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Life in Deserts: The Genetic Basis of Mammalian Desert Adaptation

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Abstract

Deserts are among the harshest environments on Earth. The multiple ages of different deserts and their global distribution provide a unique opportunity to study repeated adaptation at different timescales. Here, we summarize recent genomic research on the genetic mechanisms underlying desert adaptations in mammals. Several studies on different desert mammals show large overlap in functional classes of genes and pathways, consistent with the complexity and variety of phenotypes associated with desert adaptation to water and food scarcity and extreme temperatures. However, studies of desert adaptation are also challenged by a lack of accurate genotype–phenotype–environment maps. We encourage development of systems that facilitate functional analyses, but also acknowledge the need for more studies on a wider variety of desert mammals.

Deserts: Natural Laboratories for Studies of Adaptation

Deserts (see Glossary) are the driest environments on the planet and cover at least 33% of the land surface on Earth [1]. Although mainly characterized by aridity and water scarcity, deserts also experience daily and annual extreme thermal amplitudes, and intense UV radiation [1] Deserts have long been seen as natural laboratories for investigating how biological design is challenged by different aspects of the environment, and how organisms

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have adapted to these challenges [1,2]. They also offer unique opportunities to study **convergent evolution** at distinct points in time and space, given their well-documented geological age and diverse geographical origins [1,2].

The main challenges to life in deserts are maintaining body temperature and preserving water [2]. This is particularly difficult for species that rely heavily on evaporative water loss mechanisms (e.g., sweating, panting, and salivation) for dissipating heat [2,3]. Exposure to heat stress combined with water shortage in hot deserts triggers several pathophysiological processes resulting in heat exhaustion, heat stroke, and kidney dysfunction [1,4,5]. Exposure to extreme low temperatures in cold-arid deserts, or at night/winter in hot deserts, can lead to hypothermia [2]. The organismal responses required to survive these extreme conditions for multiple generations are usually outside the range of the **plastic responses** of most non-desert species. Thus, it is generally presumed that desert-adapted species likely experienced strong selection acting on various complex **phenotypes** related to metabolism and water retention [1,2,6-8].

While desert adaptation has been subject to much research in evolutionary ecology, there have been relatively few investigations on the underlying genetic basis of desert adaptive traits However, newly emerging research on desert mammalian case studies is contributing to our understanding of the role of past climatic processes, such as desertification, in driving **adaptation**. In this review, we focus on this nascent research field. We review different methods and synthesize current genomic work in mammalian systems. We then explore the limits and future potential of using genomics to address desert adaptation and provide explicit recommendations for future research.

Detecting Adaptation

The recurrence of diverse complex adaptive phenotypes across diverse desert organisms (Box 1 for examples) leads to a fundamental interest in their underlying genetic basis. Enabled by increasingly cost-effective sequencing technologies and computational resources for data analysis, researchers may rely on numerous methods that were designed to identify regions associated with selection, the footprints of adaptation, from large genomic data sets [9,10]. The choice of the sequencing and analytical approach should be guided by knowledge of the ecological and evolutionary context of the species, and by the possibility of biological sampling infrastructures in remote arid regions.

Population-Specific Desert Adaptation

Methods in **population genomics** are designed to detect population-specific signatures of ongoing or recent natural selection ([9,10] for detailed reviews). These methods require genome-wide sequencing or high-density SNP sampling to ensure statistical power to detect signatures of selection against a background of neutral variation [9,10]. Some methods focus on finding genomic regions with high allele frequency differentiation between one or more populations (F_{ST} scans) [11]. These methods are useful when the background genome-wide differentiation between desert and non-desert populations is relatively low (e.g., global F_{ST} <0.2; Figure 1A) [12,13]. Such evolutionary context is necessary to be able to detect

variants targeted by selection that are still segregating in the desert population (Figure 1A). Other methods can be applied to a single desert population and identify genomic regions of reduced diversity, skewed allele frequency distribution, increased haplotype homozygosity (haplotype-based) [14,15], or combinations thereof, all of which could be signatures of **selective sweeps** [9,10]. These approaches have been used to detect selection in different desert-dwelling mammals [12,13,16-18], and we highlight some specific examples herein.

Following domestication ~8000–9000 years ago (yra), sheep (*Ovis aries*) rapidly adapted to diverse agroecological zones with extreme conditions [13], including the 5.3 million-year-old cold-arid Taklamakan desert (northwest China) [19]. To find signatures of selection in native sheep of the Taklamakan and sheep from neighboring cold-arid zones, Yang *et al.* [13] focused on genomic regions with reduced variability, haplotype-based methods, and F_{ST} scans, comparing them with sheep inhabiting humid environments. These combined approaches allowed the identification of putatively selected regions harboring genes from the renin-angiotensin-aldosterone system (RAAS) and oxytocin and arachidonic acid metabolism pathways in Taklamakan sheep [13]. Similar methods on hot-desert fat-tail sheep breeds and goats (*Capra hircus*) identified many candidate regions spanning genes and/or pathways significantly enriched for fat metabolism, insulin signaling, kidney function, oxidative stress and DNA repair, response to heat and UV radiation, body size development, and melanogenesis [17,20].

Species of the genus *Peromyscus* have also been used in case studies in population genomics as examples of rapid environmental/ecological differentiation [18,21]. Different arid-dwelling species repeatedly evolved during the radiation of the genus in North America. An example is the Cactus mouse (*Peromyscus eremicus*) from southern California, which may have adapted to local desert conditions following the recent onset of southwestern hot-deserts ~10 000 yra [18,22], although it is not clear whether its immediate ancestor was also desert adapted. Genomic scans for selective sweeps in *P. eremicus* identified hundreds of genetic variants significantly under selection upstream and/or downstream of genes involved in the synthesis and degradation of proteins, sensory perception of bitter taste, and lipid metabolism [18].

Following the emergence of modern humans at least 100 000 yra, our species rapidly spread inside and out of Africa and came to inhabit some of the most inhospitable environments on Earth, including deserts [23,24]. Although life in deserts has clearly been facilitated by cultural changes and by innovations, such as clothing, fire, water/food storage, and hunting techniques [23-31], some human desert populations also appear to have adapted biologically to their environment (Box 2).

Species-Specific Desert Adaptation

When all living populations of a species descend from a desert-adapted ancestor, population-based methods may not be successful at identifying regions associated with desert adaptation. An alternative is to use methods in **comparative genomics**, which can detect selection specific to desert species by comparing them to divergent, but related, species that are not desert specialists (Figure 1B). Some of these methods focus on finding regions

with an increased nonsynonymous:synonymous substitutions ratio (dN/dS) in desert species, which can be signatures of positive selection [32-39]. Other studies focus on identifying changes in gene copy number, which may have been the result of natural selection, using models that take into account branch lengths on phylogenetic trees [18,32,34,40].

For example, species of the genus *Camelus* are desert specialists descended from a desert-dwelling ancestor that diverged from south American counterparts ~16.3 million years ago (Mya) and from cattle 55–60 Mya [32]. Jirimutu *et al.* [34] found that Bactrian camels (*Camelus bactrianus/ferus*) show differences in copy number of *CYP2* genes relative to cattle and other mammals, which may contribute to the enhanced production of a vasodilator of renal preglomerular vessels that stimulates water reabsorption at the kidney [34]. This study further suggests that extra copies of *CPY2J2*, a gene associated with high-salt diets and regulation of blood pressure [34,41], may explain the ability of camels to endure large salt ingestion without developing hypertension [41] (Box 1). Evidence from dN/dS-based tests and gene family evolution revealed complex features of adaptation in both Bactrian and Dromedary camels (*Camelus dromedarius*), including strong selection in genes from the insulin-signaling pathway, fat and water metabolism, stress responses to heat, UV radiation, and airborne dust [32].

Association with Desert Phenotypes and Climatic Variables

In the earlier sections, we highlighted approaches that were designed to explicitly target genomic footprints of natural selection (Figure 1A,B). For more examples of genomic studies of mammalian desert adaptation, see Table S1 in the supplemental information online. In most studies, selection tests have been combined with gene-function annotations and **gene ontology enrichment (GO) analysis** to make functional connections, which may or may not be related to some of the desert-related phenotypes that have been described over decades of ecophysiological research (Box 1 and Figure 1D). These methods are phenotype independent, as they do not require simultaneous sampling of both genomic and phenotypic data. Therefore, they are logistically simple to carry out, but the resulting findings are often difficult to relate directly to specific phenotypes.

To directly relate desert-adaptive phenotypes to variants at the genetic level, **genome-wide association studies (GWAS)** can be combined with selection studies to identify genetic variants affecting specific traits of interest [42]. Similar approaches, known as **genotype–environment associations (GEAs)**, can also be used to test for correlation between variants putatively under selection in desert populations and specific climatic variables of interest [13,43-45]. For example, Yang *et al.* [13] used GEAs to test for correlation between variants of Taklamakan desert sheep and precipitation, and found significant associations near candidate genes also identified with selection scans [13].

Linking **genotype** to phenotype is a general challenge in selection studies. In particular, comparative-based approaches are challenged by the fact that the candidate mutations are not segregating within a population, making further genetic studies difficult [46]. In this sense, population-based approaches have a distinct advantage in that they may identify candidate segregating variants that can be subjected to further genetic analyses,

including GWAS. However, GWAS can suffer from low power and be logistically challenging [42,47] and may not be feasible in many organisms [46]. Even when GWAS is possible (e.g., humans and model organisms), it may still be difficult to directly associate variants with specific desert adaptive traits due to **pleiotropic effects**. For example, Aboriginal Australians show signatures of selection in *KNG1*, which is involved in different physiological functions, including blood coagulation, vasodilation, induction of hypotension, natriuresis and diuresis, blood glucose levels, and nociception [12].

Gene Expression Differences and Phenotypic Plasticity

Transcriptomics can be complementary to both population and comparative genomics to identify genes associated with desert adaptation and, in contrast to GWAS, only requires sampling of blood or tissues across a few individuals (Figure 1C). Studies of desert transcriptomics have analyzed species-specific expression differences either across tissues (e.g., kidney versus spleen in banner-tailed kangaroo rat, *Dipodomys spectabilis* [36]) or distinct treatments (e.g., water-fed versus water-deprived states in *P. eremicus* [48,49]). Another approach (Figure 1Ci) has been to analyze pairwise differences in gene expression between wild-caught individuals from desert and non-desert-adapted species (e.g., desert *D. spectabilis*, desert Bailey's pocket mouse, *Chaetodipus baileyi*, and tropical forest spiny pocket mouse, *Heteromys desmarestianus* [37]) or populations (e.g., Patagonian olive mouse, *Abrothrix olivacea*, from forest and steppe [50]). Given that these studies do not control for phenotypic plasticity, they are limited in their ability to identify genetically encoded differences between populations or species. Thus, they may not identify genes underlying adaptation.

Common garden experiments are needed to control for the confounding effects of environmental conditions and plastic responses to different treatments in transcriptomics [51]. Bittner *et al.* [52] compared desert and non-desert house mice (*Mus musculus*) populations in water-fed and water-deprived conditions (Figure 1Cii), while measuring phenotypic variation in the same individuals. These analyses identified a set of co-expressed genes involved in water retention that correlated with higher blood urea and creatinine (Box 1). Bittner *et al.* [52] also demonstrated that expression changes in the plastic response of water-deprived non-desert mice were in the same direction as the genetically controlled difference between non-desert and desert mice. This points to a genetic basis for phenotypic differences in which plasticity precedes adaptation. Furthermore, the fact that desert mice have reduced expression plasticity could suggest that selection has acted to change the **norm of reaction**, hinting towards **genetic assimilation** as a possible evolutionary avenue for desert adaptation [52].

An important consideration is that, even in common garden conditions, the observed expression differences may have evolved neutrally and, thus, may not necessarily be adaptive. More importantly, it is not possible to identify genetic variation underlying expression differences through transcriptomics alone, because causal variants affecting gene expression may lie in distant enhancers or *trans*-acting factors [53].

Nevertheless, expression studies can provide molecular phenotypes associated with adaptation for further studies and may help identify molecular pathways and mechanisms underlying adaptation [51,52]. They also provide an intermediate step between genotype and organismal phenotype that provides information about the functional effects of adaptive variants and help link the results of selection studies to phenotypic variation (e.g., *BMP2* in [54]).

Convergent Evolution at the Genetic Level

Several studies of different desert mammals have identified genes, and functional classes of genes and pathways, involved in fat metabolism [17,21,32,39,55], thyroid-induced metabolism [12], salt metabolism and prevention of high blood pressure [13,16,34], insulin signaling [17,21,32,39], and water retention [13,16,17,21,32], which may provide a genetic basis for previously identified phenotypes. Such phenotypes include energy storage and enhanced use of metabolic water, reduced nonrenal water loss, low energy expenditure, ability to cope with high-salt diets without developing hypertension, adaptive tolerance to starvation and dehydration, and decreased renal water loss (Box 1 and Figure 1D). Some studies additionally identified functional categories of genes involved in stress responses (oxidative stress, DNA damage and repair, and heat stress) [13,18,32], response to radiation [32,56], dust ingestion [32], and toxic diets (perception of bitter taste [18] and xenobiotic metabolism [17,32,57]) as targets of natural selection, suggesting other biological adaptations that have not been explicitly targeted in phenotypic studies.

We synthesized the extent of overlap in gene sets and GO categories between 12 populations and/or species for which selection candidates have been previously identified, perhaps suggesting convergent evolution at the genetic level (Figure 2). For individual genes, significant overlap was mostly found among related species, such as *C. bactrianus–C. dromedarius* and arid-dwelling Asian/Taklamakan *O. aries*, possibly as the result of selection acting on inherited standing genetic variation (Figure 2A). Nonetheless, divergent ungulates [e.g., Barki sheep (*O. aries*), Yarkand deer (*Cervus elaphus yarkandensis*), and *C. bactrianus*] share significant overlap in *BMP2*, a gene involved in fat-cell differentiation in several tissues, also associated with the fat-tail phenotype [54,58-60]. This appears to support the role of localized fat as an important source of energy under scarce resources (Box 1). Even in divergent species without genome-wide significant overlap, there are some interesting observations. For example, *P. eremicus* shares with *D. spectabilis* and *C. baileyi* evidence of selection in a glucose and serum urate transporter (SLC2A9) [37,38]. Aboriginal Australians show signatures of selection at another glucose transporter (SLC2A12), involved in adaptive tolerance to dehydration [12].

There is also a remarkably high degree of significant overlap in multiple functional categories and pathways between species with very different evolutionary ages, occupying rather distinct ecological niches, with different strategies of endurance and avoidance, and in different arid regions (classified as hot-young and cold-old deserts [1]), consistent with the previously reported high overlap of adaptive phenotypes (Figure 2B). The major mechanisms shared across mammals relate to phenotypes that have been associated with adaptation to starvation and dehydration, as well as water retention at the kidney. For

instance, the highest overlap is in functional classes of genes associated with fat storage and fat metabolism, including genes that affect energy expenditures, and/or cold- and diet-induced thermogenesis [17,21,32,39,55]. Changes in genes involved in fat metabolism may relate to diverse adaptive phenotypes that result in adaptive tolerance to heat/cold (through regulation of energy expenditures and thermogenesis), dehydration (through enhanced use of metabolic water from fat) and food scarcity (energy stored in localized fat) [5,6] (Figure 1D).

In addition to fat metabolism, the strongest evidence of shared selection is in insulin signaling/response and involves genes such as glucose and serum urate transporters. Some species also share evidence of selection in pathways involved in adipocytokine signaling (implicated in insulin resistance and sensitivity) and type 2 diabetes [17,32], consistent with reported phenotypes of insulin resistance without diabetes (Box 1). Insulin resistance has relevant roles in starvation and reducing energy demands and is evolutionarily well preserved [61], suggesting that it is beneficial under selective regimes of water/food scarcity. Interestingly, desert-dwelling mammals for which changes in insulin-regulating or glucose transporter genes have been described, are clinically healthy under natural low caloric intake or low-energy diets associated with desert life, but particularly prone to obesity and diabetes under induced diet shifts and high caloric foods [12,32,62-64].

While past investigations of adaptive phenotypes underlying increased water retention at the kidney have focused on endocrine systems (e.g., vasopressin and/or RAAS-mediated osmoregulation) [65-68], significant shared evidence of selection across genomic studies (e.g., [13,16-18,34]) points to the arachidonic acid metabolism pathway as perhaps the most important adaptive water-retention mechanism driving convergent evolution in desert mammals and birds [69]. Some genes from this pathway putatively under selection (Figure 1D) may be involved in the production of vasodilators of renal preglomerular vessels [19(S)-HETE] that simulate water reabsorption at the kidney. These results hold exciting promise for further investigation of genetic changes underlying the outstanding urine-concentrating ability of desert mammals [7].

Taken together, these studies not only show that adaptive changes in fat metabolism, insulin response, and arachidonic acid metabolism may be pivotal for mammalian survival in different deserts of the world, but also that water and food deprivation, perhaps more than temperature, are likely the main drivers of convergent evolution in deserts.

Concluding Remarks and Future Directions

Selection in desert-adapted organisms appears to have targeted genes in multiple functional classes and pathways, consistent with the complexity and variety of phenotypes associated with desert adaptation. This has led some authors to suggest that phenotypic adaptation in deserts is polygenic [18,20,56]. While it *a priori* appears likely that multiple complex desert adaptive phenotypes are affected by many genes, the hypothesis of selection acting on polygenic traits has not been directly tested in desert-adapted mammals, as such tests require detailed knowledge of the genetic basis of the trait [70]. Unfortunately, this question, and many other questions regarding the genetic architecture underlying desert adaptation

(see Outstanding Questions), are limited by our lack of knowledge of the phenotypic effects of individual mutations. More research is needed on desert systems in which GWAS, other methods for genetic mapping, or functional studies can be used complementarily to selection studies for understanding how natural selection has affected phenotypes.

However, such systems (mostly model desert evaders) represent only a relative narrow set of desert phenotypes and there is also a need for more studies on a diverse set of organisms. We note that research on the genomic basis of desert adaptation in evaporator species is currently missing, despite past evidence of phenotypic adaptations in several promising biological systems [e.g., arid-dwelling Cape hare *(Lepus capensis*) [71], and desert-adapted species of the genus *Vulpes* [72]; Box 1 for more examples]. Since most desert phenotypes reported for evaporators are shared with other mammals, they may also share similar functional classes of genes and pathways. Future genomic studies in these and other organisms, and detailed phenotyping for sampled individuals, will help further elucidate convergent patterns of desert adaptation.

Combined genomic, transcriptomic, phenotypic, and/or climatic data can provide powerful approaches for linking genetic variation with expression levels, phenotypes, and environmental conditions, and the choice of study system might be guided by the possibility of obtaining such data (Box 3). Decades of classic phenotypic research in diverse mammalian species, as well as previous evidence for **aridity index** (**AI)**, precipitation, and temperature measures as predictors of certain desert phenotypes [7,50,73,74], will continue to inform genomic studies of desert adaptation.

Future research should also focus on the tempo and mode of desert adaptation, to take advantage of the fact that deserts have vastly different ages and, therefore, provide an opportunity to study adaptation at different timescales [1]. The age of deserts varies between just a few thousand years [22,75] to millions of years [19,76,77] and, throughout their lifetime, some deserts have undergone climate changes marked by alternating hyperarid and humid periods [26,30,31,75], but little is known about the age of selective events in organisms living in these deserts. Similarly, despite shared evidence of selection across species (Figure 2), it remains unclear whether this was the result of similar selective pressures acting independently on new mutations, or on ancestral standing genetic variation, or is the result of **introgression**. Demographic modeling of adaptive variants or of genomic regions putatively under selection, and methods designed to detect genome-wide introgression will add to our understanding of when and how adaptations arise, and what factors are driving adaptation and convergent evolution in deserts.

Knowledge of the genomic basis of desert adaptation will be instrumental for rescuing biodiversity currently threatened by increased desertification [78-80]. By establishing the link between phenotype, genotype, and the environment, it will be possible to predict if/how species can adapt to climate change and which functional traits may be the target of natural selection under increasingly arid conditions. Preserving and maintaining adaptive genetic variation will be an important first step to protect the adaptive potential to cope with ongoing environmental changes [78-80]. Gene editing for increased thermal tolerance or adaptive tolerance to dehydration/starvation and other genetic-rescue initiatives [81,82] may help

accelerate adaptive capacity in arid regions, although such measures remain technically challenging and controversial. Despite the challenges of establishing genotype-phenotype-environment maps, evolutionary studies of desert adaptation hold the promise to provide not only new insights into the processes driving adaptation at multiple timescales, but also a knowledgebase for future work on mitigating the effects of climate change.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

Adaptation (genetic or evolutionary)
genetic change at the population or species level resulting in increased fitness in a particular environment; often thought of as the evolutionary response to a specific selective pressure.

Aridity index (AI)
mean annual precipitation divided by mean annual evapotranspiration.

Common garden experiment
experiment to control for the environment when comparing two species (or lines) by moving them both from their native environments into a common environment. To fully control for environmental effects, the study organism, and possibly their parents, should be reared in the common garden

Comparative genomics
comparison of genomes of different species (e.g., analyses of mutational differences, or differences in number of genes, gene families, or structural variants).

Convergent evolution
independent evolution of similar adaptive traits in different species.

CRISPR-Cas9
gene-editing technology that can be used for targeted modification of DNA sequences.

Deserts
all warm or cold hyperarid regions with AI <0.05, and arid regions with AI of 0.05–0.20, excluding polar regions.

Gene ontology (GO) enrichment analysis
statistical tests identifying enrichment of certain biological functions in a candidate gene set over that expected in a random set of genes.

Genetic assimilation
reduction of phenotypic plasticity, where selection leads to expression of an ancestrally conditional phenotype in the absence of the original environmental cue.

Genome-wide association studies (GWAS)
statistical tests of association between specific genetic variants (typically SNPs) with particular phenotypes, including diseases. These studies rely on large samples of both genomic data and phenotypes.

Genotype
combination of alleles found in an individual at a particular locus.

Genotype–environment association studies (GEAs)
statistical tests of association between specific genetic variants with particular environmental variables to identify adaptive genes or genomic regions under environmental selection.

Introgression
gene flow from one species to another.

Norm of reaction
predicted plastic response to different environmental stimuli.

Phenotype
trait measurable at the individual level for an organism; may depend on the interaction of different genotypes as well as effects of the environment.

Phylogenetic comparative methods (PCMs)
statistical tests of association between variables while accounting for the non-independence of species due to common ancestry.

Plastic responses (phenotypic plasticity)
phenotypic changes (including expression changes) in response to environmental stimuli.

Pleiotropy (pleiotropic)
genes or variants that affect multiple traits.

Population genomics
study and comparison of genetic variability at the genomic level within species or populations.

Reciprocal transplant experiment
experiment in which organisms from each of two environments are introduced into the other.

Selective sweeps
genomic footprint of a ‘hitchhiking’ effect when a selected variant increases in frequency and linked neutral alleles consequently also either increase or decrease in frequency depending on the linkage pattern.

Transcriptomics

genome-wide comparison of abundance of RNA, often to identify genes differentially expressed between individuals from different populations or species, and/or in response to different treatments.

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Box 1.

Endurer–Evader–Evaporator Concept

Aiming to summarize and categorize decades of classic literature on desert adaptations in species occupying distinct ecological niches, Willmer *et al.* [2] proposed a classification system relative to extreme temperatures and body size. Animals that can evade extreme temperatures through behavior and are physiologically adapted to minimize water loss are called ‘evaders’. Mammalian evaders include small rodents that can avoid overheating by being nocturnal and hiding in burrows during the day, and are less reliant on evaporative cooling [2]. Evaders can additionally minimize water loss by concentrating highly hyperosmotic urine with low volume [7] and utilize water derived from fat metabolism (metabolic water) well beyond the abilities of non-desert counterparts (Table I for examples) [2,65].

Animals that cannot shelter behaviorally and instead rely on morphology and physiology to minimize water loss and withstand heat are called ‘endurers’ (Table I) [2]. Endurers include large ungulates and marsupials able to store heat without increasing their body temperature [2,65]. For example, Dromedary camels (*Camelus dromedarius*) can endure temperatures exceeding 42°C, and water losses >25% of their total body weight, which are both fatal to non-desert mammals [41]. Some endurers also have lower respiratory water losses [6], and can store water in their rumen, gut, or intestines for water retention [2,65]. It has also been proposed that Arabian Oryx (*Oryx leucocoryx*) use water derived from fat metabolism and that this may account for 24% of their overall water needs [5]. Endurers may also have enlarged body tissues that can store localized fat (e.g., fat tails in sheep, *Ovis aries*, and fat-filled humps of camels) to act as energy reserves during starvation [6,83].

A third category was additionally proposed for medium-sized animals that are not able to avoid extreme conditions as efficiently as evaders nor withstand heat as efficiently as endurers. These are called ‘evaporators’ and comprise lagomorphs, some marsupials, and medium-sized carnivores (Table I) [2]. Evaporator species have enlarged body extremities (e.g., large ears) to dissipate heat by conduction and use denning and nocturnal behavior to avoid extreme heat. They also have significantly low mass-adjusted nonrenal water loss [1,2] and can minimize renal water loss by concentrating highly hyperosmotic urine significantly above the levels seen in non-desert counterparts [2,7]. However, some authors have criticized this categorization due to overlap between the categories and have proposed other frameworks to synthesize desert mammalian phenotypic adaptations (e.g., [6]).

Table I.

Classic Physiological Systems Allowing Mammalian Survival in Deserts[a,b]

Environmental stressor	Upstream phenotype	Downstream phenotype
Heat + water	Decreased thyroxin[En (4,5), Ev (2,5), H]	Low metabolism or energy expenditures[En (1,2,9), Ev (1,2,8), Evap (1), H]

Environmental stressor	Upstream phenotype	Downstream phenotype
	Low metabolism/energy expenditures	Reduced nonrenal water loss[En (1,2,10), Ev (2,8), Evap (1,2), H], low respiration rate[En (1,2), Ev (6), Evap (1)], torpor[Ev (1,5)]
Cold	Nonshivering thermogenesis[Ev (1,8)]	Reduced shivering[H]
Heat	Reduced aldosterone[En (1)]	Low cardiac rate and low blood pressure[En (1)]
Water	Increased vasopressin[En (1,8), Ev (1,6,10)]; Increased aldosterone[En (1,3,4), Ev (3,4)]	Increased urine osmolality/Increased water reabsorption from the kidney[En (1,2), Ev, Evap (1,4)]; decreased urine production[Ev (1,5,7)]
	Reduced aldosterone[En (1)]	Increased urine sodium excretion[En (1)]
	Low glomerular filtration rate [En (1,3), Ev (2,5,7)]	Higher levels of plasma creatinine with no apparent kidney damage or renal impairment[En (1,2), Ev (5,7)]
	Higher urea [En (1,2), Ev (5,7)], glucose [En (1,7)], potassium [Ev (7)], sodium [En (1)], and chloride [Ev (5,7)]	Increased plasma osmolality[En (1,2), Ev (1, 5,7,10), Evap (5)]
Food/water	Increased fat storage in body tissues[En (1,7,7 ,4)]	Energy reservation during food/water scarcity
	Fat metabolism[En (1,2,4,7), Ev (13,14)]	Enhanced use of metabolic water[En (1,2,7), Ev (1,2,8, 12,13,14), Evap (1,2)]
	Higher plasma sodium[En (1)]	Tolerance of high-salt diet[En (1,6,7), Ev (1,4,8,9), Evap (5)]
	Decreased insulin secretion without diabetes[Ev (1)]	Adaptive tolerance to dehydration and starvation

[a] The phenotypes listed may themselves be adaptive or may be part of a correlated plastic response ([6,7,41,52,65,84-87] for more examples and [6,65,66,85] for detailed reviews).

[b] Superscript codes and numbers designate: En – Endurers (1, Dromedary camel, *Camelus dromedarius*; 2, Arabian oryx, *Oryx leucoryx*; 3, Black Bedouin goat, *Capra aegagrus hircus*; 4, Awassi fat-tailed sheep, *Ovis aries*; 5, Marwari sheep; 6, Desert bighorn sheep, *Ovis canadensis nelsoni*; 7, domestic Bactrian camel, *Camelus bactrianus*; 7*, wild Bactrian camel, *Camelus ferus*; 8, Ethiopian Somali goat, *Capra aegagrus hircus*; 9, Common wallaroo, *Osphranter robustus*; 10, Gemsbok, *Oryx gazella*; 11, Arabian sand gazelle, *Gazella marica*); Ev – Evaders (1, *Golden spiny mouse, Acomys russatus*; 2, Merriam's kangaroo rat, *Dipodomys merriami*; 3, Tarabul's gerbil, *Gerbillus tarabuli*; 4, Cairo spiny mouse, *Acomys cahirinus*; 5, Cactus mouse, *Peromyscus eremicus*, 6, Spinifex hopping mouse, *Notomys alexis*; 7, Sonoran desert mice, *Mus musculus*; 8, Mongolian gerbil, *Meriones unguiculatus*; 9, Fawn hopping mouse, *Notomys cervinus*; 10, Degu, Octodon degus; 11, Agile kangaroo rat, *Dipodomys agilis*; 12, Desert pocket mouse, *Chaetodipus penicillatus*; 13, Namib dune gerbil, *Gerbillurus tytonis*; 14, Fat sand rat, *Psammomys obesus*); Evap – Evaporators (1, Fennec fox, *Vulpes zerda*; 2, Rueppell's fox, *Vulpes rueppellii*; 3, Kit fox, *Vulpes macrotis*; 4, Cape hare, *Lepus capensis*; 5, Tammar wallaby, *Macropus eugenii*; 6, Springhare, *Pedetes capensis*); H, Aboriginal Australians, *Homo sapiens*.

Box 2.

Genetic Adaptations in Humans

Australians

Until European settlement of Australia 200 years ago, Aboriginal people had lived a hunter–gatherer lifestyle for at least 10 000–32 000 years [12,27]. Early anthropological studies showed that desert-dwelling Aboriginal Australians could maintain reduced metabolic rates without shivering when temperatures drop below 0°C at night [84]. Compared with people of European descent, they also have lower levels of thyroid hormone thyroxine (T4) and reduced affinity for T4-binding globulin, suggesting that selection has targeted thyroid-induced metabolism in Aboriginal Australians, resulting in increased adaptive thermal tolerance [88-91].

Malaspinas *et al.* [12] used an F_{ST}-based test to find genome-wide signatures of selection in Aboriginal Australians compared with other human populations and identified variants nearby the genes *NETO1*, related to the thyroid system, and *SLC2A12*, associated with serum urate levels, among others. Further comparisons of desert-dwelling and wet-tropical Aboriginal Australians identified putatively selected variants in the desert group harboring genes involved in several functions of relevance for life in deserts, including regulation of thyroid levels (*KCNJ2*) and vasodilation, enhanced capillary permeability, diuresis, and natriuresis (*KNG1*). These results raised the hypothesis that putatively selected variants changing expression patterns of thyroid-related genes (*KCNJ2/NETO1*, and possibly other genes) may underlie the adaptive thermal tolerance of Aboriginal Australians [12]. Another hypothesis was that selected variants in *SLC12A2* may underlie the adaptive tolerance to dehydration of Aboriginal Australians [12].

Native American

The survival of early Native American Andean populations living in the Atacama desert since at least 7000 yra relied heavily on water bodies naturally contaminated with arsenic [92]. This selective pressure has left selection signatures in the genomes of modern admixed descendants near variants that may have a role in immune defense against arsenic poisoning [92,93].

Kalahari Peoples

To test for evidence of selection in present-day southern African Khoe-San relative to ancient south Africans, Skoglund *et al.* [56] estimated allele frequency differentiation for hundreds of functional categories of genes, and found that the most divergent category was response to radiation [56]. It has since been suggested that groups that live a hunter–gather lifestyle in arid regions of the Kalahari basin adapted genetically to cope with prolonged exposure to sunlight [56]. Haplotype-based scans [14,15] in specific Khoe-San groups additionally identified variants under selection close to genes involved in fat metabolism and storage [55,57] and uptake of xenobiotic compounds [57,94], among other functions. However, these may not necessarily reflect desert adaptation as some of these groups are spread across diverse climatic conditions.

Box 3.

Functional Integration in Evolutionary Studies

For model evaders that can be captively bred, phenotypic and transcriptomic data collection under common garden experiments (Figure IA) is essential and can be integrated with genomic data from the same individuals to investigate causal genomic variants targeted by natural selection (Figure IB). Additionally, to understand a wider range of phenotype expression, data should not be limited to kidneys (e.g., [37,48,50,52]) but extended to diverse tissues and cell types. In the context of expression studies, it will be particularly interesting to understand how the norm of reaction has evolved and whether short-term adaptation proceeds by expanding the range of plastic responses or by a fixed shift in expression levels, and to test explicitly the hypothesis of genetic assimilation driving desert adaptation. Future research should also move beyond experimental dehydration when measuring plasticity and address the relative and combined effects of different environmental cues in driving differential expression of genes and phenotypes (Figure IA-C). It will be particularly exciting if **reciprocal transplants** in natural conditions are possible (Figure IA-C).

Providing a genotype–phenotype map for non-model organisms is challenging if sample sizes necessary for GWAS are unattainable. However, phenotypes expressed at the cellular level can be studied in cell culture, and **CRISPR-Cas9** (Figure IC) can be used to test explicit functional hypotheses [81]. We expect such experiments as follow-up on genomic selection scans to become an important tool in evolutionary studies of non-model organisms. Another recent advance that promises to make the challenge of establishing genotype–phenotype maps easier is the improvement in computational methods for variant effect prediction, including coding regions affecting protein structure [95] and noncoding regions affecting gene expression [96] and splicing [97].

Even without specific genotype–phenotype maps, **phylogenetic comparative methods (PCMs)** are promising as tools for generating new functional hypotheses, particular with respect to patterns of expression-level evolution, and can also be used directly to test hypotheses about phenotypic evolution [46]. These methods can be used to test for associations between different variables on a phylogeny with multiple species, some of which are desert adapted and some of which are not. For example, correlated changes between gene expression and specific traits or AI of a species can be identified [98]. Similarly, elevated dN/dS ratios in specific genes on lineages associated with switches to desert environments [99,100], or with changes in climate [101], might suggest selection acting in these genes associated with desert adaptation.

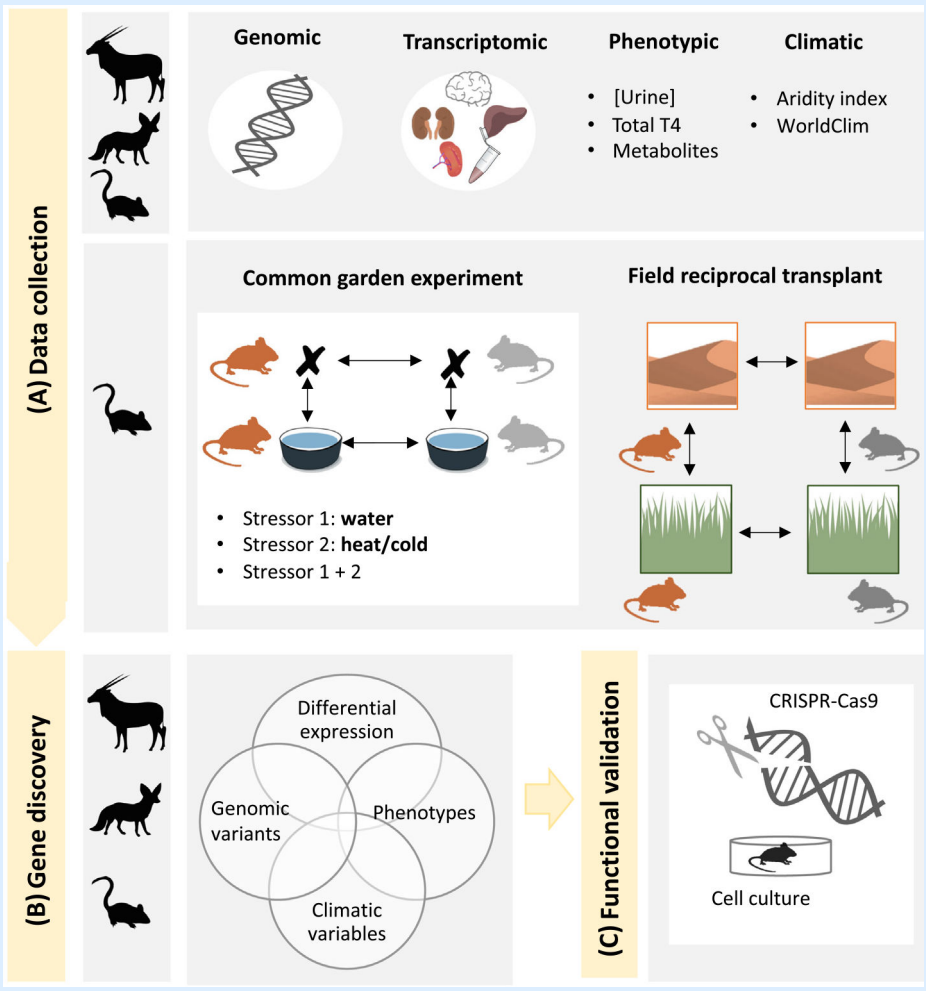

Figure I. The Different Steps for Future Research Attempting to Integrate Available Methodologies to Address the Genomic Basis of Desert Adaptation.

(A) Simultaneous collection of genomic, transcriptomic (across different tissues and also blood), phenotypic (see Box 1 in the main text), and climatic data (e.g., WorldClim database). Data collection under common garden and field reciprocal transplant experiments is suggested for model organisms (e.g., *Mus* and *Peromyscus* spp.). For common garden experiments, we suggest different combinations of environmental stressors. Different silhouettes represent distinct species, silhouettes in orange represent desert populations/species, and gray silhouettes represent non-desert populations/species; double-headed arrows represent the comparison being made; 'X' represents a condition of experimental dehydration or water deprivation, as opposed to animals being given water. (B) Diverse ways in which different data sets can be combined for methods in population and comparative genomics, depending on data availability and the evolutionary context of the study system of choice. The strength of selection studies is that they are powerful for identifying candidates for further testing. (C) Experimental validation of candidate genes under selection (CRISPR-Cas 9 and cell culture).

Outstanding Questions

Do desert-adapted traits evolve as a consequence of selection acting on multiple genes of small effect or by few genes of large effects?

Is convergent evolution among different desert-adapted species caused by introgression or independent selection? Can different levels of convergence be explained by the endurer–evader–evaporator concept or by selective regimes associated with different types of desert?

Does genetic adaptation proceed by expanding or narrowing plastic responses? Is genetic assimilation a key mechanism by which species adapt to deserts?

Is selection in protein-coding regions or in noncoding/regulatory areas of the genome most important in desert adaptation? Does the timescale of adaptation affect the answer to this question?

What are the tempo and mode for desert adaptation? How often, how fast, and when can adaptations arise? Does the timescale for adaptation matter for the genomic patterns observed?

Will the continued development of methods in comparative and population genomics deliver on the promise of genetic rescue in species currently challenged by increased desertification?

Can phenotypes and/or genotypes be predicted by climate?

Future studies investigating association of diverse bioclimatic variables with desert adaptive phenotypes and genotypes are needed. Understanding the mechanisms by which species repeatedly adapted to deserts can help elucidate future adaptative responses to increasingly arid conditions.

Highlights

The genomics of adaptation to deserts is a rapidly growing research field that provides examples of adaptation over different timescales and of vastly different organisms facing shared challenges.

Mammals inhabiting deserts show remarkable adaptive traits that have evolved repeatedly and independently in different species across the globe and in response to similar selective pressures of extreme temperatures, aridity, and water and food deprivation.

Genomic studies have shown that there are shared patterns of adaptation at the genomic level involving fat metabolism and insulin signaling, as well as arachidonic acid metabolism.

Understanding the mechanisms by which species have successfully adapted to the physical and climatic challenges of deserts is important for evaluating the possibility of evolutionary rescue of species currently challenged by increased desertification.

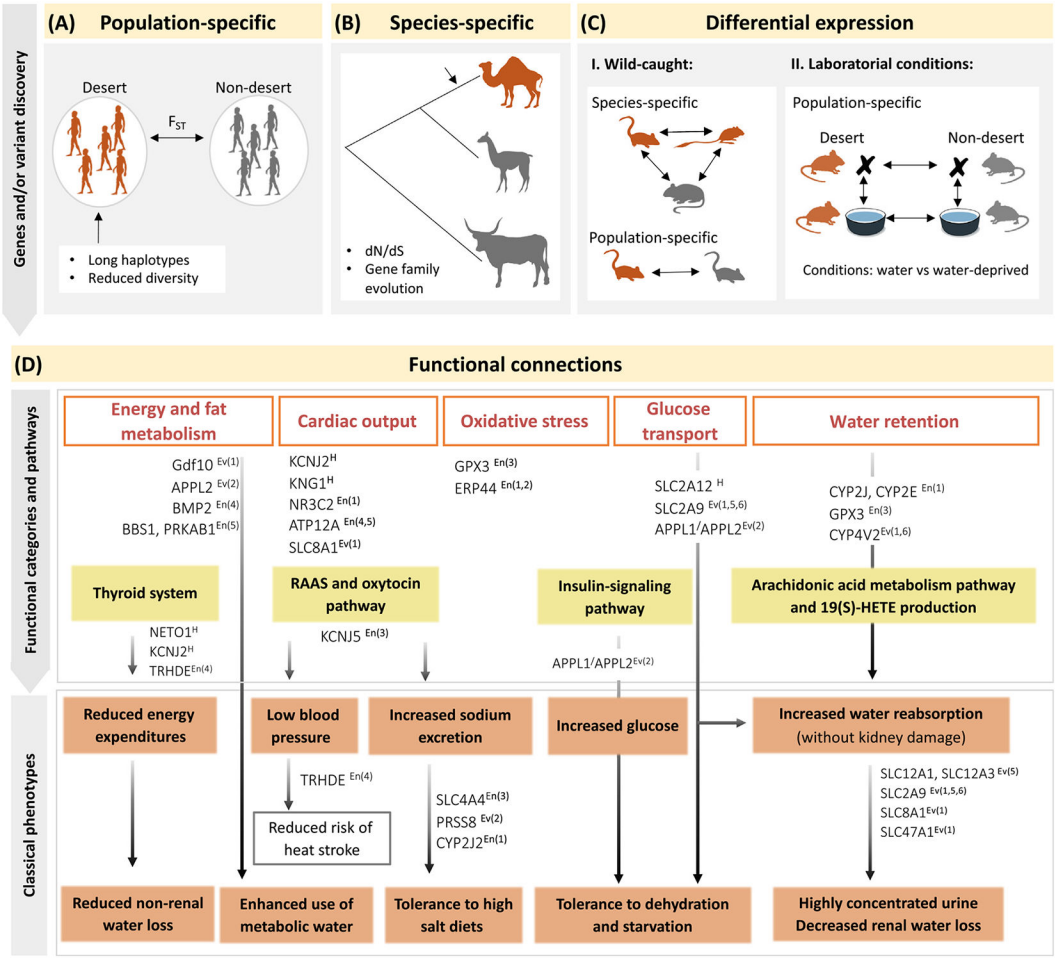

Figure 1. Genomic Approaches Used to Identify Genes Underlying Desert Adaptation.

(A) Population-based methods, (B) comparative-based methods, and (C) differential expression analyses in natural (i) and laboratory (ii) conditions. (A–C) Different silhouettes represent distinct species, silhouettes in orange represent desert populations/species, and gray silhouettes represent non-desert populations/species under comparison and outgroups; double-headed arrows represent the comparison being made, one-headed arrows represent the group or lineage targeted by the method; 'X' represents a condition of experimental dehydration or water deprivation, as opposed to animals being given water. (D) Schematic representation synthesizing and relating some of the recently discovered genes and functional gene classes to previously described phenotypes. Functional connections result from gene ontology enrichment analyses of sets of candidate genes and/or gene-function annotation (Gene Cards, OMIM, and UniProt). Some of the highlighted genes identified with population-based and comparative-based methods on whole genomes and DNA sequences of candidate genes found differentially expressed are represented with superscripts as follows: En – Endurers (1, Bactrian camel, *Camelus bactrianus*; 2, Dromedary camel, *Camelus dromedarius*; 3, Taklamakan and 4, Barki sheep, *Ovis aries*; 5, Barki goat, *Capra hircus*; 6, arid-dwelling Asian sheep); Ev – Evaders (1, Cactus mouse, *Peromyscus eremicus*; 2, Canyon mouse *Peromyscus citrinus*; 3, House mouse, *Mus musculus*; 4, Patagonian olive mouse, *Abrothrix olivacea*; 5, Banner-tailed kangaroo

rat, *Dipodomys spectabilis*; 6, Bailey's pocket mouse, *Chaetodipus baileyi*); H – human*s* (Aboriginal Australians).

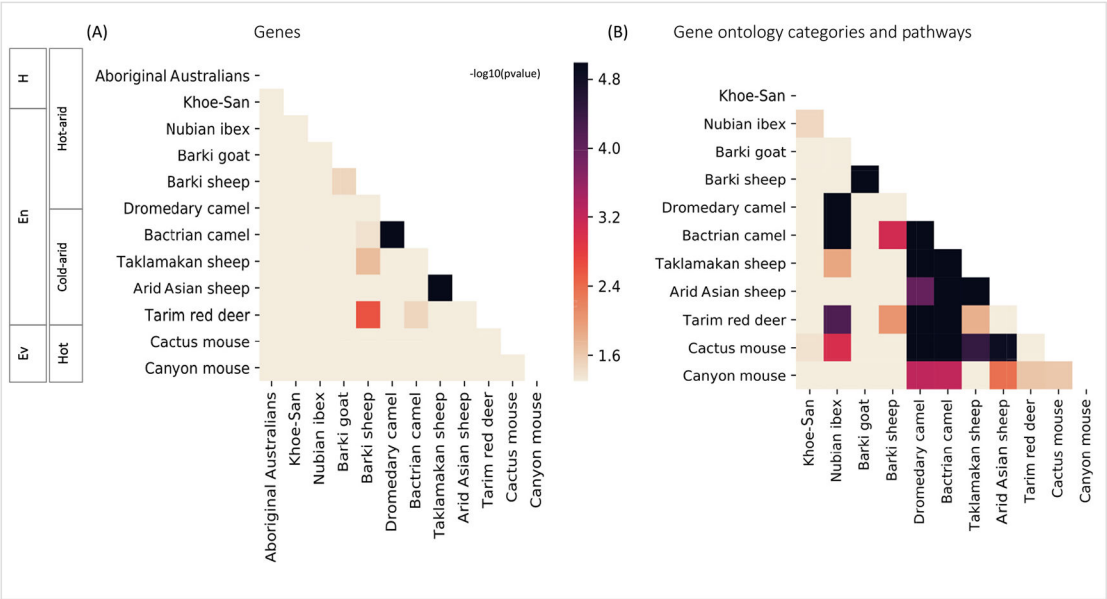

Figure 2. Shared Evidence of Selection in Genes (A) and Gene Ontology (GO) Terms and Pathways (B) Obtained from Comparative and Population Genomics in Evader (Ev), Endurer (En), and Human (H) Case Studies.

Examples reviewed here include: Cactus mouse (*Peromyscus eremicus*) [18], Canyon mouse (*Peromyscus citrinus*) [21], Tarim red deer (*Cervus elaphus yarkandensis*) [16], arid-dwelling Asian and Taklamakan desert sheep (*Ovis aries*) [13], Bactrian camel (*Camelus bactrianus*) [32,34], Dromedary camel (*Camelus dromedarius*) [32], North-African Barki sheep (*O. aries*) and goat (*Capra hircus*) [17], Nubian Ibex (*Capra nubiana*) [39], and southern African Khoe-San [57] and Aboriginal Australians [12] (*Homo sapiens*). The significance of gene and GO overlap was calculated using Fisher's exact test on a contingency table. Significant overlap is represented by colors standing out against the lightest background (marginal P values >0.05).