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Water in the Balance

James S. Famiglietti and Matthew Rodell

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Each individual was heterozygous for one de novo mutation in *LMNA*, meaning that these were new mutations (not found in the parents) that likely arose from a single nucleotide base change (*1*, *5*). However, the most common single-base mutation did not change the encoded residue. One would expect such a mutation to be silent (failing to have a mutant phenotype) rather than give rise to the severe symptoms of HGPS (*1*). It seems that the single-base change gives rise to a splice site within exon 11, resulting in the removal of 150 nucleotides from the corresponding mRNA. Consequently, this generates a 50–amino acid deletion near the carboxyl terminus of prelamin A (*4*, *5*).

The 50 amino acids that are removed by altered splicing to exon 11 include the recognition sequence for ZMPSTE24. Mice lacking the *Zmpste24* gene present many of the characteristics associated with HGPS including bone fractures, muscle weakness, and a prelamin A processing defect (*6*). Ibrahim *et al*. noted that in this mouse model of HGPS, farnesylated and methylated prelamin A accumulated in the nuclear envelope. The authors found that decreasing the efficiency of terminal methylation of prelamin A in this mouse model, resulting from the expression of a hypomorphic allele of *Icmt*, reversed progeria-like symptoms, with increased body weight, a decrease in bone fractures, and a reduction in early death. The double-mutant mice showed a restoration of normal aging, instead of the senescence associated with additional rapid cell death seen in the *Zmpste24*-null mouse. The failure of fibroblast cells in *Zmpste24*-null mice to proliferate was also suppressed by reduced expression of ICMT. Thus, of all the aspect of aging studied, mouse longevity, grip strength, and cell senescence were changed to a more normal phenotype by reducing the amount of methylated prelamin A.

Surprisingly, Ibrahim *et al*. found that the frequency of misshapen nuclei—considered a hallmark of progeroid cells—in fibroblasts carrying mutations in both *Zmpste24* and *Icmt* was not different from that of nuclei in cells lacking only *Zmpste24*. However, localization of prelamin A was altered in the double-mutant mice; it localized to the nucleoplasm rather than the nuclear envelope in hepatocytes and skeletal muscle cells. Thus, the nuclear shape abnormalities appear to have little relevance to the disease.

Although the precise mechanism by which ICMT activity exacerbates the progeroid phenotype has yet to be determined, Ibrahim *et al*. show that decreasing the amount of methylated prelamin A in the rescued mouse model of HGPS is associated with increased signaling by the AKT-mTOR pathway. This pathway promotes cell growth, proliferation, and survival. By decreasing the amount of methylated prelamin A in the rescued (double-mutant) mouse, AKT-mTOR signaling increased. The authors demonstrate interaction between prelamin A and AKT, but it is not clear if this association inhibits AKT-mTOR signaling.

In 2007, a clinical trial was launched at Boston Children's Hospital, in which 25 children aged 3 to 15 years received a farnesyltransferase inhibitor called lonafarnib for 2.5 years (*7*–*10*). The results showed modest but encouraging success that has been interpreted with caution. In 2009, another clinical trial was initiated with 45 children taking lonafarnib and two additional drugs, pravastatin and zoledronate (*7*). This combination may provide a more effective treatment than farnesyltransferase inhibitors alone, as pravastatin and zoledronate target different points in the lamin A maturation pathway (production or attachment of the farnesyl group). These two drugs themselves improved the phenotype of progeria cells and extended life span in mouse models of progeria (*7*).

That reducing isoprenylcysteine methylation pharmacologically may be helpful for children affected by HGPS is an important implication of the basic research by Ibrahim *et al*. However, treatments for this disorder are not likely to be seen soon in the medicine cabinet of most 80-year-olds, as HGPS does not cause rapid aging but mimics it (*11*). There is some evidence that progerin is produced in the body with normal aging. For example, progerin has been found in aging blood vessels (*12*), which suggests that it may play a role in cardiovascular aging. Aging is an emergent property of complex systems, and it is fascinating to see how alterations in large molecules can affect aging-like outcomes.

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ENVIRONMENTAL SCIENCE

Water in the Balance

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Satellite data may enable improved management of regional groundwater reserves.

Earth's climate is changing, and so is its hydrologic cycle. Recent decades have witnessed rising rates of global precipitation, evaporation, and freshwater discharge (*1*). Extreme flooding is occurring with greater intensity and frequency in some regions; in others, extreme drought is becoming more common (*2*). Most climate models indicate that by the end of this century, the dry regions of the world will become drier, whereas the wet areas will become wetter (*3*). Meanwhile, groundwater reserves, the traditional backup for water supplies during extended periods of drought, are in decline globally (*4*–*6*). GRACE (the Gravity Recovery and Climate Experiment, a joint U.S.-German satellite mission) monitors these variations on monthly to decadal time scales, providing detailed data on the water cycle that are an essential prerequisite for contemporary water management.

Since its launch in 2002, GRACE has mapped monthly changes in Earth's gravity field with unprecedented accuracy (*7*). The main process driving the measured gravitational variations at monthly time scales is the redistribution of water, allowing GRACE to monitor changes in freshwater resources on land. For regions of 200,000 km^2 or more, GRACE functions as a giant "scale in the sky" weighing the total amount of water (snow, surface water, groundwater, and soil moisture) that enters or leaves a region each month with

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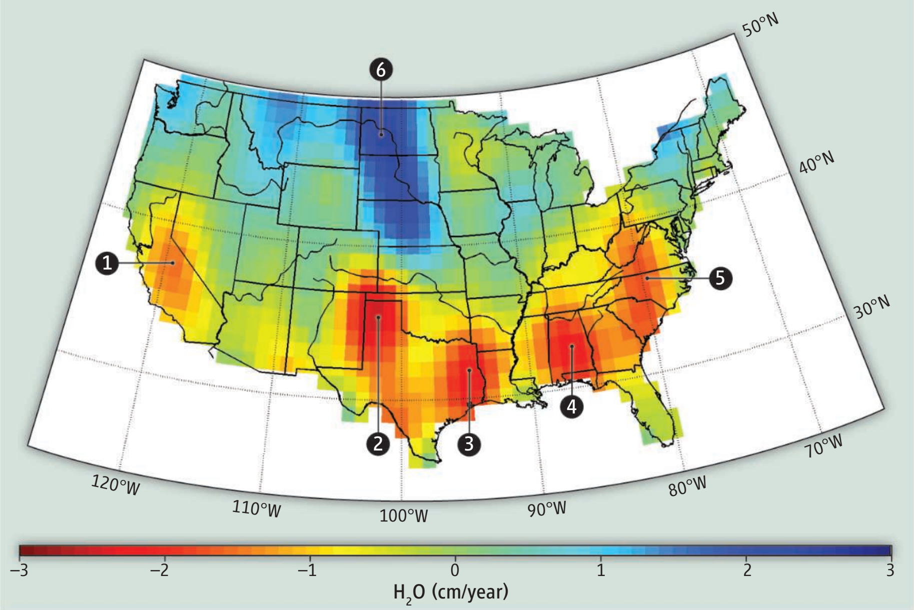

Mixed picture. Between 2003 and 2012, GRACE data show water losses in agricultural regions such as California's Central Valley (**1**) (–1.5 ± 0.1 cm/year) and the Southern High Plains Aquifer (**2**) (–2.5 ± 0.2 cm/year), caused by overreliance on groundwater to supply irrigation water. Regions where groundwater is being depleted as a result of prolonged drought include Houston (**3**) (–2.3 ± 0.6 cm/year), Alabama (**4**) (–2.1 ± 0.8 cm/year), and the Mid-Atlantic states (**5**) (–1.8 ± 0.6 cm/year). Water storage is increasing in the flood-prone Upper Missouri River basin (**6**) (2.5 ± 0.2 cm/year). See fig. S1 for monthly time series for all hot spots. Data from (*15*) and from GRACE data release CSR RL05.

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an accuracy of 1.5 cm equivalent water height.

Because GRACE measures changes in total water storage, it integrates the impacts of natural climate fluctuations, global change, and human water use, including groundwater extraction, which in many parts of the world is unmeasured and unmanaged. GRACE-derived rates of groundwater losses in the world's major aquifer systems (*4*–*6*) underscore the critical need to improve monitoring and regulation of groundwater systems before they run dry.

Regional flooding and drought are driven by the surplus or deficit of water in a river basin or an aquifer, yet few hydrologic observing networks yield sufficient data for comprehensive monitoring of changes in the total amount of water stored in a region. GRACE observations have helped to fill this gap. They have been used to characterize regional flood potential (*8*) and to assess water storage deficits in the U.S. Drought Monitor (*9*) and are included in annual State of the Climate reports (*10*). As an integrated measure of all surface and groundwater storage changes, GRACE data implicitly contain a record of seasonal to interannual water storage variations that can likely be exploited to lengthen early warning periods for regional flood and drought prediction (see the figure).

The lack of comprehensive measurements also makes large-scale hydrological models, key tools for predicting future water availability, difficult to validate. Low-resolution GRACE data, when combined with higher-resolution model simulations, provide an independent constraint on simulated water balances, while also adding spatial detail to GRACE's low-resolution perspective (*11*). They are widely used to evaluate land surface models used by weather and climate forecasting centers around the world (*12*).

Evapotranspiration is a key factor in interbasin water allocations, yet because it disperses into the atmosphere in the vapor phase, it confounds standard measurement techniques. The ability of GRACE to weigh changes in water stored in an entire river basin allows evapotranspiration to be estimated in a water balance framework (*13*).

Transboundary water availability issues require sharing hydrologic data across political boundaries. However, national hydrological records are often withheld for political, socioeconomic, and defense purposes, complicating regional water management discussions. Several studies have used GRACE data to circumvent international data denial practices, including in those involving lakes (*14*), river basins (*6*), and aquifers (*4*, *6*). Likewise, regional and global maps of emerging trends in water availability (see the figure) can underpin discussions of geopolitical water security, conflict, and water diplomacy (*6*).

Although it still collects 10 months of data per year, GRACE has long outlived its planned 5-year life span. The GRACE Follow-On (GRACE-FO) mission, planned for launch in 2017, should enable continued collection of critical water and related climate observations for at least a decade, forestalling potential data gaps before a more advanced satellite gravimetry system is developed and launched, as tentatively planned for the 2020s.

For GRACE and its successors to maximize their value for water management, key issues must be addressed. First, the current 2- to 6-month latency before GRACE data are released must be substantially reduced to enable their use in seasonal prediction. Second, GRACE data should be better integrated into the modeling and decision support systems used by operational water management centers. Finally, next-generation missions beyond GRACE-FO should aim to achieve higher spatial (<50,000 km^2) and temporal (weekly or biweekly) resolution, for example through novel orbital configurations, so that smaller river basins and aquifers can be observed directly. The availability of GRACE data at these finer scales, at which most planning decisions are made, would likely ensure their broader use in water management.

The GRACE-FO mission is on schedule for a 2017 launch, but a next-generation, improved GRACE mission is still under design and as yet unconfirmed. Given its demonstrated contributions to date and the potential for much more, a future without a GRACE mission in orbit would be an unfortunate and unnecessarily risky backward step for regional water management.

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Supplementary Materials

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Fig. S1

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