way activation when compared with those of single-hotspot mutations. This results in enhanced tumor growth in vivo. Therapeutically, breast cancer cells with double *PIK3CA* mutations show enhanced sensitivity to alpelisib in vitro and in vivo, compared with that of single-hotspot mutants. Moreover, a retrospective analysis of clinical responses to PI3K inhibitors in breast cancer trials showed that patients with tumors with multiple *PIK3CA* mutations experience a greater overall response to alpelisib as compared with patients with single-mutant tumors.

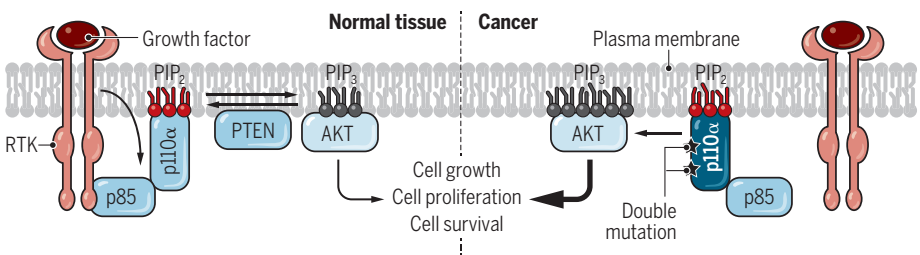
Although single and double mutations in *PIK3CA* are prevalent in some cancers, hyperactivation of the PI3K-AKT pathway is observed in more than 50% of human tumors (*6*). Multiple other genetic alterations in genes that either regulate or transduce PI3K signaling are also frequent. These include amplification or mutations of RTKs, such as members of the epidermal growth factor receptor (EGFR) family, and oncogenic activating mutations or amplification in the three AKT genes: *AKT1*, *AKT2*, and *AKT3* (*6*). Signal termination in the PI3K pathway is achieved primarily through the action of lipid phosphatases, including the tumor suppressor proteins phosphatase and tensin homolog (PTEN), inositol polyphosphate 4-phosphatase type II B (INPP4B), PH domain and leucine-rich repeat protein phosphatase 1 (PHLPP1), and PHLPP2 (*7*). Genetic inactivation of these tumor suppressors in mice leads to enhanced PI3K-AKT signaling and occurs in many human cancers. Thus, genetic mutations in components of the PI3K pathway render it the most frequently mutated pathway in human cancer.

However, single-hotspot mutations in *PIK3CA* are typically insufficient to promote malignancy, and additional "second hit" mutations in cancer-causing genes are required. Vasan *et al.* propose that the presence of double *PIK3CA* mutations in the same allele follows the "oncogene addiction" paradigm (*8*), in which tumors depend on a single gene for malignant transformation and are thus likely to die when the corresponding oncoprotein is therapeutically targeted, whereas single *PIK3CA* hotspot mutations coexist in the same cell and tumor with other PI3K pathway lesions, such as *PTEN* inactivation or *AKT* oncogenic mutations.

These findings are likely to renew interest in the clinical development of PI3K inhibitors. Dose-limiting toxicities and acquired resistance have been noted in patients treated with PI3K inhibitors (*9*), and therefore combination strategies with chemotherapy, immunotherapy, and other targeted agents will likely be most effective. Although alpelisib is potent and highly selective, it is not a p110α-mutant–specific inhibitor, and this may limit efficacy. PI3K inhibitors under clinical evaluation, such as GDC-0077, appear to be selective for mutant p110α (*10*) and therefore may be more effective in patients with double *PIK3CA* mutations. Could double mutations recur in other oncogenes? The approach of Vasan *et al.* could reveal a more complex mutational spectrum in other oncogenes than previously appreciated. ■

Growth factor signaling in normal tissues and cancer

In normal tissues, growth factors activate RTKs, leading to recruitment of PI3K, which converts PIP_2 to PIP_3. This leads to recruitment of downstream effectors, such as AKT, that stimulate cell growth, proliferation, and survival. In cancer, the double mutant *PIK3CA* oncogene encodes hyperactive p110α that is independent of RTK signaling, producing excess PIP_3, which leads to hyperactivation of AKT and uncontrolled cell growth and survival.



PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit α; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol 3,4,5-triphosphate; PTEN, phosphatase and tensin homolog; RTK, receptor tyrosine kinase.

REFERENCES AND NOTES

1. D. A. Fruman *et al.*, *Cell* **170**, 605 (2017).
2. N. Vasan *et al.*, *Science* **366**, 714 (2019).
3. F. André *et al.*, *N. Engl. J. Med.* **380**, 1929 (2019).
4. D. Juric *et al.*, *Nature* **518**, 240 (2015).
5. Y. Samuels *et al.*, *Science* **304**, 554 (2004).
6. B. D. Manning, A. Toker, *Cell* **169**, 381 (2017).
7. A. Papa, P. P. Pandolfi, *Biomolecules* **9**, 153 (2019).
8. I. B. Weinstein, A. Joe, *Cancer Res.* **68**, 3077 (2008).
9. A. B. Hanker, V. Kaklamani, C. L. Arteaga, *Cancer Discov.* **9**, 482 (2019).
10. R. Hong, Y.-R. Kao, T.-C. Lee, C.-W. Wu, *Cancer Res.* **78**, 4984 (2018).

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PSYCHOLOGY AND CULTURE

Explaining the puzzle of human diversity

Centuries of Church exposure promote more individualistic and less conforming psychology

By **Michele J. Gelfand**

One of the biggest puzzles facing the social sciences is understanding our immense cultural variation. Over the past several thousand years, humanity has evolved to the point where there now exist 195 countries, more than 7000 languages, and thousands of religions. Research has begun to describe psychological variation across the globe (*1*–*4*), yet only recently have we begun to understand ecological, historical, and sociopolitical factors that produce such differences. Often absent from this mix is how religion and psychological variation are interrelated (*5*, *6*). On page 707 of this issue, Schulz *et al.* (*7*) break new ground in showing how the specific practices of a branch of one of the world's largest religions—Christianity—can in part explain widespread variation in human psychology around the world.

Schulz *et al.* present an intriguing thesis: The Western Catholic Church's Marriage and Family Program (MFP), launched during the Middle Ages (in 506 CE), can partially explain the distinctively individualistic and nonconformist psychology of Western, Educated, Industrialized, Rich, and Democratic (WEIRD) societies in modern times. The MFP radically altered the institution of marriage by prohibiting nuptials within extended families and often requiring newly married couples to set up independent households. Schulz *et al.* predict that longer exposure to the MFP, along with weaker kinship ties that presumably arose from such practices, would drastically alter human psychology, from one that emphasized in-group loyalty, obedience, and conformity, to one that was more individualistic, prosocial toward strangers, and less conforming.

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GRAPHIC: KELLIE HOLOSKI/*SCIENCE*

The authors compiled an enormous amount of data on psychological variation in the modern era, along with historical data on the MFP and kinship intensity, to examine their hypothesis across nations around the world, within regions in Europe, and among second-generation immigrants of various backgrounds living in Europe. At the national level, exposure was defined as the number of centuries the population was under the control of the Western Church prior to 1500 CE (when the MFP was at its most intense). Exposure at the regional level was quantified as the number of bishoprics—administrative centers in the Church's hierarchy—across 440 regions of Europe.

The intensity of kin-based institutions was defined using two measures: a Kinship Intensity Index, which averaged five key variables from the Ethnographic Atlas (e.g., cousin marriage preference, polygynous marriage, co-residence of extended families), and a measure of the prevalence of cousin marriage in the 20th century at the country and regional levels. Psychological variation—the main outcome of interest—was captured by previously collected data on 24 variables that the authors grouped into three categories: individualism and independence, conformity and obedience, and impersonal prosociality. These captured not only self-reported behaviors and preferences, but also behavioral data such as that from measures of creativity, public goods games, and even unpaid New York City parking tickets issued to diplomats to the United Nations.

The results are striking. Cross-nationally, the authors found that both longer exposure to the Western Church and weaker kinship intensity (which were negatively related, as expected) were associated with greater individualism and independence, less conformity and obedience, and greater prosociality toward strangers—relationships that mostly held when controlling for a range of geographic variables. The results were replicated across 440 regions in 36 European countries: Longer exposure to the Western Church was generally associated with the same WEIRD psychological shifts, even when controlling for alternate explanations (e.g., the influence of Roman political institutions, schooling, migration).

To further test their hypothesis, Schulz *et al.* compared second-generation immigrants who grew up in the same European country but whose parents originated from different countries, effectively allowing the authors to isolate the effect of intergenerational transmission. Second-generation immigrants whose parents had more Western Church exposure and weaker kinship intensity evidenced more WEIRD psychology.

One major contribution of this research is that it expands the way we think about religion in a cultural evolutionary framework. Other research has shown that religion can affect many aspects of behavior, from prosociality (*8*, *9*), to inequality (*10*), to intergroup conflict (*11*). For example, belief in a moralizing supernatural agent has been linked to cooperation (*6*) and cultural complexity (*8*, *12*). Schulz *et al.* build on this psychological account by examining structural aspects of religion that go beyond belief to capture the top-down influence of Church practices on human psychology. Further, their paper focuses on characteristics that are specific to one of the largest religions in the world: Western Christianity. Although multiple religions have moralizing supernatural agents (*6*), the authors argue that Western Christianity is unique in its emphasis on specific marriage practices and kinship structures that have shaped psychological profiles lasting for generations. Schulz *et al.*'s massive historical and geographic effort simultaneously expands upon the culture and religion literature and the cultural psychology literature on the origin of WEIRD psychology.

To be sure, numerous critical questions await future investigation. The central question of interest—the impact of the Church on later psychological processes—requires longitudinal designs in order to provide a truly convincing causal account. Moreover, although exploratory mediational analyses tested the extent to which the Western Church influenced psychology via its impact on kinship intensity, many tests were subject to low power and do not provide precise estimates. The mechanisms through which Church exposure influences psychological variation remain an important open question. Empirical analyses are also needed to document the forces that led the Church to adapt such practices in the first place. It is possible, for example, that MFP practices were embraced in communities that were already evolving WEIRD social and psychological characteristics for other reasons. And although the Church's practices were clearly related to variance in WEIRD psychological variables, to provide a full cultural evolution account of global psychological variation, it will be necessary to understand through causal modeling the impact of the Church along with other ecological and historical factors shown to be related to WEIRD psychological variation (*4*, *13*).

Understanding human diversity is not only critical for the advancement of science, but also for bridging cultural divides. Illuminating the ways in which cultures vary—and why they have evolved in different ways given certain socioenvironmental forces—can help us to empathize with those who are different. By documenting how a very specific religious agenda in late antiquity may have had far-reaching effects on the development of cultural differences between the West and the rest of the world, Schulz *et al.* help us to decipher part of the puzzle of human diversity. ■

A couple being married by a clergyman, by Henricus von Assia (13th century). Marriage practices of the Church appear to influence modern psychology.

IAMGE: PHAS/UNIVERSAL IMAGES GROUP VIA GETTY IMAGES

REFERENCES AND NOTES

1. R. Inglehart, *Cultural Evolution: People's Motivations Are Changing, and Reshaping the World* (Cambridge Univ. Press, 2018).
2. H. R. Markus, S. Kitayama, *Psychol. Rev.* **98**, 224 (1991).
3. S. H. Schwartz, in *Advances in Experimental Social Psychology* (Academic Press, 1992), vol. 25, pp. 1–65.
4. M. J. Gelfand *et al.*, *Science* **332**, 1100 (2011).
5. J. Henrich *et al.*, *Science* **327**, 1480 (2010).
6. B. G. Purzycki *et al.*, *Nature* **530**, 327 (2016).
7. J. F. Schulz *et al.*, *Science* **366**, eaau5141 (2019).
8. A. Norenzayan *et al.*, *Behav. Brain Sci.* **39**, e1 (2016).
9. A. F. Shariff, A. K. Willard, T. Andersen, A. Norenzayan, *Pers. Soc. Psychol. Rev.* **20**, 27 (2016).
10. J. Watts, O. Sheehan, Q. D. Atkinson, J. Bulbulia, R. D. Gray, *Nature* **532**, 228 (2016).
11. M. K. Johnson, W. C. Rowatt, J. LaBouff, *Soc. Psychol. Personal. Sci.* **1**, 119 (2010).
12. H. Whitehouse *et al.*, *Nature* **568**, 226 (2019).
13. T. Talhelm *et al.*, *Science* **344**, 603 (2014).

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