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

Meera E. Modi[1, 2], Brianna R. Golewski[1], Elizabeth D. Buttermore[1, 2], Pin-Fang Chen[1, 2], Maya Chopra[1], Kira A. Dies[1], Mustafa Sahin[1, 2]

[1]Translational Neuroscience Center, Boston Children's Hospital, Boston, MA

[2] Department of Neurology, Harvard Medical School, Boston, MA

Boston Children's Hospital | Translational Neuroscience Center

SUPPORT HEALTH EQUITY END RACISM

Background

Rare genetic neurological disorders have become a major focus of neuroscience drug discovery in the pharmaceutical industry.

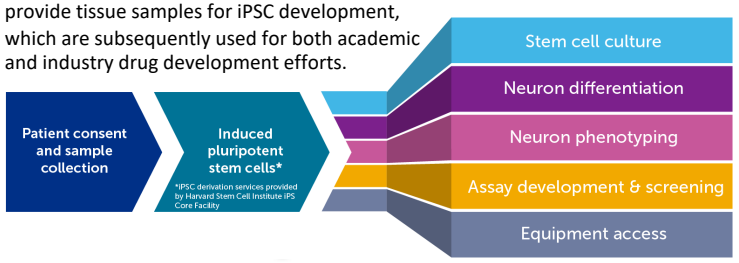
The paradigmatic shift towards precision medicine in drug discovery has been empowered by induced pluripotent stem cells (iPSC) technology which enables the modeling of diseases in a dish.

The de novo somatic mutations that give rise to many genetic neurological disorders occur at equal frequencies across ethnic populations.

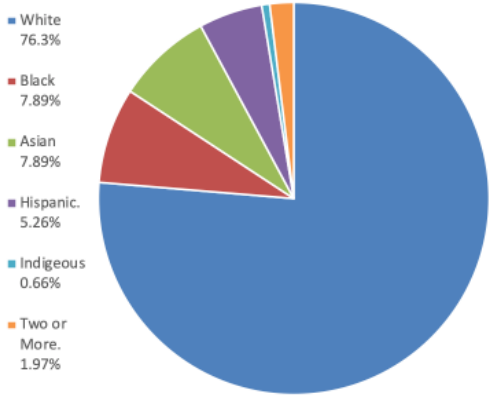
Therefore, most genetic neurological disorders should have a diverse patient constituency, which should be reflected in iPSC lines used for drug discovery.

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.



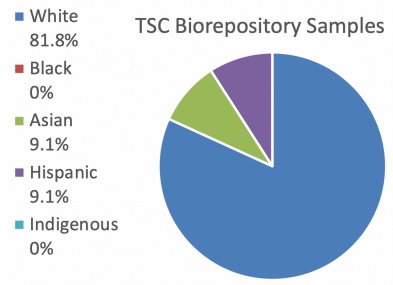
Racial Diversity of Primary Samples in the Biorepository



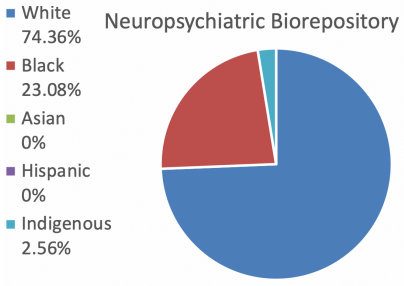
Currently, patients are recruited based on phenotypic and genotypic profiles, **without attention to generating racial diversity**.

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 in samples from genetically defined disorders



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).

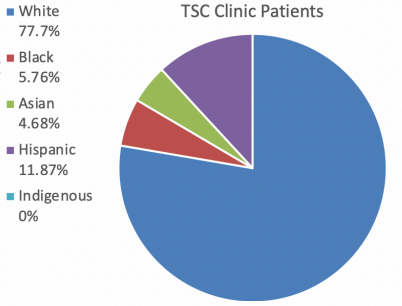


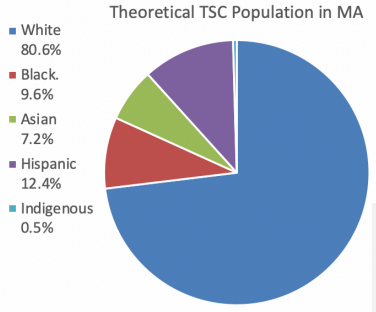
In the absence of **active curation**, there is less diversity in iPSC repository samples (11 samples) from the **genetically defined** neurological disorder, TSC, than for **phenotypically defined** neuropsychiatric disorders (39 samples).

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

The **lack of diversity in TSC biorepository samples is not seen in the total patient population** that receives care at the Multidisciplinary TSC Clinic at Boston Children's Hospital. The racial demographics of the clinic match the racial demographics of Massachusetts and the expected demographics of the regional TSC population.

This suggests that the diversity of patients receiving clinical care is lost during the recruitment of clinic patients into research.





Should we actively curate biorepositories to capture racial diversity?

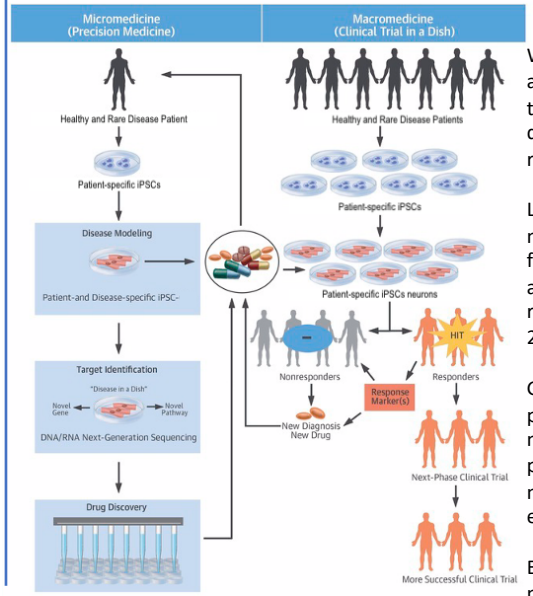
Sample	Number of regions	Number of populations	Variance components and 95% confidence intervals (%) Within populations	Among populations within regions	Among regions
World	1	52	94.6 (94.3, 94.8)	5.4 (5.2, 5.7)	
World	5	52	~~93.2 (92.9, 93.5)~~	2.5 (2.4, 2.6)	~~4.3 (4.0, 4.7)~~
World	7	52	94.1 (93.8, 94.3)	2.4 (2.3, 2.5)	3.6 (3.3, 3.9)
World-B97	5	14	~~89.8 (89.2, 90.2)~~	5.0 (4.8, 5.3)	~~5.2 (4.7, 5.7)~~
Africa	1	6	96.9 (96.7, 97.1)	3.1 (2.9, 3.3)	
Eurasia	1	21	98.5 (98.4, 98.6)	1.5 (1.4, 1.6)	
Eurasia	3	21	98.3 (98.2, 98.4)	1.2 (1.1, 1.3)	0.5 (0.4, 0.6)
Europe	1	8	99.3 (99.1, 99.4)	0.7 (0.6, 0.9)	
Middle East	1	4	98.7 (98.6, 98.8)	1.3 (1.2, 1.4)	
Central/South Asia	1	9	98.6 (98.5, 98.8)	1.4 (1.2, 1.5)	
East Asia	1	18	98.7 (98.6, 98.9)	1.3 (1.1, 1.4)	
Oceania	1	2	93.6 (92.8, 94.3)	6.4 (5.7, 7.2)	
America	1	5	88.4 (87.7, 89.0)	11.6 (11.0, 12.3)	

Rosenberg, 2002

94% of genetic diversity exists in local populations

Only an additional 3.6% of genetic variation is gained looking across regional populations

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).



Adapted from Sayad, 2016

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 the path for precision medicine. Failure to recruit diverse populations into early precision medicine research tempts exacerbating health inequities.

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.

Genevieve et al (2020) Structural racism in precision medicine: leaving no one behind. BMC MedEthics 21(1): 17.
Ghaffari et al (2018) Representing Diversity in the Dish: Using Patient-Derived in Vitro Models to Recreate the Heterogeneity of Neurological Disease. Front. Neurosci. 12:56.
Kingswood et al (2017) TuberOus Sclerosis registry to increase disease Awareness- baseline data on 2093 patients. Orphanet J Rare Dis 12(1): 2.
Perez-Rodriguez & de la Fuente (2017) Now is the Time for a Post racial Medicine: Biomedical Research, the NIH, and the Perpetuation of Scientific Racism. AJOB, 17:936-47.
Rosenberg et al (2002) Genetic structure of human populations. Science 298(5602):2381-5.