Developing Cell Lines to Identify Schizophrenia Disease Mechanisms

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Abstract

Schizophrenia is a serious psychiatric disorder which affects 4.6 out of 1000 people at any given time. Despite decades of research and a wide array of experimental approaches, there is still no comprehensive explanatory model. The recent advance of genomic sequencing studies increasingly supports a combination of rare and common genetic variation in schizophrenia. These developments offer significant potential toward improved understanding of the pathophysiology. In order to translate these recent insights into a better understanding of the disease mechanism, we propose a repository of induced pluripotent stem cells be assembled from schizophrenic patients. The benefits of this approach are immediately obvious. Instead of waiting for post-mortem brain samples, a researcher will be able to obtain cell cultures already developed from live patients, and use them to characterize the relationship between rare variants, biological pathways, and clinical phenotypes.

Schizophrenia Background

No validated cause
Parent link
-10% risk if parent has Schizophrenia—10x greater than population
Twin studies
- Monozygotic twins have a 50% chance if one twin is schizophrenic
- Dizygotic twins have a 15% chance if one twin is schizophrenic

Genetic markers
- No common genes found yet
- More rare genetic defects and mutations
- Common markers with autism, ADHD, bipolar disorder, depression

Other factors
- Marijuana uses has been implicated but not proven
- More likely to have had intrauterine or birth complications

Unmet Needs

Existing therapeutics fail to adequately treat a portion of the patient population. An understanding of the etiology and biology of the disease allows this treatment deficit to exist. Diagnostics and biomarkers could greatly contribute to treatment specificity using current therapeutics as well as research initiatives. To that end, established research resources have failed to yield answers to the aforementioned needs. The field of schizophrenia research lacks an annotated tissue repository akin to the Simmons Simplex Collection found in autism research. *In vitro* and *in vivo* models that closely recapitulate the disease are also lacking. Finally, a method to comprehensively assess genetic influences on cellular and disease phenotype is in need of development.

1. Define clinical phenotypes – train professionals to classify patients into them
2. Work with academic health centers to identify and enroll patients and their families
3. Classify patients into defined phenotypes, obtain samples, develop cell lines
4. Disseminate cell lines to multiple research groups

Figure #1. Repository Development Table

Research Approach

Once samples are obtained, they will be induced to form pluripotent stem cells. These cultures will be maintained and distributed to research groups pursuing research in schizophrenia. In order to minimize noise in cellular characterizations of *de novo* contributions, family members of sporadic schizophrenia cases will be sampled as well.

The documentation of clinical presentation is the most valuable asset of this approach. It will enable groups to associate any differences in cellular phenotypes with the actual pathology witnessed in live patients. Past initiatives into schizophrenia research have used post-mortem brain tissue to attempt to characterize the disease biology. With a steady supply of stem cells, research groups will be able to conduct more experiments with more reliable tissues. Instead of studying frozen or treated tissue, the live tissue will be a valuable *in vivo* resource. Additionally, the stem cells can be differentiated to explore how neurons and other tissues differ in schizophrenia.

There are limitations to this approach as well. The environmental factors associated with the disease are not testable. Additionally, these cell lines are by no means comparable to the complexity of the brain.

Top genome-wide association results for schizophrenia

SNP	Chr.	Mb	Alleles	Frequency	*P* (GC-adjusted *P*)	OR (95% CI)	Consistency of direction	Gene	Distance (kb)
					5.72×10^{-7} (6.52×10^{-7})	1.14 (1.08–1.19)			
rs1625579	1q21.3[a]	98.3	TG	0.80	$\mathbf{2.65 \times 10^{-8}}$ (n.a.)	1.11 (1.07–1.16)	+++++++++	*MIR137*	Intragenic
					$\mathbf{1.59 \times 10^{-11}}$ ($\mathbf{6.87 \times 10^{-10}}$)	1.12 (1.09–1.16)			
					3.09×10^{-6} (2.60×10^{-7})	1.22 (1.13–1.30)			
rs17662626	2q32.3[a]	193.7	AG	0.91	$\mathbf{1.70 \times 10^{-5}}$ (n.a.)	1.16 (1.06–1.27)	+ −+ +++	*PCGEM1*	343
					$\mathbf{4.65 \times 10^{-8}}$ (1.25×10^{-6})	1.20 (1.13–1.26)			
					$\mathbf{4.30 \times 10^{-11}}$ ($\mathbf{2.76 \times 10^{-7}}$)	1.18 (1.13–1.23)			
rs2021722	6p21.3-p22.1	30.3	CT	0.78	$\mathbf{1.55 \times 10^{-5}}$ (n.a.)	1.10 (1.03–1.17)	+ ++ +++	*TRIM26*	Intragenic
					$\mathbf{2.18 \times 10^{-12}}$ ($\mathbf{2.88 \times 10^{-10}}$)	1.15 (1.11–1.19)			
					3.84×10^{-7} (4.71×10^{-6})	1.14 (1.09–1.19)			
rs10503253	8p23.2[a]	4.2	AC	0.19	$\mathbf{7.60 \times 10^{-5}}$ (n.a.)	1.08 (1.01–1.14)	+ ++ +++	*CSMD1*	Intragenic
					$\mathbf{4.14 \times 10^{-8}}$ (8.98×10^{-7})	1.11 (1.07–1.15)			
					$\mathbf{1.45 \times 10^{-8}}$ (3.22×10^{-7})	1.16 (1.11–1.21)			
rs7004633	8q21.3[a]	89.8	GA	0.18	**0.011** (n.a.)	1.05 (1.01–1.10)	++−++++++	*MMP16*	421
					$\mathbf{2.75 \times 10^{-8}}$ (7.03×10^{-7})	1.10 (1.07–1.14)			
					1.58×10^{-7} (2.27×10^{-6})	1.11 (1.07–1.15)			
rs7914558	10q24.32[a]	104.8	GA	0.59	$\mathbf{1.07 \times 10^{-5}}$ (n.a.)	1.08 (1.03–1.13)	+ ++ +++	*CNNM2*	Intragenic
					$\mathbf{1.82 \times 10^{-8}}$ ($\mathbf{3.11 \times 10^{-8}}$)	1.10 (1.07–1.13)			
					$\mathbf{2.23 \times 10^{-8}}$ (4.58×10^{-7})	1.22 (1.15–1.29)			
rs11191580	10q24.33[a]	104.9	TC	0.91	$\mathbf{5.09 \times 10^{-5}}$ (n.a.)	1.09 (1.02–1.16)	+++++++++	*NT5C2*	Intragenic
					$\mathbf{1.11 \times 10^{-6}}$ (3.72×10^{-7})	1.15 (1.10–1.20)			
					$\mathbf{2.91 \times 10^{-8}}$ (5.69×10^{-7})	1.20 (1.13–1.26)			
rs548181	11q24.2	125.0	GA	0.88	0.068 (n.a.)	1.04 (0.98–1.11)	++++++−+	*ST8SIA4*	1
					8.87×10^{-7} (1.74×10^{-5})	1.11 (1.07–1.16)			
					1.00×10^{-6} (1.03×10^{-5})	1.10 (1.06–1.14)			
rs12966547	18q21.2	50.9	GA	0.58	$\mathbf{2.29 \times 10^{-5}}$ (n.a.)	1.08 (1.04–1.12)	+−+++++++	*CCDC68*	126
					$\mathbf{2.60 \times 10^{-10}}$ ($\mathbf{5.99 \times 10^{-9}}$)	1.09 (1.06–1.12)			

Figure #2. Schizophrenia - Associated Loci

Genome-wide association identifies five new schizophrenia loci, (2011)

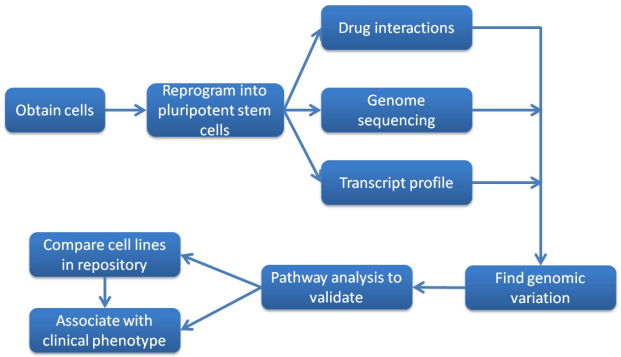

Figure #3. Research Pipeline

Conclusions/ General Impact

- Establish reproducible panel of schizophrenia stem cell lines
- General impact
  - Elucidate drug mechanisms on cells derived from a patient with schizophrenia
  - Establish biomarkers for disease
  - *In vitro* testing will help accelerate the association of genes with biological pathways and clinical phenotypes
  - Advance the understanding in terms of molecular interaction, genomic variation, and clinical phenotypes and move away from purely behavioral diagnostic
  - Future trials focused on a molecular basis of disease

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