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Here's Another Reason to Not Marry Your Cousin



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By **Alan Mozes**
HealthDay Reporter



WEDNESDAY, April 4, 2018 (HealthDay News) -- Children born to parents who are cousins have a significant risk for developing a mood disorder -- such as depression or anxiety -- when they grow up, a new study suggests.

For adults whose parents are first-cousins, the risk is triple that of people whose parents are unrelated, the researchers reported. And, mood disorder risk is also significantly higher among children of second-cousins, they said.

"The size of this association is significant, and understanding why children of 'related parents' are at an increased risk of psychoses and common mood disorders warrants further research," said study lead author Aideen Maguire. She is a lecturer with the Center for Public Health at Queen's University Belfast in Northern Ireland.

The findings -- based on an analysis of nearly 364,000 people born in Northern Ireland between 1971 and 1986 -- may seem unremarkable at first glance. But fully 10 percent of people worldwide are born to parents who are first- or second-cousins, largely in Asia and eastern Africa.

Fewer than 1 percent of Western marriages fall into this category of what is known as "consanguineous marriage." Though marriage between blood relatives increases the risk of genetic defects in offspring, the practice is banned in only three nations: the United States, North Korea and China.

The study findings were published online April 4 in *JAMA Psychiatry*.

Of the men and women included in the current study, 609 -- or 0.2 percent -- had been born to parents who were first- or second-cousins. Of those, 349 were born to second-cousin parents, and 260 were resulted from first-cousin pairings.

The researchers inferred adult mental illness when any offspring had been prescribed an antidepressant, anti-anxiety or anti-psychotic medication at least once between 2010 and 2014.

Thirty-six percent of adults who had been born to first-cousin couples had been prescribed either an antidepressant or anti-anxiety drug. This compared with about 31 percent of second-cousin offspring, and about 27 percent of those born to unrelated parents, the findings showed.

Almost 9 percent of first-cousin offspring had been given antipsychotic meds, compared with roughly 4 percent of second-cousin offspring, and about 3 percent of unrelated offspring, the study authors said.

Based on those findings, Maguire suggested that couples should be counseled about the reproductive risks associated with consanguineous unions.

Dr. Philip Muskin, secretary of the American Psychiatric Association, called the findings unsurprising and suggested that they be taken with a grain of salt.

When couples who are close relatives have children, genes that may be rare in the general population are more likely to appear in their offspring, he said.

"But identifying a single gene that causes depression, schizophrenia, anxiety disorders and so on has not happened, nor is it likely to happen," said Muskin, who is also a professor of psychiatry at Columbia University Medical Center in New York City. "These genetic influences are more subtle and determined by many genes."

What's more, the study doesn't prove cause and effect, and Muskin said it has significant limitations.

"For example, we know nothing about the parents," he noted. "Their health, their mental health, their background. Nothing. And a lot of times things get prescribed incorrectly, or for the wrong thing. So you can't really feel comfortable saying the prescriptions are true proxies for having an actual illness."

In addition, people figured out thousands of years ago that close relatives shouldn't reproduce, Muskin said. This study simply reinforces that.

"People figured out way back that when it happened there was something not right with the offspring," Muskin said. This study "says that these societal norms are substantiated by our data. It basically says it's a big deal."

More information

There's more on genetics and mental health at the [U.S. National Institute of Mental Health](#).

SOURCES: Aideen Maguire, Ph.D. epidemiology lecturer, Centre for Public Health, Queen's University Belfast, Northern Ireland, U.K.; Philip R. Muskin, M.D., M.A., professor of psychiatry, Columbia University Medical Center, New York City, and secretary, American Psychiatric Association; April 4, 2018, *JAMA Psychiatry*, online

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Mood disorders more common in children of first-cousin parents, study finds

 geneticliteracyproject.org/2018/04/04/mood-disorders-more-common-in-children-of-first-cousin-parents-study-finds/



Having parents who are first cousins doubles the risk of inheriting a single-gene condition, from 2.5 percent to about 5 percent. But it's harder to quantify risk for psychiatric illnesses because they typically arise from interactions among genes and environmental factors. But now a study from Northern Ireland published in *JAMA Psychiatry* shows that offspring of cousin-cousin parents are at higher risk for common mood disorders.

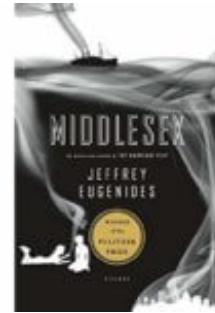
The study found that children from these unions face a three-fold increase in the likelihood of taking antidepressants and a two-fold increase in taking antipsychotics. For purposes of the study, taking an antidepressant or anti-anxiety drug was a stand-in for having a mood disorder and taking an antipsychotic represented conditions with a psychotic component, such as schizophrenia.

Shared grandparents

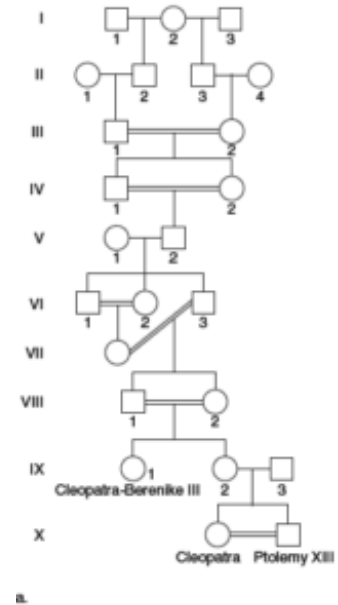
First cousins share a pair of grandparents, and as a result, have in common at least one-eighth of their gene variants. It's very unlikely to inherit two copies of a recessive gene that is extremely rare in a large population – that's why it's extremely rare – but not so unlikely when

identical mutations come from a father and mother who in turn inherited it from grandma.

A good example of the increased risk of inheriting a rare disease in an inbred family comes from one of my favorite books, the Pulitzer Prize-winning fictional novel Middlesex, by Jeffrey Eugenides. Protagonist Cal's grandparents, who were brother and sister, wed aboard a ship fleeing the Greco-Turkish war, in 1922. Each carried a recessive mutation for 5-alpha reductase deficiency, in which XY individuals appear female from a blockage in the male sex hormone pathway. Due to a cousin-cousin marriage in the second generation, Cal inherited the condition.



A partial pedigree of Egypt's Ptolemy dynasty is so riddled with relatives marrying relatives – called consanguinity, for “shared blood” – that it looks like a ladder. The double lines indicate relatives marrying relatives. From 323 B.C. to Cleopatra's death in 30 B.C., the family had one pairing between cousins related through half-brothers, four brother-sister pairings, and an uncle-niece marriage. Cleopatra married her brother, Ptolemy XIII, when he was 10 years old! The inbreeding was an effort to preserve the “royal blood.”



But as mentioned earlier, inheritance of mental disorders is harder to trace than single-gene traits or diseases.

Population-wide study

Aideen Maguire, PhD, of Queen's University in Belfast and colleagues compared prescription medication records of everyone born in Northern Ireland from 1971 through 1986 and information on whether the parents were blood relatives. They followed up on 363,960 people still in the nation in 2014, and considered prescription of psychotropic medications and use for at least three months since 2010.

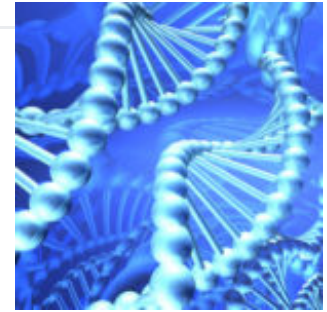
Only 609, or 0.2 percent, of the parents were blood relatives, which is similar to other populations. After accounting for environmental factors associated with compromised mental health for Northern Ireland (low birth weight, birth order, parental age, social deprivation, and living in a rural area), the researchers found that children of first-cousin parents were 3.01 times as likely to take antidepressants or anti-anxiety meds and 2.13 times as likely to take antipsychotics compared to children whose parents weren't related.

But the risks are relative. For example, the lifetime prevalence of schizophrenia is 0.30 percent to 0.66 percent. Doubling that for a child of cousins is still a low number. The numbers are more alarming for depression, with a 10 percent lifetime risk in the general population tripling

in cousins' kids. The researchers conclude, "A child of consanguineous parents is at increased risk of common mood disorders and psychoses."

Consanguinity Is common

Western nations tend to take a dim view of marrying blood relatives, but it's an accepted practice in many nations and cultures. The 2011 report from the [Geneva International Consanguinity Workshop](#) lists the percentage of consanguineous marriages in several regions: 25-30 percent in Afghanistan, 14-24 percent in Egypt, 7-42 percent in south India, and 44-49 percent in Sudan, to name a few.



Consanguineous relationships are most often between cousins or between uncles and nieces. When inbred families migrate, they bring the closed genetic community with them. For example, marriage between first cousins occurs in about a third of the Pakistani community in England, a population that researchers have been following to track birth defect rate, which is about double, but still less than 4 percent of births.

Many of the rare genetic diseases described in *Online Mendelian Inheritance in Man*, the "bible" of genetics, indicate inbred relationships, such as this entry for [Joubert syndrome](#): "In the children of healthy, consanguineous Turkish parents, van Dorp et al. observed a severely retarded male child with neurologic anomalies." Marriage among blood relatives is a question I always ask genetic counseling patients.

Sometimes blood relatives can have children together and not know they're related. This tends to happen in "endogamous" communities in which people come from the same place. An orthopedic condition, [Steel syndrome](#), for example, is much more common among residents of East Harlem of Puerto Rican ancestry than it is among people of other Hispanic origins. Noting the symptoms in a person of Puerto Rican ancestry can alert doctors to avoid a hip surgery that can harm someone with Steel syndrome, but help others.

A more modern consanguineous circumstance arises from families using the same sperm donor. See "[Accidental incest between donor-conceived people](#)."

Inbreeding problems less than predicted

Even though theoretically the sharing of 1 in 8 genes suggests that genetic disease will be more common among the consanguineous, incidence of such illnesses is lower than predicted. Some studies show that cousins tend to share different hunks of their genomes, which would counter the pairing of "identical-by-descent" pathogenic genes in offspring.



Another possible protection is that natural selection ditched dangerous gene variants by preventing sick individuals from reproducing. This may have happened to the cheetah, a highly inbred species whose numbers plummeted through population bottlenecks. About 4,000 of the

animals living mostly in six southern Africa countries today seem rather healthy, despite the fact that they are so closely related that most could swap organs with nary a rejection reaction. Natural selection might have kept the healthiest genes.

Getting back to people, Charles Darwin studied consanguinity among inmates of lunatic asylums and found no greater representation. He was perhaps especially attuned to inbreeding because his family practiced it. He married his first cousin and his family had many other relatives-marrying-relatives. But the three of Darwin's ten children who died young had infectious diseases – which could have reflected poor immune responses or close proximity easing transmission.



Flaws in the study

Psychotropic drugs are not exact proxies for the associated conditions – they're often prescribed off-label. The same drug, for example, was prescribed for my father, who had severe psychotic depression, and another relative who is just sad to be in a nursing home.

A second issue is the assumption that all consanguineous relationships are equal in terms of funneling disease-causing gene variants into the same descendants. The degree of genetic uniformity is much different for a pair of cousins who fall in love and marry at a young age, the only relatives in the extended family to do so, compared to populations that arise from many generations of uncle-niece and cousin-cousin couples, tying pedigrees up in slanted steps and loops of connectivity. And the investigators didn't consider whether or not the parents had mental illnesses – just that they were cousins.

The third and most disturbing issue to arise from the new study is the possibility of the findings fueling a self-fulfilling prophecy towards a mood disorder, anxiety, or psychosis. The situation isn't the same as the predictable 25 percent risk of an autosomal recessive disease in a child of two carrier parents, with easy-to-identify symptoms and confirmatory genetic testing available.

Might the headlines and memes that are likely to reverberate from the new report propel someone who knows her parents are first cousins to fit how she feels into the suggested paradigm of depression, or bipolar disorder, or even schizophrenia? Genetic determinism, the



idea that genes underlie nearly everything, can be helpful or harmful. I hope that the new findings lead some people to seek help, but that they don't also induce panic in or stigmatize others.

Ricki Lewis is the GLP's senior contributing writer focusing on gene therapy and gene editing. She has a PhD in genetics and is a genetic counselor, science writer and author of *The Forever Fix: Gene Therapy and the Boy Who Saved It*, the only popular book about gene therapy. [BIO](#). Follow her at her [website](#) or Twitter [@rickilewis](#).