UC Irvine UC Irvine Previously Published Works

Title

Leverage points for improving global food security and the environment

Permalink

https://escholarship.org/uc/item/68q6540x

Journal

Science, 345(6194)

ISSN

0036-8075

Authors

West, Paul C Gerber, James S Engstrom, Peder M <u>et al.</u>

Publication Date

2014-07-18

DOI

10.1126/science.1246067

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at https://creativecommons.org/licenses/by/4.0/

Peer reviewed

FOOD SECURITY

Leverage points for improving global food security and the environment

Paul C. West,¹* James S. Gerber,¹ Peder M. Engstrom,¹ Nathaniel D. Mueller,² Kate A. Brauman,¹ Kimberly M. Carlson,¹ Emily S. Cassidy,³ Matt Johnston,¹ Graham K. MacDonald,¹ Deepak K. Ray,¹ Stefan Siebert⁴

Achieving sustainable global food security is one of humanity's contemporary challenges. Here we present an analysis identifying key "global leverage points" that offer the best opportunities to improve both global food security and environmental sustainability. We find that a relatively small set of places and actions could provide enough new calories to meet the basic needs for more than 3 billion people, address many environmental impacts with global consequences, and focus food waste reduction on the commodities with the greatest impact on food security. These leverage points in the global food system can help guide how nongovernmental organizations, foundations, governments, citizens' groups, and businesses prioritize actions.

ustainably meeting global food demands is one of humanity's grand challenges and has attracted considerable attention in the past few years (1–7). However, there have been few attempts to systematically test the effectiveness of potential strategies and identify where to target different proposed solutions. In particular, finding whether proposed solutions can truly scale to the global scope of the problem remains a challenge.

In this study, we aimed to identify a small set of regions, crops, and actions that provide strategic global opportunities to increase yields, reduce the environmental impact of agriculture, and deliver food more efficiently from what is already grown. In order to identify these "leverage points" where interventions would have a high global impact in one or more of the three categories, we used recently published geospatial data and models to analyze how specific issues at the nexus of agriculture and the environment vary across the globe.

We focused our analysis on 17 key global crops (table S1), composing the 16 highest-calorie– producing crops consumed as food, as well as cotton, because of its intensive water and nutrient use. These 17 crops cover 58% of the global cropland area harvested and produce 86% of the world's crop calories. They also account for most resource use on croplands: 95% of irrigated area, 92% of irrigation water consumption, and ~70% of all nitrogen and phosphorus application. The percentages in the main text are all relative to the 17 major crops. Additional details for individual crops and methods are provided in the supplementary materials (8).

One goal for achieving future food security is to grow more food on the existing land base in ways that limit additional pressure on natural ecosystems (*9–11*). Current yields are 50% below realistically attainable potentials in many regions of the world (*3, 12*). This difference between the current and attainable yields is commonly referred to as the "yield gap" (*3, 9*). To assess possible production increases on existing croplands, we calculated the yield gap using previously developed methods (*3, 13*). Increasing yields in low-performing areas by closing the yield gap to 50% of attainable yields (Fig. 1) could increase total production by 358 megatons per year [8.5×10^{14} kilocalories (kcal)] (table S2, A and B), which is enough calories to meet the basic needs of ~850 million people.

These potential gains from closing the yield gap to 50% are not evenly distributed. For example, half of these potential gains are concentrated in only ~5% of the total harvested area for these crops. Approximately 92% of these gains $(4.3 \times 10^{14} \text{ kcal})$ are in Africa (43%), Asia (29%), and Europe (mainly eastern) (20%) (table S2C). Maximizing calorie gains is essential for improved food security, but nutrition, access, and cultural preferences must also be addressed. Further, the yield gap estimates are based on current yield and climate conditions. Climate change will generally decrease mean yields (*14*) and thus probably also change the magnitude and possibly the location of leverage points.

Although humanity needs to produce more food to meet future demand, agriculture is the major driving force on the planet for greenhouse gas (GHG) emissions (7, 15), water quality degradation from soil loss and nutrient runoff (16), and water use (17). Prioritizing a small set of leverage points could greatly increase the efficiency and sustainability of food production.

Agriculture accounts for 20 to 35% of global GHG emissions (7, 15). The largest sources of agricultural GHGs are carbon dioxide (CO₂) from tropical deforestation, methane (CH₄) from livestock and rice production, and nitrous oxide (N2O) from nutrient additions to croplands (7, 15). The bulk of GHG emissions from croplands are concentrated in just a few countries. Approximately 51% of 2000-2012 tropical deforestation (in areas with >50% tree canopy cover) occurred in Brazil (34%) and Indonesia (17%) (18). Deforestation in these countries is linked mainly to timber, cattle, and soy production in Brazil (19) and oil palm and wood plantations in Indonesia (20). Similarly, methane emissions from rice cultivation are produced mainly in China (29%) and India (24%) (21).

For N_2O , we estimated the distribution of emissions from major crops using the Intergovernmental Panel on Climate Change Tier 1 approach



Fig. 1. Increasing crop production from closing the yield gaps to 50% of potential yields. Increasing yields to 50% of the potential yield in all low-performing areas could increase annual production by 8.46×10^{14} kcal, which is enough to meet the basic caloric requirements of ~850 million people. Further, half of these potential gains (4.2×10^{14} kcal) are concentrated in only 5% of the harvested area for the 17 crops analyzed here.

¹Institute on the Environment, University of Minnesota, St. Paul, MN 55108, USA. ²Center for the Environment, Harvard University, Cambridge, MA 02138, USA. ³Environmental Working Group, Washington, DC 20009, USA. ⁴Institute of Crop Science and Resource Conservation, University of Bonn, Katzenburgweg 5, D-53115 Bonn, Germany. *Corresponding author. E-mail: pcwest@umn.edu



Fig. 2. Leverage points to reduce agriculture's effect on climate, water quality, and water consumption. The majority of global environmental effects of agriculture are in a few countries, driven by a few commodities. All nutrient and irrigation values are relative to the 17 major crops in this study. Figures S1 to S3 provide maps of N₂O emissions, nutrient input and excess, and water consumption, respectively. Irrigation consumption is relative only to precipitation-limited areas.

(22), with data sets of global fertilizer and manure use, atmospheric nitrogen deposition, and crop nitrogen fixation (8). We find that China, India, and the United States contribute 56% of all N₂O emissions from croplands, with 28% coming from China alone. Three crops (wheat, maize, and rice) account for 68% of global N₂O emissions from the 17 major crops analyzed here (table S3A). These results highlight the fact that agriculture's biogeochemical influence on global climate is not evenly distributed and that there are several key leverage points for reducing GHG emissions. Fortunately, regional efforts have been effective at reducing CO_2 from deforestation (23), and similar strategies are proposed for reducing N2O and CH_4 in other regions (15, 24).

Although nutrient inputs on farmland are needed to grow crops, nutrient loss from agricultural areas is a major source of pollution for freshwater and coastal ecosystems (*16*). We estimated the amount of excess nutrient application (defined as the difference between rates of nutrient input versus nutrient removal from plant harvesting) for the 17 major crops using a simple nutrient mass balance model and spatial data sets for each of the nutrient inputs and outputs (*8*). Across the 17 crops, we find that ~60% of nitrogen and ~48% of phosphorus inputs are in excess (table S3, A and B, and fig. S2).

Excess nutrients are not evenly distributed across regions or crops. We find that ~50% of the excess nitrogen and phosphorus is concentrated in only 24% and 21% of the world's cropland area, respectively. China, India, and the United States together account for ~64 to 66% of excess nitrogen and phosphorus (Fig. 2 and fig. S2). Furthermore, rice, wheat, and maize alone are responsible for ~58 to 60% of the excess nitrogen and phosphorous of the 17 crops we analyzed globally. Using a yield-response model (*I3*), we estimate that nitrogen and phosphorus applied to wheat, rice, and maize could be reduced by 14 to 29% and 13 to 22%, respectively, while maintaining current yields (table S3). Targeting reductions in fertilizer use to a small set of crops and countries could therefore have a large effect on global nitrogen and phosphorus pollution. Further efficiency gains are possible by altering the timing, placement, and type of fertilizer (*25*).

Irrigation accounts for ~70% of global water withdrawals and ~90% of water consumption and is frequently a driver of water stress (*17*). To identify hot spots of irrigation use, we used spatially explicit, crop-specific irrigation data (*6*). We restricted the analysis to precipitationlimited areas, defined here as places where potential evapotranspiration exceeds precipitation.

We find that India, Pakistan, China, and the United States account for 72% of all irrigation water used in precipitation-limited areas, with India alone accounting for 36% (fig. S3) (8). However, water productivity varies widely among countries. For example, although China consumes 13% of irrigation in precipitation-limited areas, it is responsible for just 2% of irrigation consumption in systems with very low water productivity (below the 20th percentile). Raising very low water productivity in precipitationlimited regions up to the 20th percentile has the potential to decrease water consumption by about 8 to 15% while keeping food production constant (26).

Relative to the 17 major crops, rice and wheat together cover 63% of the total irrigated area and

consume 59% of irrigation water globally. Cotton, maize, and sugarcane use an additional 30% of total irrigation water. Despite covering only 3% of cropland area globally, sugarcane and cotton are the most water-intensive crops, with mean irrigation water consumption that is 2.4 and 1.6 times, respectively, the amount used for each hectare of wheat (table S4).

Meat and dairy consumption is increasing globally and generally increases with wealth (11, 27). Between 1961 and 2009, the percentage of calories from crop production consumed as food decreased from 57 to 51% (fig. S4). Although crops used for animal feed ultimately produce human food in the form of meat and dairy products, they do so with a substantial loss of caloric efficiency. If current crop production used for animal feed and other nonfood uses (including biofuels) were targeted for direct consumption, ~70% more calories would become available, potentially providing enough calories to meet the basic needs of an additional 4 billion people (28). The human-edible crop calories that do not end up in the food system are referred to as the "diet gap."

Using methods described in Cassidy *et al.* (28), Food and Agriculture Organization (FAO) Food Balance Sheets (29), and crop production data (30), we estimate that the United States, China, Western Europe, and Brazil account for 26, 17, 11, and 6% of the global diet gap, respectively (fig. S5). Changing crop allocation to directly feed people in these four regions alone could provide enough calories to meet the basic needs of 2.4 billion people. Maize represents the largest potential gain, accounting for 41% of the global diet gap. Maize in the United States accounts for 19%

Food	Calorie supply (29) (kcal per capita day ⁻¹⁾	Consumer food waste (<i>31</i>) (% and kcal per capita day ⁻¹)	Embodied feed in calorie waste (kcal per capita day ⁻¹)	Harvested area required to support waste (m ² per capita year ⁻¹⁾
United States	3688*			
Wheat and rice	693	27% (187)	_	65
Vegetables	76	28% (21)	-	8
Beef	110	11% (12)	278	43
Pork	132	11% (15)	136	21
Poultry	193	11% (21)	199	31
China	3036†			
Wheat and rice	1380	20% (276)	_	59
Vegetables	205	15% (31)	_	10
Beef	27	8% (2)	33	9
Pork	355	8% (28)	178	47
Poultry	59	8% (5)	30	8
India	2321‡			
Wheat and rice	1168	3% (35)	_	14
Vegetables	46	7% (3)	_	3
Beef	5	4% (<1)	3	2
Pork	3	4% (<1)	1	1
Poultry	6	4% (<1)	2	2

Table 1. Calories lost to consumer food waste and associated land requirements for key food commodities in the United States, India, and China.

*22% from cereals, with the remainder mostly a mix of vegetable oils, sweeteners, meat, and dairy. meat, vegetables, oils, and starchy roots. \$57% from cereals, with the remainder mostly a mix of sugar, vegetable oils, dairy, and pulses.

of the global diet gap, which is enough calories for 760 million people; maize in China represents 9% of the diet gap. Although the diet gap presents opportunities to improve food security, cultural preferences and political obstacles create large challenges to reducing meat as well as overconsumption. However, adapting how these crops are used could provide short-term relief and serve as a safety net or release valve in years with high production losses from weather or pests.

Another major opportunity for increasing crop availability is to reduce food waste. Approximately ~30 to 50% of food production is wasted (31). Several broad strategies are recommended for reducing waste along different points in the supply chain, but they provide little insight into the relative impact of waste among food groups. For example, we estimate that wasting 1 kg of boneless beef has ~24 times the effect on available calories as wasting 1 kg of wheat (~98,000 kcal versus ~3800 to 4125 kcal), because of inefficiencies in converting feed to animal calories and protein (8). Wasting 1 kg of other animal products, such as poultry and pork, has a less dramatic effect on edible calorie losses. This analysis applies only to animals raised in feedlot systems.

We compared consumer food waste in the United States, China, and India to illustrate the connections among waste, diet, and crop yields. Per-capita food losses range from <3 kcal per person day⁻¹ for pork or vegetables in India to as much as 290 kcal per person day⁻¹ for beef in the United States (Table 1). Consequently, the land base required to support this waste is ~7 to 8 times greater in the United States than in India. Curbing consumer waste of major food crops

(i.e., wheat, rice, and vegetables) and meats (i.e., beef, pork, and poultry) in these three countries alone could feed ~413 million people year⁻¹ if the feed calories embodied in meat are included (8). This illustration demonstrates that small changes in the consumption and waste of animal products could have a large effect on available calories.

The challenges and opportunities for improving global food security and the environment are not evenly distributed across the globe. The analyses here illustrate, in principle, what is possible and where to focus such possible actions. Local and regional successes in any of these leverage points can have national or global impact, and provide examples of increasing food production, reducing deforestation, and managing water and nutrients more efficiently. Additional analysis is needed to estimate how the leverage points identified here may change in response to changes in climate, diet, technology, and markets. Although this large-scale analysis is useful for identifying the major leverage points to create a more sustainable food system, there are many other regional and global factors that would need to be included to address food security and environmental sustainability-and the tradeoffs among the many ecosystem services in agricultural landscapesmore holistically.

More work is needed for the widespread adoption of best practices by adapting current successful approaches to local socioeconomic and environmental conditions, within the context of a changing climate. Fortunately, many institutions, including NGOs, foundations, governments, citizens' groups, and businesses, are committed to improving global and local food security while reducing environmental harm. The leverage points presented here represent a relatively small set of regions, crops, and actions that could provide additional food to a growing world, as well as address a sizeable fraction of agriculture's global environmental impact.

REFERENCES AND NOTES

- International Assessment of Agricultural Knowledge, Science, and Technology for Development, *Agriculture at a Crossroads* (Island Press, Washington, DC, 2009).
- The Royal Society, Reaping the Benefits: Science and the Sustainable Intensification of Global Agriculture (The Royal Society, London, 2009).
- 3. J. A. Foley et al., Nature 478, 337-342 (2011).
- 4. H. C. J. Godfray et al., Science 327, 812-818 (2010).
- J. Kearney, Philos. Trans. R. Soc. London Ser. B 365, 2793–2807 (2010).
- S. Siebert, P. Döll, J. Hydrol. (Amst.) 384, 198–217 (2010).
 S. J. Vermeulen, B. M. Campbell, J. S. I. Ingram, Annu. Rev.
- S. J. Verneuren, B. M. Campbell, J. S. I. Ingram, Annu. R Environ. Resour. **37**, 195–222 (2012).
 Materials and methods are available as supplementary
- Materials and methods are available as supplementary materials on *Science* Online.
 K. G. Cassman, A. Dobermann, D. T. Walters, H. Yang
- K. G. Cassman, A. Dobermann, D. T. Walters, H. Yang, Annu. Rev. Environ. Resour. 28, 315–358 (2003).
 P. C. West et al., Proc. Natl. Acad. Sci. U.S.A. 107, 19645–19648
- (2010). 1 D. Tilman C. Balzer, I. Hill, B. L. Befort, Proc. Natl. Acad. Sci. U.S.A.
- D. Tilman, C. Balzer, J. Hill, B. L. Berort, *Proc. Natl. Acad. Sci. U.S.A* 108, 20260–20264 (2011).
 D. B. Lobell, K. G. Cassman, C. B. Field, *Annu. Rev.*
- D. D. Lobell, N. d. Cassman, C. D. Heid, Anna. Rev. Environ. Resour. 34, 179–204 (2009).
 N. D. Mueller et al., Nature 490, 254–257 (2012).
- 14. A. J. Challinor et al., Nat. Clim. Change 4, 287–291 (2014).
- 15. P. Smith et al., Philos. Trans. R. Soc. London Ser. B 363, 789–813 (2008).
- 16. S. R. Carpenter et al., Ecol. Appl. 8, 559-568 (1998).
- P. H. Gleick, H. Cooley, M. Morikawa, The World's Water 2008-2009: The Biennial Report on Freshwater Resources (Island Press, Washington, DC, 2009).
- M. C. Hansen *et al.*, *Science* **342**, 850–853 (2013).
 D. C. Morton *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 1007
- 14637–14641 (2006). 20. K. M. Carlson et al., Nat. Clim. Change **3**, 283–287 (2013).
- X. Yan, H. Akiyama, K. Yagi, H. Akimoto, Global Biogeochem. Cycles 23, n/a (2009).

- C. De Klein et al., in 2006 IPCC Guidelines for National Greenhouse Gas Inventories (Intergovernmental Panel on Climate Change, IGES, Hayama, Japan, 2006), vol. Technical, chap. 11, p. V4.
- M. N. Macedo et al., Proc. Natl. Acad. Sci. U.S.A. 109, 1341–1346 (2012).
- W.-F. Zhang et al., Proc. Natl. Acad. Sci. U.S.A. 110, 8375–8380 (2013).
- R. T. Venterea et al., Front. Ecol. Environ 10, 562–570 (2012).
- K. A. Brauman, S. Siebert, J. A. Foley, *Environ. Res. Lett.* 8, 24030 (2013).
- T. Kastner, M. J. I. Rivas, W. Koch, S. Nonhebel, Proc. Natl. Acad. Sci. U.S.A. 109, 6868–6872 (2012).
- E. S. Cassidy, P. C. West, J. S. Gerber, J. A. Foley, *Environ. Res. Lett.* 8, 034015 (2013).
- FAO, Food Balance Sheets (FAO, Rome, 2011); http://faostat. fao.org/site/368/default.aspx#ancor.

- C. Monfreda, N. Ramankutty, J. Foley, *Global Biogeochem.* Cycles 22, GB1022 (2008).
- J. Gustavsson, C. Cederberg, U. Sonesson, R. van Otterdijk, A. Meybeck, *Global Food Losses and Food Waste: Extent, Causes and Prevention* (FAO, Rome, 2011).

ACKNOWLEDGMENTS

This research greatly benefited from discussions with J. Foley. S. Carpenter, and E. Bennett, and three anonymous reviewers provided critical feedback that strengthened this paper. Research support was primarily provided by the Gordon and Betty Moore Foundation. Additional research support was from the Institute on the Environment, NASA's Interdisciplinary Earth Science program and Laurel Salton Clark Memorial Fellowship, the McKnight Foundation, the Grantham Foundation, the World Wildlife Fund, the Nature Conservancy, and Stanford University. NSF provided support for N.D.M. The Natural Sciences and Engineering Research Council of Canada provided support for G.K.M. Contributions by General Mills, Mosaic, Cargill, Pentair, Google, Kellogg's, Mars, and PepsiCo supported stakeholder outreach and public engagement. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. Additional data and method details are provided in the supplementary materials.

SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/345/6194/325/suppl/DC1 Materials and Methods Figs. S1 to S5 Tables S1 to S4 References (32–53) 16 September 2013; accepted 17 June 2014 10.1126/science.1246067

ALTERNATIVE SPLICING

Human tRNA synthetase catalytic nulls with diverse functions

Wing-Sze Lo,^{1,2} Elisabeth Gardiner,^{3,4} Zhiwen Xu,^{1,2} Ching-Fun Lau,^{1,2} Feng Wang,^{1,2} Jie J. Zhou,^{1,2} John D. Mendlein,⁴ Leslie A. Nangle,⁴ Kyle P. Chiang,⁴ Xiang-Lei Yang,^{1,3} Kin-Fai Au,⁵ Wing Hung Wong,⁶ Min Guo,⁷ Mingjie Zhang,^{1,8} Paul Schimmel^{1,3,7*}

Genetic efficiency in higher organisms depends on mechanisms to create multiple functions from single genes. To investigate this question for an enzyme family, we chose aminoacyl tRNA synthetases (AARSs). They are exceptional in their progressive and accretive proliferation of noncatalytic domains as the Tree of Life is ascended. Here we report discovery of a large number of natural catalytic nulls (CNs) for each human AARS. Splicing events retain noncatalytic domains while ablating the catalytic domain to create CNs with diverse functions. Each synthetase is converted into several new signaling proteins with biological activities "orthogonal" to that of the catalytic parent. We suggest that splice variants with nonenzymatic functions may be more general, as evidenced by recent findings of other catalytically inactive splice-variant enzymes.

minoacyl tRNA synthetases (AARSs) establish the genetic code by esterifying specific amino acids to the 3' ends of their cognate tRNAs (1–5) and have adaptations of this reaction for specific physiological responses (6). A few literature examples show that natural proteolysis or alternative splicing of AARS can reveal previously unknown AARS proteins (7, 8) with new functions (9–11). With this in mind, we investigated potential mechanisms for achieving

*Corresponding author. E-mail: schimmel@scripps.edu

genetic efficiency through functional expansions. The enzymes are divided into two classes of 10 proteins each, with each class being defined by the architecture of the highly conserved catalytic domain (CD) that is retained through evolution (12-14). As the Tree of Life is ascended, 13 new domains, which have no obvious association with aminoacylation or editing, have collectively been added to AARSs and maintained over the course of evolution, with no appreciable benefit or detriment to primary function (15-17). The extent of these domain additions appears to be particular to AARSs (15). Some of these new domains are appended to each of several synthetases, whereas others are specific to a single synthetase. Notably, these novel domain additions are accretive and progressive; and while their persistence provides no major benefit to aminoacylation, the strong evolutionary pressure for their retention suggests they are not random functionless stochastic fusions, but may be conserved for a specific biological purpose, perhaps distinct from the canonical enzymatic function.

We made a comprehensive search for alternative splice variants of AARSs to understand how splicing changes the domain organization

and underlying architecture of each synthetase. We selectively targeted the AARS family of genes by enriching the AARS transcriptome in six distinct human samples [human fetal and adult brain, primary human leukocytes, and three cultured leukocyte cell types (Raji B cells, Jurkat T cells, and THP1 monocytes)]. A polymerase chain reaction (PCR)-based gene-capture and enrichment method was integrated with high-throughput deep sequencing to increase sequencing depth for each AARS transcript (materials and methods and Fig. 1A). This methodology allowed for high enrichment of AARS mRNAs and mainly targeted exon-exon junctions for discovery of exon-skipping events. We defined the AARS transcriptome as the transcripts of 37 AARS genes, including those for 17 cytoplasmic synthetases, 17 mitochondrial synthetases, and 3 that encode both cytoplasmic and mitochondrial forms. For efficient capture, transcripts were amplified by multiplex PCR using AARS gene-specific primers and optimized PCR conditions (see materials and methods). Sensitive detection of low-abundance splice variants was achieved with an optimized multiplex PCR that amplified gene regions close to exon-exon junctions of AARS transcripts and produced short PCR fragments (Fig. 1A). Fragments were assembled into cDNA libraries and sequenced by high-throughput deep sequencing (18, 19).

Approximately 42 million 50-base reads were obtained and analyzed, using established methods (19). About 70% (30.4 million) mapped to the 37 AARS genes, and about two-thirds of the AARS-specific reads (21.4 million) covered AARS exon-exon junctions. When compared to previously published whole-transcriptome studies (20, 21). the AARS transcriptome enrichment method employed here successfully improved sequencing depth so that we could detect all of the 61 previously reported exon-exon junctions for AARS transcripts, as well as identify 248 previously unreported junctions (Fig. 1B and table S1). These new splice forms allowed for the ablation of specific coding regions and simultaneous creation of new exon-exon junctions.

In addition, the tissue origin and the overlap of AARS splice variants in different tissues were examined. Although there was obvious tissue

¹IAS HKUST–Scripps R&D Laboratory, Institute for Advanced Study, Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, China, ²Pangu Biopharma, Edinburgh Tower, The Landmark, 15 Queen's Road Central, Hong Kong, China. ³The Scripps Laboratories for tRNA Synthetase Research. The Scripps Research Institute, 10650 North Torrey Pines Road, La Jolla, CA 92037, USA. ⁴aTyr Pharma, 3545 John Hopkins Court, Suite 250, San Diego, CA 92121, USA. ⁵Department of Internal Medicine, University of Iowa, Iowa City, IA 52242, USA. ⁶Department of Statistics, Stanford University, Stanford, CA 94305, USA. ⁷The Scripps Laboratories for tRNA Synthetase Research, Scripps Florida, 130 Scripps Way, Jupiter, FL 33458, USA. ⁸Division of Life Science, State Key Laboratory of Molecular Neuroscience, Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, China