The Need for Diversity in Stem Cell Repositories of Rare Genetic Neurological Disorders

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Background
Rare genetic neurological disorders have become a major focus of neuroscience drug discovery in the pharmaceutical industry. The paradigmatic shift towards precision medicine in drug discovery has been empowered by induced pluripotent stem cells (iPSC) technology which enables the modeling of diseases in a dish.

The de novo somatic mutations that give rise to many genetic neurological disorders occur at equal frequencies across ethnic populations. Therefore, most genetic neurological disorders should have a diverse patient constituency, which should be reflected in iPSC lines used for drug discovery.

The Human Neuron Core at Boston Children’s Hospital
Recruit patients with neurological disorders to provide tissue samples for iPSC development, which are subsequently used for both academic and industry drug development efforts.

As of June 2016, 152 samples (33 unique individuals) are stored in the Human Neuron Core at Boston Children’s Hospital, which is the largest iPSC repository for neurological disease. The racial distribution of all primary samples (152 samples) collected across all disorders within the Core evenly reflects the racial demographics of the state of Massachusetts.

Decreased diversity also is seen in other rare genetic disorders including SSADH (succinic semialdehyde dehydrogenase deficiency; 91% white out of 11 samples).

Tuberous Sclerosis Complex (TSC) is a genetic disorder most frequently caused by spontaneous de novo mutations that occurs with an incidence of 1 in 5,800 individuals equally across racial and ethnic groups (Kingswood, 2017).

In the absence of active curation, there is less diversity in iPSC repository samples (11 samples) from the genetically defined neurological disorder, TSC, than for phenotypically defined neuropsychiatric disorders (39 samples).

Decreased diversity in samples from genetically defined disorders

Should we actively curate biorepositories to capture racial diversity?

<table>
<thead>
<tr>
<th>Sample</th>
<th>Number of regions</th>
<th>Number of populations</th>
<th>Within populations</th>
<th>Among populations within regions</th>
<th>Among regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>1</td>
<td>52</td>
<td>99.3% (94.1%, 97.5%)</td>
<td>2.5% (0.4%, 4.6%)</td>
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<tr>
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<td>21</td>
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<tr>
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<td>92.0% (89.9%, 94.0%)</td>
<td>0.3% (0.2%, 0.4%)</td>
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<tr>
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<td>91.1% (89.4%, 92.8%)</td>
<td>0.7% (0.5%, 0.9%)</td>
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The rationale for actively curating biorepository samples from a racially and ethnically diverse population cannot be rooted in genetics, as the gain in genetic variation from a diverse population is minimal. This is aligned with the call for post-racial medicine to limit the scientific racism inherent in using race as a variable in research (Perez-Rodriguez, 2017).

Conclusion
While racial diversity need not be actively curated, its absence reflects the institutional failure to include diverse patient populations in research.

Lower participation in research by minority groups is either due to failures in recruitment (due to accessibility or research design) or reluctance to participate (Genevieve, 2020).

Genetic neurological disorders are paving a path for precision medicine. Failure to recruit diverse populations into early precision medicine research tempts exacerbating health inequalities.

Equitable recruitment for genetic neurological disorders must focus on curating pathogenic genetic diversity (Ghaffari, 2018) in a manner that results in the repository diversity reflecting prevalence of the disorder across racial and ethnic groups.

Racial Diversity of Primary Samples in the Biorepository

TSC Clinical Patients

Theoretical TSC Population in MA

Adapted from Szeyd, 2016

Decreased diversity in samples from genetically defined disorders

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