{-3}$



Mitochondrion
$p = 3.6E^{-8}$

Homogenate

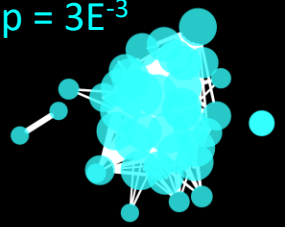
Cytoskeleton
$p = 4.9E^{-3}$



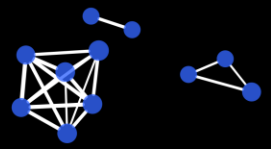
Mitochondrion
$p = 3.6E^{-8}$

Synaptosome

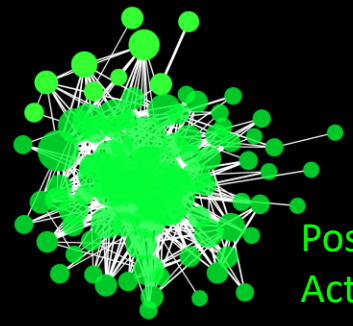
Postsynaptic
$p = 3E^{-3}$



Kinase
$p = 4.6E^{-4}$

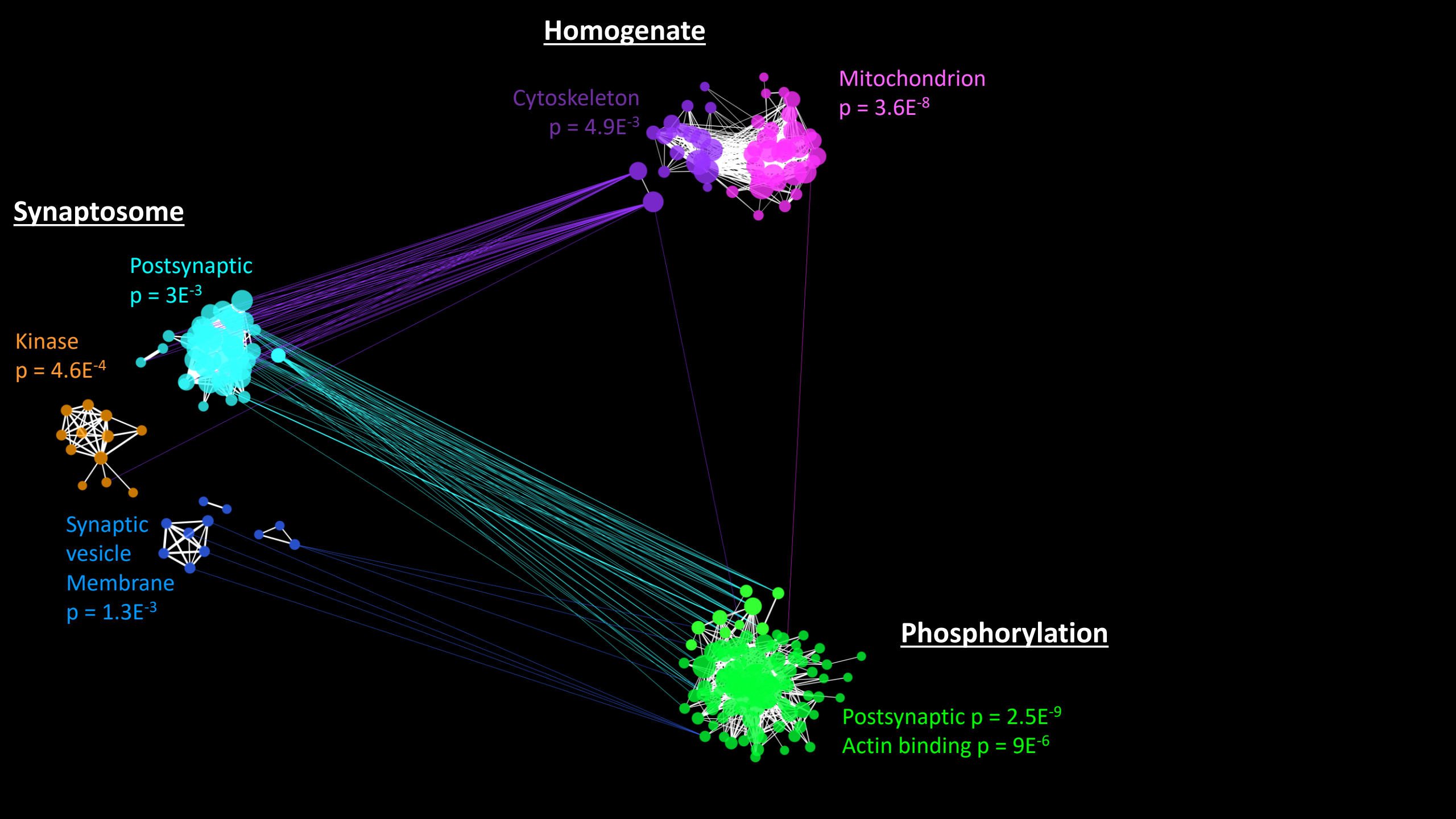


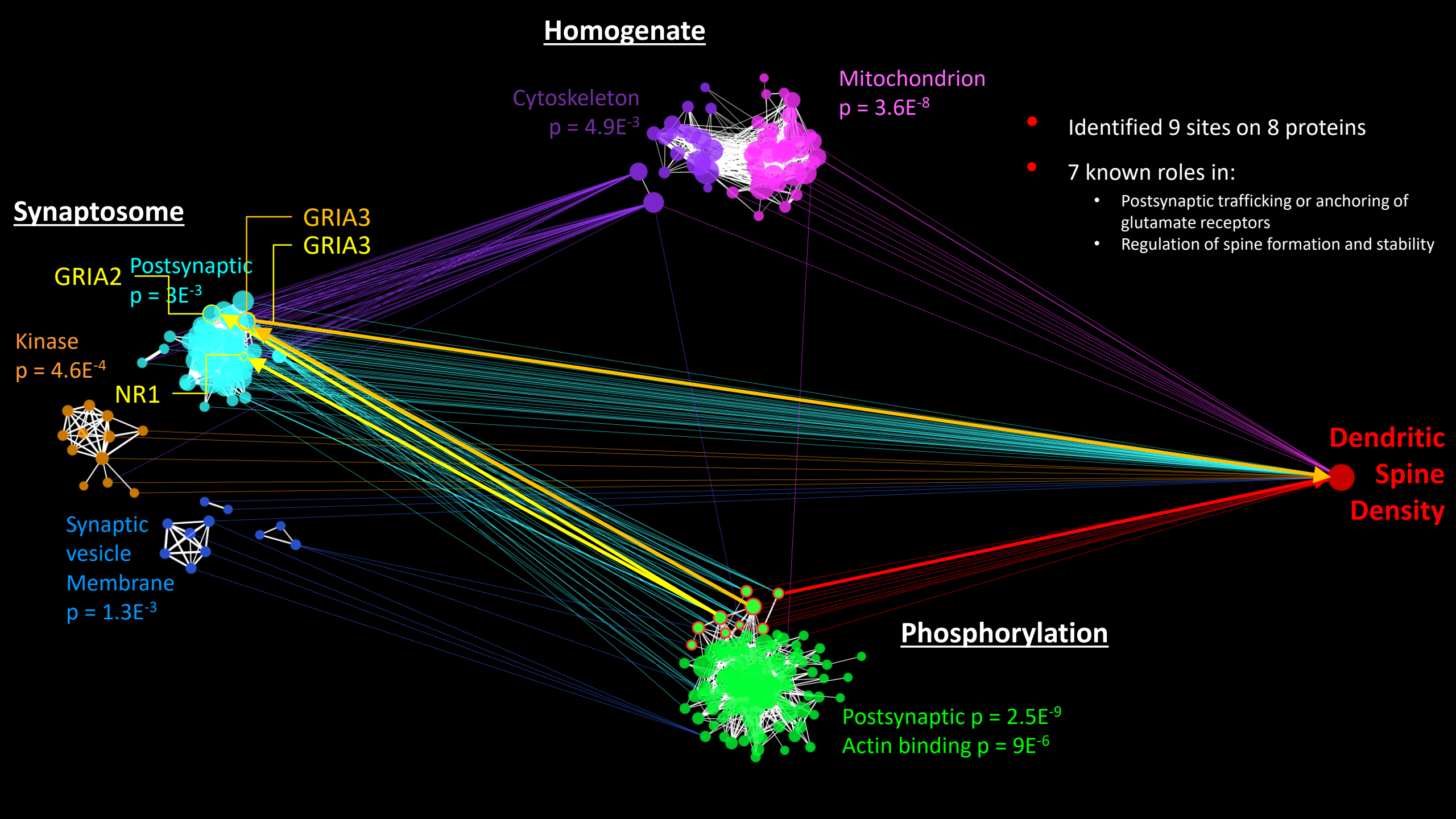
Synaptic
vesicle
Membrane
$p = 1.3E^{-3}$



Phosphorylation

Postsynaptic $p = 2.5E^{-9}$
Actin binding $p = 9E^{-6}$


Homogenate
Cytoskeleton
p = 4.9E-3
Mitochondrion
p = 3.6E-8
Synaptosome
Postsynaptic
p = 3E-3
Kinase
p = 4.6E-4
Synaptic
vesicle
Membrane
p = 1.3E-3
Phosphorylation
Postsynaptic p = 2.5E-9
Actin binding p = 9E-6


Homogenate
Cytoskeleton
p = 4.9E-3
Mitochondrion
p = 3.6E-8
Identified 9 sites on 8 proteins
7 known roles in:
Postsynaptic trafficking or anchoring of glutamate receptors
Regulation of spine formation and stability
Synaptosome
GRIA3
GRIA3
GRIA2
Postsynaptic
p = 3E-3
Kinase
p = 4.6E-4
NR1
Dendritic Spine Density
Synaptic vesicle Membrane
p = 1.3E-3
Phosphorylation
Postsynaptic p = 2.5E-9
Actin binding p = 9E-6

Those are some fancy network diagrams and it's a nice story but it's all correlative.

CRISPy Candidate Phosphorylation Induces Schizophrenia-like Pathology.

MAP2 426S → E

Phenotypes:

- ↓ MAP2-microtuble interactions
- Impaired protein translation
- Decreased dendritic arborization
- Decreased auditory cortex volume

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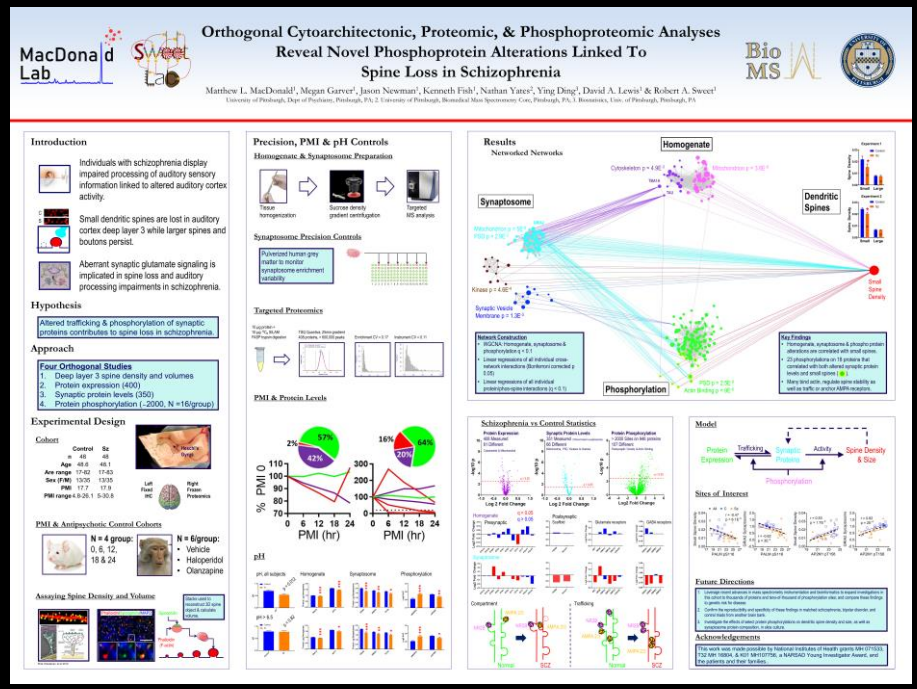
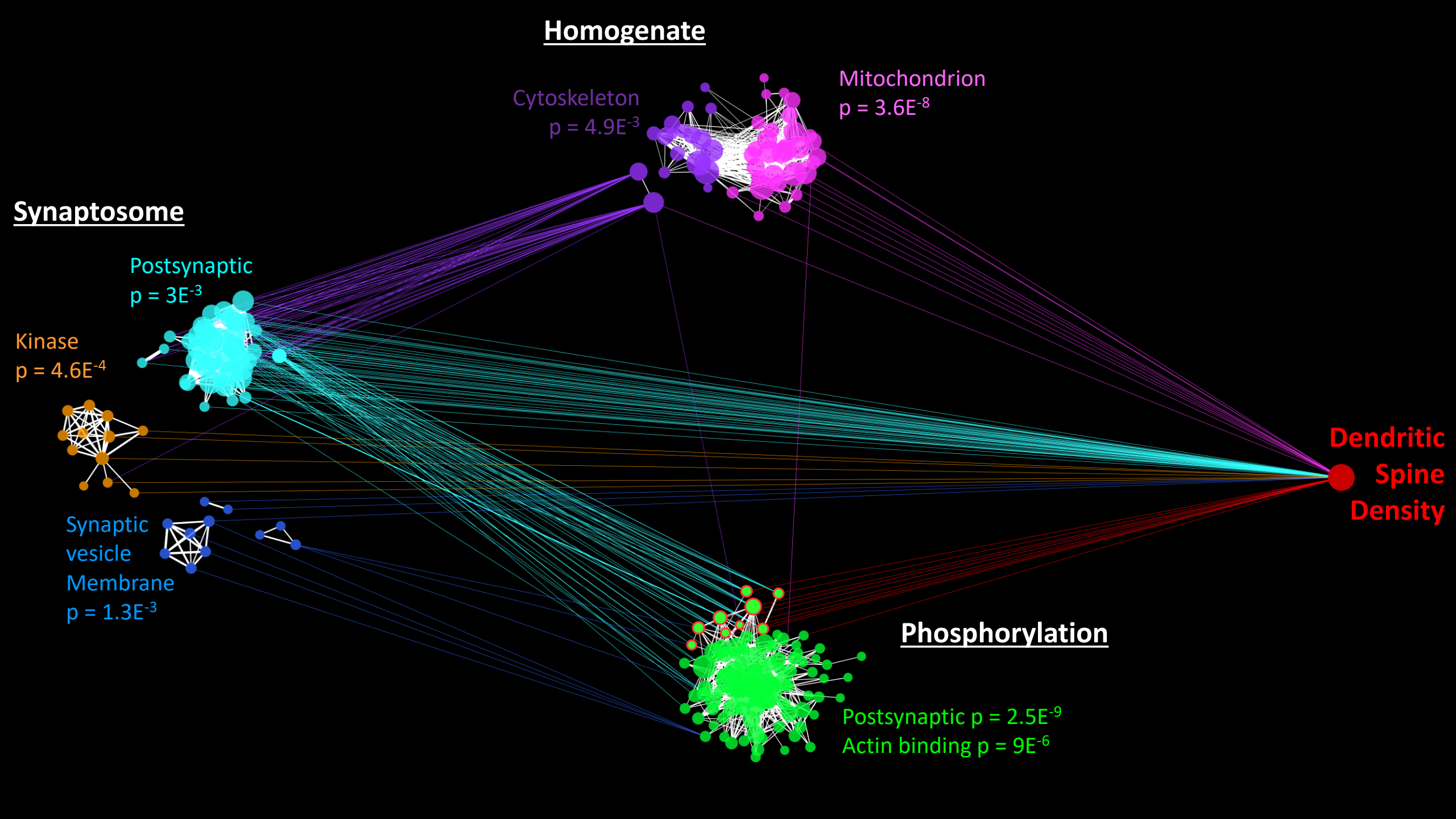
Patients and Their Families

Poster #




Homogenate
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p = 4.9E-3
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vesicle
Membrane
p = 1.3E-3
Dendritic
Spine
Density
Phosphorylation
Postsynaptic p = 2.5E-9
Actin binding p = 9E-6