Evidence for and against genetic predispositions to acute and chronic altitude illnesses

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Abstract

Humans exhibit marked variation in their responses to hypoxia, with susceptibility to acute and chronic altitude illnesses being a prominent and medically important example. Many have hypothesized that genetic differences are the cause of these variable responses to hypoxia; however, until recently, these hypotheses were based primarily on small (and sometimes anecdotal) reports pertaining to apparent differences in altitude illness susceptibility between populations, the notion that previous history of altitude illness is indicative of subsequent risk, the heritability of hypoxia-related traits, and candidate gene association studies. In the past 5 years, the use of genomic techniques has helped bolster the claim that susceptibility to some altitude illnesses is likely the result of genetic variation. For each of the major altitude illnesses, we summarize and evaluate the evidence stemming from three important characteristics of a genetic trait: (i) individual susceptibility and repeatability across assessments, (ii) biogeographical differences and familial aggregation, and (iii) association(s) with genetic variants. Evidence to support a genetic basis for susceptibilities to acute mountain sickness (AMS) and high-altitude cerebral edema (HACE) is limited, owing partially to the subjective and unclear phenotype of AMS and the rarity and severity of HACE. In contrast, recent genomic studies have identified genes that influence susceptibility to high-altitude pulmonary edema (HAPE), chronic mountain sickness (CMS), and high-altitude pulmonary hypertension (HAPH). The collection of more individual, familial, and biogeographical susceptibility data should improve our understanding of the extent to which genetic variation contributes to altitude illness susceptibility, and genomic and molecular investigations have the potential to elucidate the mechanisms that underpin altitude illness susceptibility.

Introduction

Hypoxia is a potent stress for humans: reductions in oxygen tension impair the delivery of oxygen to cells, disrupting homeostasis and instigating a cascade of responses across many levels, from molecular to whole body. At high altitude, the physiological stress of hypoxia is unavoidable (West, 1996), impeding travel to, and residence in, high-altitude environments. Yet, despite the stress of hypoxia, millions of humans travel from near sea level to altitudes above 2500 m each year (Dumont et al., 2005; Plant and Aref-Adib, 2008), and millions more reside permanently at altitudes above 2500 m (Moore, 2001) and as high as 5100 m (West, 2002). The ability of humans to cope in high-altitude environments is enhanced through acclimatization, developmental adaptations, and evolutionary adaptations. The process of acclimatization involves transient adjustments that occur within an individual's lifetime (Bärtsch and Saltin, 2008; Houston et al., 1987; Martin et al., 2010); developmental adaptations involve irreversible but non-heritable adjustments in an individual arising from high-altitude exposures during periods of development (Frisancho 2013); and evolutionary adaptations are irreversible and heritable adjustments that arise in populations following generations of exposure to high altitude (Moore 2001; Beall 2007; Gilbert-Kawai, 2014). This review will focus on acclimatization and evolutionary adaptations to high-altitude environments.

There is marked variation in the physiological responses of humans to acute and chronic hypoxia exposures (e.g. cardiovascular, respiratory, and hematological responses (Martin et al., 2010); however, the variation in response to hypoxia is perhaps most apparent in the differential susceptibility to acute and chronic altitude illnesses (MacInnis et al., 2010). Indeed, under identical hypoxic conditions, some high-altitude sojourners and residents will remain well while others will develop altitude illnesses, which can be potentially fatal. Understanding the sources of

variation in hypoxia acclimatization and adaptation is a major area of research for high-altitude biology (MacInnis et al., 2010; Simonson, 2015). In general, the concept that there is a genetic contribution to altitude illness susceptibility is supported by the apparent differences in susceptibility between populations, the notion that previous history of altitude illness is indicative of subsequent risk, the heritability of hypoxia-related traits, and the association of specific genetic variants with susceptibility to altitude illness.

The primary focus of this review will be to present and evaluate the evidence for and against genetic predisposition to each of the major acute and chronic altitude illnesses. Since the previous edition of this review (MacInnis et al., 2010), substantial progress has been made in identifying genes with putative roles in altitude illness susceptibility through the use of genome-wide techniques. Accordingly, we will focus on data obtained from genome-wide association studies (GWAS) rather than candidate gene association studies (CGAS), which were the primary source of data for previous reviews (MacInnis et al., 2010; Rupert and Koehle, 2006). The reader is directed elsewhere for reviews of basic genetic terminology (Attia et al., 2009a; MacInnis et al., 2011), genetic association studies (Attia et al., 2009b; 2009c; Manolio, 2010), and the pathophysiology of altitude illness (Bartsch and Bailey, 2013; Bartsch and Swenson, 2013; Schoene and Swenson, 2013).

Testing for genetic predisposition to a trait

A genetic predisposition (or inherited susceptibility) to a trait (*e.g.*, altitude illness) is simply a greater chance of developing that trait because of the presence of one or more causal genetic variants. Evidence for and against a genetic predisposition to a particular altitude illness can be attained from various sources. Firstly, for a trait to be considered genetic, the phenotypic

variation in a population must be due to genetic variation (Hirschhorn and Daly, 2005; Visscher et al., 2008); however, without individual differences in susceptibility to altitude illnesses, it is difficult to discern the role of genetics, at least in that population. Secondly, susceptibility to altitude illness should be relatively stable within individuals, such that, under certain conditions, those who are susceptible always develop the illness and those who are not susceptible do not (Visscher et al., 2008); however, external forces (*e.g.*, medicine, nutrition, exercise, etc.) and longitudinal effects (*e.g.*, changes in behavior, age, etc.) can modify the severity and/or presentation of many traits. Thirdly, with all other factors being equal, the frequency of altitude illness susceptibility should differ in populations (*e.g.*, biogeographic groups, families) with different frequencies of the causal genetic variant(s). For example, if susceptibility to altitude illness were genetic, it should aggregate in families, as family members are more genetically similar to each other than to non-relatives. Finally, specific genetic variants should be overrepresented in those who are susceptible to altitude illness compared to those who are not susceptible. Genetic association studies can involve several polymorphisms selected based on *a priori* hypotheses (*i.e.*, CGAS) or thousands to millions of polymorphisms selected without specific *a priori* hypotheses (*i.e.*, GWAS). While GWAS can potentially provide greater insights into traits for which the molecular mechanisms are undetermined, they typically require very large sample sizes, meaning that GWAS are relatively expensive and difficult to implement and interpret (Hirschhorn and Daly, 2005).

Understanding the genetic basis of a trait does not immediately (or necessarily) improve clinical outcomes. Even if those genes that conferred susceptibility to altitude illness were identified, the clinical utility of a genetic test would still have to be determined. In other words, it

would be necessary to show that the information provided by the genetic test would improve health outcomes by directing individuals toward effective strategies to mitigate altitude illness.

Acute altitude illness

The term acute altitude illness generally encompasses three illnesses: acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE). Collectively, these illnesses affect millions of the high-altitude sojourners that travel above 2500 m each year, with consequences including interrupted travel, reduced productivity, and limited recreation. Without rapid medical intervention, HAPE and HACE can be lethal. Genetic differences have been postulated to explain individual variation in susceptibility to these conditions (MacInnis et al., 2010).

Acute mountain sickness (AMS)

AMS: BACKGROUND

Acute mountain sickness (AMS) is a transient condition developing at altitudes above 2500 m, characterized by non-specific symptoms (headache, nausea, fatigue/weakness, dizziness/lightheadedness, insomnia; (Hackett and Roach, 2001; Roach et al., 1993). The exact physiological mechanisms that lead to the development of AMS are unknown (Bartsch and Bailey, 2013), but symptoms are hypothesized to arise due to cerebral perturbations resulting from hypoxia (Bailey et al., 2009; Bartsch and Bailey, 2013), whether normobaric or hypobaric (Richard et al., 2014; Roach et al., 1996). The incidence of AMS is highly variable, depending largely on the rate of ascent and the altitude attained (Bloch et al., 2009; Maggiorini et al., 1990). For example, a rapid ascent to moderate altitude causes most humans to develop AMS (*e.g.*, a 3-h drive from sea level to 4200 m; Forster, 1985).

The presence/absence and severity of AMS are determined through self-report questionnaires (*e.g.,* Lake Louise Score [LLS], Roach et al., 1993; Environmental Symptom Questionnaire [ESQ-III], Beidleman et al., 2007; Sampson et al., 1983). While these questionnaires are relatively simple and rapid to use, the validity of each is difficult to establish without an objective gold standard for the assessment of AMS. Recent work from our research group (MacInnis et al., 2013b) and others (Hall et al., 2014) has demonstrated that the Lake Louise definition of AMS likely represents multiple clinical syndromes that occur on exposure to hypoxia, with impaired sleep quality appearing to be independent from other effects. These potential inconsistencies in the phenotype of AMS could introduce excessive variability into the assessment of the genetic contribution to this syndrome, complicating the interpretation of data.

AMS: INDIVIDUAL SUSCEPTIBILITY AND REPEATABILITY

One of the traditional rationales for a genetic basis for AMS has been the notion that previous history is a useful predictor of susceptibility to AMS (Hackett and Roach, 2001; Imray et al., 2011; West, 2012). While previous history has been associated with greater risk of developing AMS on occasion (Richalet et al., 2012), previous history was a poor predictor of AMS in a large meta-analysis (MacInnis et al., 2015a; Figure 1). Furthermore, across two blinded and identical normobaric hypoxia exposures (13% O_2, ~4000 m equivalent) – separated by at least 14 days – AMS severity was not repeatable (MacInnis et al., 2014). Other studies reported AMS to be repeatable (Forster, 1984; Rexhaj et al., 2011) did not include sham trials, which is problematic for a condition measured with subjective self-reported symptoms. An individual's susceptibility to AMS might eventually stabilize with repeated exposures (*e.g.,* mountaineers who frequently ascend to altitude); however, this hypothesis remains untested.

AMS: BIOGEOGRAPHICAL AND FAMILIAL DATA

Despite its relatively high incidence, a dearth of biogeographical and family data is available for AMS susceptibility. Most biogeographical data compares Tibetans to other groups. For example, a large epidemiological study reported that, upon exposure to ~4500 m, Tibetans living at low altitudes had a much lower incidence of AMS than Han Chinese arriving from the same low altitudes (Wu et al., 2009). In a large prospective field study (MacInnis et al., 2013a), those with Tibetan ancestry (determined by surname; Thornton et al., 2011) were at a lower risk of developing AMS than those of Indo-Caucasian ancestry on a rapid ascent to 4380 m (Unpublished data; MacInnis and Koehle). Smaller anecdotal reports suggested that Tibetans and Sherpas are less likely to develop AMS than trekking groups of Han Chinese and Japanese ancestry (Wu et al., 2005). In all of these studies, it is difficult to account for the potentially confounding effects of environmental differences, such as health, diet, and cultural practices. To our knowledge, susceptibility to AMS has not been studied in Andeans, preventing biogeographical comparisons between Andeans and other populations.

Whether a family history of AMS increases one's risk of developing AMS is an unanswered question that should be addressed. In a large group of Nepalese pilgrims, the LLS of brothers was correlated, but insufficient familial data were available to make strong conclusions related to the predictive value of family history (MacInnis et al., 2013a). Twin studies suggest that AMS incidence is similar within pairs of twins, although only infants (Yaron et al., 2002) and children (Masschelein et al., 2014) have been studied. More research is needed to understand

the influence of biogeographical group and family history on AMS susceptibility and whether either variable would be useful for predicting susceptibility.

AMS: GENETIC ASSOCIATION STUDIES

Numerous CGAS have tested associations between AMS susceptibility and specific genetic variants (reviewed by MacInnis et al., 2011; Table 1); however, none of these studies has identified a genetic variant that has a strong association with AMS. For example, four separate studies (n = 103 – 284 subjects), which were performed on three different continents, reported that the angiotensin converting enzyme (*ACE*) gene was not associated with AMS (Table 1). More recently, we published the first GWAS on AMS susceptibility (MacInnis et al., 2015b). In that study, *FAM149A* (Table 2) was provisionally associated with AMS in a group of Nepalese pilgrims who rapidly ascended to 4380 m. This gene is highly expressed in the trigeminal and superior cervical ganglia (Su et al., 2004), tissues that are plausibly related to AMS pathophysiology (Bartsch and Bailey, 2013); however, in validation cohorts, the selected *FAM149A* polymorphism was not associated with AMS, suggesting that this association was potentially a false positive or that it has a relatively small effect size. No other genes were associated with AMS in that study.

The hypoxia-inducible factor (HIF)-1α pathway has been implicated in AMS susceptibility, but the one reported association has yet to be replicated. HIF-1α is an important transcription factor that regulates cellular homeostasis under conditions of hypoxic stress. Under normoxic conditions, prolyl hydroxylase 2 (PHD2), an oxygen sensor encoded by the *EGLN1* gene, degrades HIF-1α. In several investigations into the genomic basis of high-altitude adaptation, particular *EGLN1* variants have been overrepresented in Tibetans and Andeans

(Aggarwal et al., 2010; Bigham et al., 2010; Peng et al., 2011; Simonson et al., 2010; Xu et al., 2011). Based on these studies, Zhang et al. (2014) examined the role of *EGLN1* variants (Table 2) in AMS and reported that variants in the 5'-untranslated region of *EGLN1* were associated with AMS in a relatively large sample of Han Chinese (190 cases, 190 controls); however, this association has not been replicated.

High-altitude cerebral edema (HACE)

HACE: BACKGROUND

High-altitude cerebral edema (HACE) is another cerebral form of altitude illness; however, unlike AMS, HACE is a rare encephalopathy. Some researchers suspect that HACE is a severe endpoint of AMS (Hackett and Roach, 2001), and AMS typically precedes HACE (Hackett and Roach, 2004; 2001); however, this is not always true, and HACE can occur without any symptoms of headache (Wu et al., 2006). A common pathophysiology for the two conditions has not been proven.

HACE usually occurs at least 2 days after ascent to an altitude above 3000 m (but usually above 4000 m (Bartsch and Swenson, 2013)). The incidence of HACE is relatively low, with estimates of 1% (Hackett et al., 1976) and 0.28% (Wu et al., 2007). Clinically, HACE is marked by ataxia of gait, severe lassitude, and changes in consciousness (Hackett and Roach, 2004; 2001). There is no questionnaire to diagnose HACE, and other conditions can have similar presentations (*e.g.*, central nervous system infection, hypoglycemia, hypothermia; Hackett and Roach, 2001). Magnetic resonance imaging (MRI) studies of those with, or recovering from, HACE demonstrated vasogenic edema (Hackett et al., 1998) and microhemorrhages in the corpus collosum (Dickinson et al., 1983; Kallenberg et al., 2008; Schommer et al., 2013), indicating

disruptions in the blood-brain barrier. Left untreated, HACE may progress to coma followed by death due to brain herniation within 24 hours (Bartsch and Swenson, 2013). To our knowledge, there have been no investigations into the potential genetic basis of HACE.

High-altitude pulmonary edema (HAPE)

HAPE: BACKGROUND

High-altitude pulmonary edema (HAPE) is a rare altitude illness. HAPE is a non-cardiogenic form of pulmonary edema, secondary to exaggerated pulmonary artery pressure and hypoxic pulmonary vasoconstriction (Maggiorini et al., 2001; Swenson et al., 2002). These high vascular pressures are believed to cause the extravasation of fluid from pulmonary capillaries to alveolar spaces, which impairs diffusion in the lung, causing severe hypoxemia (Maggiorini et al., 2001; Swenson et al., 2002). Accordingly, HAPE is characterized by fatigue, breathlessness, coughing, frothy sputum, inspiratory crackles, cyanosis, tachypnea, and tachycardia (Hackett and Roach, 2001; Schoene and Swenson, 2013). The presence of patchy alveolar infiltrates on radiographs is an objective marker for HAPE.

The onset of HAPE is generally two days after arrival at a new altitude (usually above 3000 m; Hackett and Roach, 2001; Schoene and Swenson, 2013). The risk of HAPE increases with ascent rate and the altitude attained. For example, in those with an unknown history of HAPE, the condition occurs in 0.2%, 2%, and 6% on 4-day, 7-day and 1-day or 2-day ascents to 4500 m and in 15% on a 1-2 day ascent to 5000 m (Bartsch and Swenson, 2013).

HAPE: INDIVIDUAL SUSCEPTIBILITY AND REPEATABILITY

In some respects, HAPE is more amenable to research than AMS or HACE. Firstly, there is clear individual susceptibility in HAPE: this illness is extraordinarily rare in those who have previously ascended to altitude without developing HAPE, but it is repeatable in those who have previously developed HAPE (*i.e.*, risk of recurrence is ~60% in those who ascend to 4500 m in 2 days; Bartsch et al., 2002; Bartsch and Swenson, 2013). Secondly, HAPE has objective signs, which increase confidence in its diagnosis. Susceptible and non-susceptible individuals can be accurately identified and studied prospectively with strong confidence in the quality of the phenotype data.

HAPE: BIOGEOGRAPHICAL AND FAMILIAL DATA

Several instances of HAPE susceptibility within siblings and within parent-offspring pairs have been reported (Fred et al., 1962; Hultgren et al., 1961; Lorenzo et al., 2009; Norboo et al., 2004; Scoggin et al., 1977). The clinical utility of a family history of HAPE is unknown, but these cases of familial aggregation are supportive of a genetic etiology. To our knowledge, biogeographical comparisons are not available for HAPE.

HAPE: GENETIC ASSOCIATION STUDIES

Many candidate genes have been investigated as markers of HAPE susceptibility but these studies have not identified any associations with clinical utility (Table 1); however, two GWAS have recently identified several candidate genes for HAPE susceptibility that merit further investigation. The first of these studies, from Kobayashi and colleagues (2013), reported an association between the Tissue Inhibitor of Metalloproteinase 3 gene (*TIMP3;* Table 2) and HAPE in a Japanese population. TIMP3 regulates the degradation of the extracellular matrix of

lung tissue, and the interaction of TIMP proteins and matrix metalloproteinases have been associated with various lung pathologies related to decreased structural integrity (*e.g.*, edema, emphysema, fibrosis; Loffek et al., 2011). Although this finding is intriguing, it has not yet been replicated and was not identified in another similar study of HAPE. That second GWAS for HAPE susceptibility compared the frequency of genetic variants among HAPE-susceptible subjects, HAPE-resistant subject, and native highlanders. From the initial analysis, putative associations were found between HAPE susceptibility and variants of apelin (*APLN*), apelin receptor (*APLNR*), and nitric oxide synthase 3 (*NOS3*; Mishra et al., 2015; Table 2). Apelin induces vasodilation by increasing nitric oxide production via a NOS3 pathway, and in hypoxic conditions, HIF increases apelin expression, which augments vasodilation. In follow-up assays, apelin-13 and nitrite concentrations were lower in the blood of HAPE-susceptible subjects relative to HAPE-resistant subjects, which corresponded with (1) the lower gene expression of *APLN*, *APLNR*, and *NOS3* in HAPE-susceptible subjects, (2) the higher methylation of *APLN* CpG islands in HAPE-susceptible subjects, and (3) the results of an *APLN* promoter assay.

As with AMS, the association of *EGLN1* with high-altitude adaptation has prompted investigations into its potential role in HAPE susceptibility (Table 2). Firstly, Aggarwal et al. (2010) identified two variants of *EGLN1*, which were associated with its expression, that were more common in those who developed HAPE relative to native highlanders. In a large comparison of HAPE patients and HAPE controls sojourning above 3000 m, seven *EGLN1* polymorphisms, including those identified by Aggarwal et al., were associated with HAPE susceptibility, and *EGLN1* expression (Mishra et al., 2012). In the same study, *EGLN1* gene expression was inversely related to arterial oxygen saturation at altitude and was approximately

four-fold higher in blood samples from HAPE patients relative to the controls (Mishra et al., 2012).

While these genetic studies of HAPE are intriguing, further work is needed to confirm their validity (*i.e.*, these associations have not been independently replicated). Furthermore, whether these associations can be generalized to other populations and whether they have clinical utility has not been established.

Chronic altitude illness

Chronic altitude illnesses affect residents of high-altitude environments, whether they are temporary residents, long-term residents, or multi-generation high-altitude natives (Leon Velarde et al., 2014; León-Velarde and Villafuerte, 2011). The major chronic altitude illnesses are chronic mountain sickness (CMS) and high-altitude pulmonary hypertension (HAPH). While much of the focus of high-altitude biology has been on the successful adaptation of high-altitude natives to hypoxia (*e.g.*, Tibetans, Andeans, Ethiopians), efforts have also been made to explain the individual variation in susceptibility to chronic altitude illness within these biogeographical groups.

Chronic mountain sickness (CMS)

CMS: BACKGROUND

Chronic mountain sickness (CMS) affects high-altitude natives and long-time residents of high altitude (León-Velarde et al., 2005). CMS generally develops after years of exposure to high altitude (≥2500 m), and it resolves with descent to lower altitudes (León-Velarde et al., 2005). Excessive erythrocytosis is the primary sign of CMS, but severe hypoxemia and pulmonary

hypertension may also be present (León-Velarde et al., 2005). The pulmonary hypertension associated with CMS can cause right-heart failure and congestive heart failure (Leon Velarde et al., 2014).

The presence and severity of CMS is ascertained through a questionnaire. The signs and symptoms of interest are breathlessness/palpitations, sleep disturbance, cyanosis, dilatation of veins, paresthesia, headache, tinnitus, and hemoglobin concentration (León-Velarde et al., 2005). To confidently diagnose CMS, diseases with similar presentations (*e.g.*, chronic pulmonary diseases) must be excluded (León-Velarde et al., 2005).

CMS: INDIVIDUAL SUSCEPTIBILITY AND REPEATABILITY

Despite being exposed to the same conditions, only some highlanders develop CMS. The prevalence ranges from 0-5% among native highlanders in Asia, Africa, and South America. To treat CMS, subjects typically require ongoing venesection. Symptoms typically resolve with descent to low altitude, but they recur on re-ascent to high altitude (León-Velarde et al., 2005). These points demonstrate that there is individual susceptibility to CMS and that susceptibility to CMS is relatively stable.

CMS: BIOGEOGRAPHICAL AND FAMILIAL DATA

The prevalence of CMS varies geographically. Andeans are more likely to have CMS than Tibetans (~5% vs. <1%, respectively), despite occupying similar altitudes (Leon Velarde et al., 2014; Moore, 2001). The lower incidence in Tibetans than Andeans might be a consequence of Tibetans' generally higher alveolar ventilation and hypoxic ventilatory response and lower hemoglobin concentration (Beall, 2007; Beall et al., 1998; 1997; Moore, 2000). Having spent

generations at high altitude seems to decrease the likelihood of CMS, as the prevalence of CMS in Tibetan highlanders is much lower than that of Han Chinese immigrants who occupy the same altitudes (Moore, 2001). Familial data related to CMS is surprisingly scant; however, an early study reported familial aggregation of CMS in a South American population (Reátegui, 1969). CMS has not been reported in Ethiopian highlanders (Leon Velarde et al., 2014).

CMS: GENETIC ASSOCIATION STUDIES

Several CGAS have been performed on Andeans with and without CMS, but these studies have not identified a strong candidate gene to explain the differential susceptibility to CMS among Andeans (Table 1). A recent study that sequenced whole genomes of 10 individuals with CMS and 10 individuals without CMS identified several genomic regions of interest (Zhou et al., 2013). Genes from two of these regions (*SENP1* and *ANP32D*; Table 2) had greater expression in CMS-derived cultured fibroblast cells relative to non-CMS-derived cells and decreasing the expression of these genes in flies increased their survival when exposed to hypoxia. One of the identified genes, *SENP1*, regulates erythropoiesis (Cheng et al., 2007; Yu et al., 2010), suggesting that its upregulation could contribute to the erythrocytosis seen in CMS. The putative role of *ANP32D* in the pathophysiology of CMS is unknown. These results were partially replicated: *SENP1* was, but *ANP32D* was not, associated with CMS in two cohorts of Andean highlanders from Cerro de Pasco, Peru (Cole et al., 2014). The sample size of the replication study (84 cases; 91 controls) was much larger than the original study, and the CMS patients from the two studies had similar degrees of erythrocytosis. Given that the two genes were in linkage disequilibrium and the potential role of *ANP32D* is unclear, Cole et al. suggested that *SENP1* could be driving the association.

Andeans with CMS are not a homogeneous group: Recent work from Villafuerte et al. (2014) demonstrated erythropoietin (EPO) concentrations to be elevated in some, but not all, Andeans with CMS. The authors suggested these phenotypes could represent genetically distinct subtypes of CMS; however, several genes related to the EPO pathway were not associated with CMS in previous CGAS (Table 1). More work is needed to understand whether genetic differences in genes related to the EPO pathway contribute to variation in CMS susceptibility.

High-altitude pulmonary hypertension (HAPH)

HAPH: BACKGROUND

High-altitude pulmonary hypertension (HAPH) is a chronic form of altitude illness that can develop in high-altitude natives and life-long, high-altitude residents following prolonged stays above 2500 m (León-Velarde et al., 2005). HAPH is known by many names, including chronic mountain sickness of the vascular type, high-altitude heart disease, and subacute mountain sickness (León-Velarde et al., 2005). HAPH is characterized by excessive pulmonary artery pressure as well as elevated pulmonary vasoconstriction and pulmonary artery pressure (León-Velarde et al., 2005). Pulmonary vasculature remodeling, right ventricular hypertrophy, and congestive right-heart failure may occur in patients with HAPH (León-Velarde and Villafuerte, 2011). HAPH can occur independent of, or in conjunction with, CMS (Penaloza and Sime, 1971). To diagnose HAPH, other forms of pulmonary hypertension as well as chronic obstructive pulmonary diseases, interstitial diseases, and cardiovascular diseases must be excluded (León-Velarde et al., 2005).

HAPH: INDIVIDUAL SUSCEPTIBILITY AND REPEATABILITY

Similar to CMS, only some highlanders develop HAPH. In a group of Kyrgyz highlanders, 23% of males and 6% of females had ECG signs of cor pulmonale (Aldashev et al., 2002), which is likely an overestimation of the incidence of HAPH, as only those with exertional dyspnea were screened. While pulmonary artery pressure decreases on descent to lower altitude, it rises to pathological values on return to high altitude in those with HAPH (Wilkins et al., 2014), suggesting HAPH is relatively stable.

HAPH: BIOGEOGRAPHICAL AND FAMILIAL DATA

Tibetans generally have less pulmonary hypertension than Andeans (Groves et al., 1993), but to our knowledge direct comparisons of HAPH incidences across biogeographical groups have not been made. For example, Tibetans living at 3,658 m had a mean pulmonary artery pressure of 15 mmHg, whereas the corresponding values from Andeans living at ~3700 m ranged from 20-23 mmHg (reviewed in Groves, et al., 1993). High-altitude heart disease (*i.e.*, HAPH) was reported in multiple family members from three separate families living at high-altitude in China (Ge and Helun, 2001). The relatively stable nature of HAPH, like CMS, would facilitate more familial and biogeographical studies.

HAPH: GENETIC ASSOCIATION STUDIES

Most of the HAPH genetics studies to date have been CGAS, and relatively few genes have been investigated (Table 1). Although some variants have been statistically associated with HAPH, their clinical utility is unclear (MacInnis et al., 2010). A recent exome sequencing study of Kyrgyz highlanders identified *GUCY1A3* as a candidate gene for HAPH susceptibility (Table 2; Wilkins et al., 2014). That study revealed a rare missense mutation of the *GUCY1A3* gene in

three individuals with normal pulmonary artery pressure (and in 0/28 of those with elevated pulmonary artery pressure). This variant altered the activity of the soluble guanylyl cyclase enzyme in functional assays (Wilkins et al., 2014), suggesting that the missense mutation enhances sensitivity to nitric oxide, a vasodilating compound, to potentially reduce pulmonary hypertension. This association cannot fully explain the differential susceptibility to HAPH in the entire sample; however, this result is an example of the potential contribution of relatively rare variants to the variability in traits (Manolio et al., 2009).

Advancing our understanding of altitude illness: Summaries and challenges

The purpose of this review was to (i) summarize and weigh the evidence for the genetic basis of altitude illness susceptibility and (ii) highlight the recent progress in our understanding of the genetic contributors to altitude illnesses. Since our most recent review in this area (MacInnis et al., 2010), progress in understanding the extent to which genetic variability influences altitude illness susceptibility has been limited. In general, more data is needed to understand the repeatability/stability of each altitude illness and the extent to which altitude illness susceptibility aggregates in families and differs across biogeographical groups. Whereas CGAS studies were predominant in the past, genome-wide techniques now dominate the research. This shift to a genomics-based approach has proved advantageous for HAPE, CMS, and HAPH, but work is still needed to validate provisionally associated genes and determine their clinical utility.

Relatively little new information relating to the genetic basis of AMS has been published in the past six years. In our opinion, the current paucity of evidence for a genetic predisposition for AMS might have more to do with the quality of phenotype data than the influence of genetics on hypoxia tolerance *per se*. Some clarity is necessary in terms of the diagnosis and classification

of AMS before investigators can more definitively quantify its heritability and better investigate its genetic determinants. Our understanding of genetic susceptibility to AMS is hindered by the unclear pathophysiology of AMS (Hall et al., 2014; Luks, 2014), the low repeatability of AMS (MacInnis et al., 2014; 2015a), and the subjective nature of the current AMS criteria (Roach et al., 1993). As the pathophysiology is unclear, and symptoms could arise from multiple pathways, researchers should consider examining high-altitude headache and aspects of oxygen transport/delivery that might contribute to hypoxia acclimatization (MacLeod et al. 2013).

As with AMS, there has been minimal progress in our understanding of the genetic basis of HACE. To our knowledge, there are no published reports of individuals suffering repeated episodes of HACE, biogeographical or familial aggregation of HACE, or genetic association studies of HACE. Compared to AMS, the HACE phenotype is better defined, with imaging of the brain permitting objective diagnoses; however, HACE research is restricted by its rare and severe nature. Obtaining sufficient sample sizes to perform genetic association studies would likely require the establishment of HACE databases that track cases from large geographical areas or international collaborations that share data. Investigations of HACE might be well informed by animal models (Huang et al., 2015).

Among the acute altitude illnesses, genetic predisposition to HAPE susceptibility has the strongest support. Opportunistic field studies are difficult to implement with HAPE because of its relatively low incidence (and relatively longer time to onset than AMS); however, because of its strong repeatability and the high confidence in diagnosis, the establishment of a HAPE registry could prove a useful tool to study HAPE susceptibility from a genetic perspective. More family studies, including prospective data on the clinical utility of a familial history of HAPE, would likely be very informative (and useful, from an applied perspective). Five genes have been

identified that appear to affect HAPE susceptibility, either through structural changes in the lung, through the regulation of the HIF pathway, or through apelin and nitric oxide signaling pathways. Studies have not replicated these associations, so more work is needed before this information can better inform our understanding of HAPE pathophysiology and susceptibility.

The genetic work from Zhou and colleagues (2013) has identified intriguing candidate genes for CMS, and in our opinion, genetic susceptibility to CMS has the best support of all the altitude illnesses: *SENP1* was identified through a genome-wide analysis, *SENP1* has a putative role in the pathophysiology of CMS, and the association between *SENP1* and CMS was independently replicated. Further attempts at replicating and understanding this association are warranted. While the differential susceptibility between Han Chinese, Tibetan, and Andean populations is suggestive of a genetic basis to CMS, it is not conclusive. Familial data within each highland population could help to determine the extent to which CMS is an inherited condition, and the chronic and stable nature of CMS would facilitate these types of studies.

The first genome-wide study of HAPH has identified a candidate gene with a plausible role in HAPH; however, unlike CMS, this association has not been replicated. More studies – biogeographical, family, and genetic – are needed to determine whether HAPH susceptibility has a strong genetic component and to confirm the association between HAPH and *GUCY1A3*. Because HAPH is a relatively rare condition that occurs in remote populations, large studies are difficult. Attempting to identify the genes influencing variation in the pulmonary artery pressure response to hypoxic gas in lowlanders could be beneficial, as it could alleviate these issues.

In summary, over the past six years, there has been some progress in understanding the genetic underpinnings of altitude illness, but the search for genes that influence altitude illness susceptibility is proving more difficult than previously anticipated (MacInnis et al., 2010). The

main challenges appear to be inconsistent stimuli (*e.g.*, ascent rate, weather, and altitude achieved), the rarity of the conditions, the remoteness of the affected populations (particularly high-altitude natives), and inconsistencies and uncertainties in the phenotypes. Progress has been greatest for those conditions that are repeatable and stable with objective signs (*i.e.*, HAPE, CMS, HAPH). Understanding the influence of genetic differences on altitude illness susceptibility may ultimately help with the treatment and management of these potentially life-threatening illnesses; however, an improved understanding of high-altitude physiology and adaptation is the more likely and more immediate outcome of continued research in this area.

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Figure Legends

Figure 1. (A) Cross-hairs plot for the acute mountain sickness data showing sensitivity as a function of the false-positive rate (FPR) for each study. Error bars show unique estimates of the 95% CI for sensitivity and FPR. (B) The summary receiver-operator characteristic curve based on the bivariate model. The black line is the summary ROC curve; the dashed line is the positive diagonal (shown for reference). The open circle represents the point estimate for the summary sensitivity and FPR. The ellipse represents the 95% confidence region based on the variability and correlation between sensitivity and FPR. Reprinted from MacInnis et al. (2015a).