

U-M study reveals surprising lack of genetic diversity in the most widely used human embryonic stem cell lines

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ANN ARBOR, Mich.---The most widely used human embryonic stem cell lines lack genetic diversity, a finding that raises social justice questions that must be addressed to ensure that all sectors of society benefit from stem cell advances, according to a University of Michigan research team.

In the first published study of its kind, the U-M team analyzed 47 embryonic stem cell lines, including most of the lines commonly used by stem cell researchers. The scientists determined the genetic ancestry of each line and found that most were derived from donors of northern and western European ancestry.

Several of the lines are of Middle Eastern or southern European ancestry. Two of the lines are of East Asian origin. None of the lines were derived from individuals of recent African ancestry, from Pacific Islanders, or from populations indigenous to the Americas.

In addition, U-M researchers identified several instances in which more than one cell line came from the same embryo donors, further reducing the overall genetic diversity of the most widely available lines.

"Embryonic stem cell research has the potential to change the future of medicine," said Sean Morrison, director of the U-M Center for Stem Cell Biology and one of the study leaders. "But there's a lack of diversity among today's most commonly used human embryonic stem cell lines, which highlights an important social justice issue."

"We expected Europeans to be overrepresented, but we were surprised by how little diversity there is," he said.

For the study, Morrison teamed up with two colleagues at the U-M Life Sciences Institute: stem cell scientist Jack Mosher and population geneticist Noah Rosenberg. Their findings are scheduled to be published online Wednesday in the *New England Journal of Medicine*.

A fundamental principle of medical research is that new therapies are tested on patients that mirror the diversity in society, because certain groups may respond to medications

and treatments differently. By evaluating new therapies in diverse patients, researchers are more likely to detect the different effects these therapies might have.

Embryonic stem cell lines are being used to develop new cellular therapies for spinal cord injuries and various diseases, to screen for new drugs and to better understand inherited diseases. It's crucial that diverse lines are available for this research to ensure that all patients benefit from the results, Morrison said.

"If that's not done, we run the risk of leaving certain groups in our society behind," said Morrison, who is a Howard Hughes Medical Institute investigator at U-M.

The U-M report comes as Michigan researchers launch new projects made possible by a recent state constitutional amendment allowing researchers in the state to derive new human embryonic stem cell lines using approaches already used in the rest of the country.

The Michigan initiatives are getting underway as stem cell scientists across the nation respond to sweeping policy changes issued by the Obama administration. On Dec. 2, the U.S. National Institutes of Health announced it had approved 13 new human embryonic stem cell lines for use by federally funded researchers.

Since that announcement, 40 lines have been approved for federal funding, including 22 lines that were part of the U-M genotyping study. Estimates of the total number of human embryonic stem cell lines in the world range up to 700.

"While there are likely other lines out there that come from populations not represented in our study, those are not the lines that are most widely distributed and employed in stem cell research," said Rosenberg, a research associate professor at LSI.

In Michigan, U-M researchers announced on Dec. 8 that they received approval from the Medical School's Institutional Review Board and the university's Human Pluripotent Stem Cell Research Oversight Committee to begin accepting donated embryos that will be used to derive the university's first human embryonic stem cell lines. It is the first U-M project made possible by Proposal 2, the state constitutional amendment approved by Michigan voters in November 2008, easing restrictions on human embryonic stem cell research in the state..

The derivation project will be conducted by the university's new Consortium for Stem Cell Therapies, which includes researchers from across campus, as well as collaborators at Michigan State University and Wayne State University. Project scientists expect to begin accepting the first donated embryos early next year and to achieve their first embryonic stem cell line by mid-2010.

All donated embryos must have been created for the purpose of fertility treatment.. They must either be unsuitable for clinical use or surplus to the clinical need, such that they would otherwise be discarded if not donated for research. This work must also abide by additional restrictions imposed by the Michigan Constitution and by federal regulations.

A top priority for the consortium is to derive lines that carry the genes responsible for inherited diseases. Morrison, a member of the consortium's scientific advisory board, said the University of Michigan "will also make it a priority to derive new embryonic stem cell lines from underrepresented groups, including African-Americans."

But progress could be undermined by a package of bills now before the Michigan Legislature, Morrison said. The bills seek to impose new restrictions on embryonic stem cell research that could block much of the research approved by voters under Proposal 2, he said.

In the U-M study, Mosher extracted DNA from embryonic stem cells and identified the pattern of genetic variation at nearly 500,000 sites within the genome, a process called genotyping. Rosenberg then compared the stem-cell genotypes to databases containing genetic information from 2,001 individuals of known ancestry.

"If we find that a stem cell line is very similar genetically to people from a certain population that has previously been studied, then that's good evidence that the embryonic stem cell line was derived from donors belonging to that population, or a closely related population," Rosenberg said.

Mosher noted that the U-M Life Sciences Institute was created to bring together researchers with different sets of expertise to collaborate on problems they couldn't solve individually.

"This is a perfect example of that type of cross-disciplinary collaboration," said Mosher, an assistant research scientist at LSI. "By combining two seemingly disparate scientific approaches, we were able to make a discovery that adds important new insights.."

In addition to Mosher, Morrison and Rosenberg, the paper's authors are Trevor Pemberton, Kristina Harter, Chaolong Wang and Erkan Buzbas of the University of Michigan, Petr Dvorak of Masaryk University in the Czech Republic, and Carlos Simon of Valencia University in Spain.

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