Autoimmunity by haploinsufficiency
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and a long-term commitment is required to restore or recover them.

A third implication of the multiple framings concerns the role of valuation. Most environmental decisions are made on the basis of economic arguments that consider costs and benefits, usually based on monetary values. By not having good metrics or by rejecting the idea of valuation in principle (*20*) because of its stark formulation in a "nature for people" framing, conservationists may cause nature to be excluded from such decisions. If the benefits provided by nature are assigned no value, they are treated as having no value, and current trends in the decline and deterioration of natural systems will continue.

The differences among the framings are not as stark as they appear. Despite its strong focus on humans, "people and nature" may actually be very similar to "nature for itself." Both framings can include people's hopes and desires about the environment that they wish to live in and leave to their descendants. "People and nature" has traction with other societal needs from the environment and connects better to policy because it has a broader focus. Yet there is a risk that any implementation of "people and nature" will lack the analytical foundations that made the earlier framings both deliverable and measurable.

Hopefully the many important features of "people and nature" will continue to be the focus for conservation over the coming decades. By sustaining a coherent and inclusive focus and by developing the relevant science, tools and decisions should emerge that can ensure a better future for people and nature. ■

REFERENCES

1. M. E. Soulé, *Bioscience* **35**, 727 (1985).
2. K. H. Redford *et al.*, *Conserv. Biol.* **27**, 437 (2013).
3. W. M. Adams, *Against Extinction: The Story of Conservation* (Earthscan, London, 2004).
4. J. Hutton *et al.*, *Forum Dev. Stud.* **32**, 341 (2005).
5. S. L. Pimm, G. J. Russell, J. L. Gittleman, T. M. Brooks, *Science* **269**, 347 (1995).
6. G. C. Daily, *Nature's Services: Societal Dependence on Natural Ecosystems* (Island, Washington, DC, 1997).
7. R. Costanza *et al.*, *Nature* **387**, 253 (1997).
8. A. Balmford *et al.*, *Science* **297**, 950 (2002).
9. R. K. Turner, G. C. Daily, *Environ. Resour. Econ.* **39**, 25 (2008).
10. Millennium Ecosystem Assessment, *Ecosystems and Human Well-Being: Synthesis* (World Resources Institute, Washington, DC, 2005).
11. K. H. Redford, W. M. Adams, *Conserv. Biol.* **23**, 785 (2009).
12. S. R. Carpenter *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 1305 (2009).
13. E. Ostrom, *Science* **325**, 419 (2009).
14. M. Soule, *Conserv. Biol.* **28**, 637 (2014).
15. S. H. M. Butchart *et al.*, *Science* **328**, 1164 (2010).
16. B. Fisher *et al.*, *Ecol. Appl.* **18**, 2050 (2008).
17. B. J. Cardinale *et al.*, *Nature* **486**, 59 (2012).
18. G. M. Mace *et al.*, *Trends Ecol. Evol.* **27**, 19 (2012).
19. *UN Convention on Biological Diversity: Strategic Plan for Biodiversity 2011–2020* (Montreal, 2010).
20. D. J. McCauley, *Nature* **443**, 27 (2006).

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IMMUNOLOGY

Autoimmunity by haploinsufficiency

Partial deficiency in the protein CTLA4 underlies severe autoimmune disease with incomplete penetrance

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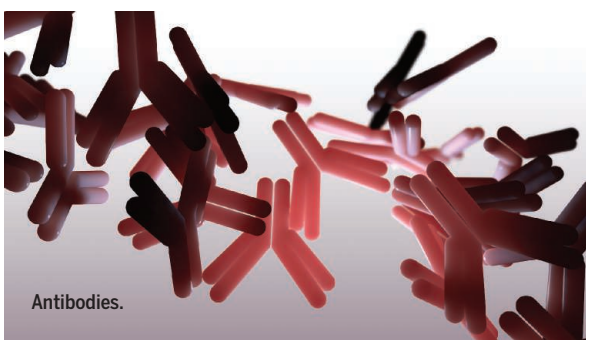
Autoimmunity arises from self-reactive T and/or B lymphocytes, and underlies a wide range of conditions, from endocrine disorders to blood cytopenias. Genetic epidemiological studies have long suggested that many autoimmune conditions have an inherited component. Autoimmunity is often described as having polygenic or complex inheritance. However, both descriptions are too general to adequately describe the considerable heterogeneity in patients and conditions. Spectacular progress in the genetic dissection of autoimmunity has come from Mendelian studies of young patients with rare, distinctive conditions. Less has been learned from population-based, genome-wide association studies of more common, clinically less homogeneous conditions. The three best-characterized monogenic autoimmune disorders are autoimmune polyendocrinopathy syndrome type 1, X-linked immunoproliferative enteropathy, and autoimmune lymphoprolierative syndrome (*1*). On page 1623 of this issue, Kuehn *et al.* (*2*) add to this list. Patients with only one functional copy of the gene encoding cytotoxic T lymphocyte antigen 4 (CTLA4) suffer from severe autoimmunity. These heterozygous mutations result in a new phenotype, with infiltration of nonlymphoid organs, such as the intestine, lungs, and brain, by hyperactive T cells and B cells, along with more classic signs of autoimmunity.

CTLA4 is expressed on the surface of T cells. It competes with CD28 to bind B7 molecules expressed on antigen-presenting cells and its activation inhibits the proliferation of effector T cells and stimulates the suppressive functions of regulatory T cells (*3*). These effects help maintain tolerance to self-antigens, as shown by the severe autoimmunity in mice lacking both copies of the *Ctla4* gene (*4*). The physiological importance of human CTLA4 was recently highlighted by the success of treatments based on CTLA4-blocking antibodies in patients with some cancers (*5*). Kuehn *et al.* report that patients heterozygous for a loss-of-function *CTLA4* allele have a phenotype similar to that of mice homozygous for a loss-of-function *Ctla4* allele, whereas heterozygous mice have no detectable phenotype (*2*, *4*). Moreover, autosomal dominant *CTLA4* deficiency displayed incomplete penetrance, as some heterozygous individuals were asymptomatic. This illustrates the similarities and differences between the small number of inbred mouse strains studied in experimental conditions and the large numbers of outbred human kindreds observed in natural conditions (*6*).



Antibodies.

Since the identification of mutations in the *ADA* gene encoding adenine deaminase as causal for severe combined immunodeficiency in 1985 (*7*), the genetic basis of more than 250 inborn errors of immunity has been determined. Studies initially focused on the conditions underlying severe infections described in the 1950s, but then shifted to the analysis of inherited forms and combinations of infection, allergy, autoinflammation, and autoimmunity (*8*).

The field of primary immunodeficiencies has also diversified considerably in terms of the modes of inheritance. The autosomal dominant pattern of inheritance is common to only about 50 immunological conditions, most of which have been discovered in the past decade. Even more unusual is the underlying mechanism of haploinsufficiency, which was first reported in 1989 for a condition called angioedema (*9*). Haploinsuf-

ILLUSTRATION: V. ALTOUNIAN/*SCIENCE*

Autosomal dominant inborn errors of immunity (haploinsufficiency)

GENE	CONDITION	PENETRANCE	DE NOVO
C1INH	Angioedema	High	Yes
CFH	HUS, glomerulonephritis, AMD	High	Yes
TERC	Dyskeratosis congenita, bone marrow failure	High	Yes
CD46	HUS	High	Yes
CFI	HUS, glomerulonephritis, AMD	High	Yes
CHD7	CHARGE syndrome and T cell immunodeficiency	**Complete**	Yes
FAS	Autoimmunity and lymphoproliferative syndrome	Intermediate*	Yes
TERT	Dyskeratosis congenita, bone marrow failure	High	No
NLRP12	Periodic fever syndrome	Complete?†	No†
GATA2	Myeloid disorders, deafness, lymphedema	High	Yes
TBK1	Herpes simplex encephalitis	Intermediate†	No†
IFNGR2	Mendelian susceptibility to mycobacterial disease	Low	No
RPSA	Isolated congenital asplenia	**Complete**	Yes
CTLA4	Autoimmunity	Intermediate	No

Autosomal dominant inborn errors of immunity for which a negative dominance was either experimentally shown or not tested were excluded. Incomplete penetrance is somewhat arbitrarily divided into low, intermediate, and high penetrance. HUS, hemolytic and uremic syndrome; AMD, age-related macular degeneration.

*Penetrant in the presence of a somatic lesion on the other *FAS* locus. †Too few kindreds to draw firm conclusions.

ficiency is defined by the occurrence of a phenotype in heterozygotes despite the lack of negative dominance of the mutant allele over its wild-type counterpart. This is less common than in other fields of human genetics and to our knowledge, only 14 inborn errors of immunity have been confirmed as autosomal dominant by haploinsufficiency. Some of them, such as isolated congenital asplenia (*10*), are actually not typical, hematopoietic-lineage restricted inborn errors of immunity.

Penetrance is incomplete for at least 11 of the 14 autosomal dominant immunological conditions involving haploinsufficiency (see the table). Indeed, haploinsufficiency favors incomplete penetrance more so than dominant negative mutations, given the predicted 50% residual function of the gene product. To date, only the mutations in chromodomain helicase DNA binding protein 7 (CHD7) and ribosomal protein SA (RPSA), which underlie the haploinsufficiency autoimmune disorders called CHARGE syndrome and isolated congental asplenia, respectively, have been convincingly shown to display complete penetrance, but even then, sometimes in association with marked variations in expression (*CHD7*). The observed proportion of de novo mutations (those that arise in a patient's parental germ cell) increases with both the degree of penetrance and the impact of the phenotype on reproduction.

So, what accounts for the incomplete penetrance of CTLA4 haploinsufficiency? Modifier genes as well as environmental factors may be involved. Somatic events may also play an important role, as already shown for haploinsufficiency in FAS, a protein that triggers cell death in activated T and B cells. Surprisingly, somatic *FAS* mutations alone can underlie a condition that is phenotypically similar to autoimmune lymphoproliferative syndrome, which is often caused by germline *FAS* mutations (*11*–*13*). Even more surprisingly, somatic mutations of the second *FAS* allele, or somatic uniparental isodisomy of large regions encompassing the second *FAS* allele (a person harbors two copies of a chromosome segment from one parent only as a result of duplication-deletion events in somatic cells), have been found in symptomatic individuals with autosomal dominant FAS deficiency by haploinsufficiency, but not in those without symptoms (*14*). This suggests that most, if not all, individuals truly heterozygous for a single loss-of-function, nondominant negative mutation of *FAS* require a second, somatic *FAS* lesion for expression of the disease. Somatic variants of *CTLA4*, or of other genes, may also influence the penetrance of autosomal dominant CTLA4 deficiency.

Incomplete penetrance does not imply the absence of a causal relationship between the *CTLA4* genotype and the autoimmune phenotype. On the contrary, it suggests that more common forms of autoimmunity may consist of a myriad of rare monogenic lesions driving disease by haploinsufficiency and with incomplete penetrance. Instead of a polygenic theory of autoimmunity that involves multiple common alleles in an individual patient, we can consider a monogenic theory of autoimmunity, with high locus and allelic heterogeneity at the population level (*15*). Heterozygous, haploinsufficient variants would play an important role in this scenario, given that they account for a higher proportion of variants and have a lower penetrance than dominant negative variants. Of course, monoallelic lesions are more common and less penetrant than biallelic lesions. This would be consistent with the non-Mendelian pattern of inheritance observed for most autoimmune diseases in most families. A condition with strict Mendelian inheritance, as defined by complete penetrance of a monogenic lesion in all genetic backgrounds, is more an exception than a rule, as humans are not single-gene organisms protected against somatic changes and environmental pressure. Although rarely Mendelian, autoimmunity in the general population may therefore often be monogenic—that is, polygenic with a single pilot, one or more co-pilots, and many passengers. Fortunately, a monogenic architecture of autoimmunity would be amenable to in-depth experimental investigation. Causal relationships that are proposed without a clear demonstration of the underlying mechanisms rarely stand the test of time. ■

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REFERENCES

1. M. H. Cheng, M. S. Anderson, *Annu. Rev. Immunol.* **30**, 393 (2012).
2. H. S. Kuehn *et al.*, *Science* **345**, 1623 (2014).
3. M. F. Krummel, J. P. Allison, *J. Exp. Med.* **182**, 495 (1995)
4. P. Waterhouse *et al.*, *Science* **270**, 985 (1995).
5. X. Fan, S. A. Quezada, M. A. Sepulveda, P. Sharma, J. P. Allison, *J. Exp. Med.* **211**, 715 (2014).
6. J. L. Casanova, L. Abel, L. Quintana-Murci, *Cold Spring Harb. Symp. Quant. Biol.* **78**, 157 (2013).
7. D. T. Bonthron, A. F. Markham, D. Ginsburg, S. H. Orkin, *J. Clin. Invest.* **76**, 894 (1985).
8. J. L. Casanova, L. Abel, *Science* **317**, 617 (2007).
9. T. Ariga *et al.*, *J. Clin. Invest.* **83**, 1888 (1989).
10. A. Bolze *et al.*, *Science* **340**, 976 (2013).
11. F. Rieux-Laucat *et al.*, *Science* **268**, 1347 (1995).
12. G. H. Fisher *et al.*, *Cell* **81**, 935 (1995).
13. E. Holzelova *et al.*, *N. Engl. J. Med.* **351**, 1409 (2004).
14. A. Magerus-Chatinet *et al.*, *J. Clin. Invest.* **121**, 106 (2011).
15. J. K. Pritchard, *Am. J. Hum. Genet.* **69**, 124 (2001).

10.1126/science.1260791