THE EVOLUTION OF LACTASE PERSISTENCE: MILK CONSUMPTION, INSULIN-LIKE GROWTH FACTOR I, AND HUMAN LIFE-HISTORY PARAMETERS

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Abstract

For most mammals and humans, production of the intestinal enzyme lactase is a life history trait that corresponds roughly to the duration of nursing. However, some human populations with long histories of using dairy animals have high frequencies of alleles for lactase persistence (LP), production of the enzyme lactase throughout the lifespan. Several hypotheses have been proposed to account for this variation, but little evidence exists for specific fitness advantages of LP. Here I propose the hypothesis that LP alleles allow for milk consumption beyond infancy, which results in higher circulating insulin-like growth factor I (IGF-I) concentrations. IGF-I has been suggested as a mechanism that coordinates a variety of life history outcomes. Milk is a source of IGF-I, but IGF-I is degraded in the processing of milk into dairy products. Serum IGF-I concentrations rise with milk intake, and less consistently with other dairy product intake. Higher circulating IGF-I may contribute to more rapid growth and larger body size, earlier sexual maturation, or positively impact other

physiological systems. There may also be negative pleiotropic consequences that contribute to later life diseases such as cancer. This hypothesis describes a mechanism by which milk consumption could enhance fitness among ancestral dairying populations.

Introduction

Variation in the alleles that allow for milk digestion in adulthood is well described across human populations (Itan et al., 2010). Only populations with long histories of using dairy animals have high frequencies of the alleles for lactase persistence (LP), the production of the enzyme lactase throughout the lifespan. Lactase is the enzyme required to digest the unique milk sugar lactose into its component monosaccharides for absorption and utilization for energy. Individuals who are lactase non-persistent (LNP) frequently experience negative gastrointestinal symptoms of lactose intolerance (e.g. diarrhea, cramps, gas) when they consume milk, especially in large quantities (Shaukat et al., 2010). LP alleles appear to have spread after the adoption of dairying, and while may seem obvious why LP alleles were selected for among populations that adopted dairying, since milk is a nutrient-rich food that would be accessible throughout the lifespan, to date there is little evidence for the specific fitness advantages of life-long lactase production.

Not all dairying populations have high LP frequencies. In part this is attributable to the fact that milk can be easily processed into dairy products such as yogurt or cheese that are low in lactose, obviating the need for continued lactase production. Lactose is only found in fluid milk or unfermented whey. Three questions arise: (1) do populations with high frequencies of LP alleles consume substantial amounts of fresh milk or whey, which are the only lactose-rich dairy products? (2) what advantage would continuous exposure to lactose-rich foods, rather than dairy foods more generally, confer to LP individuals? and (3) what evidence exists for positive fitness outcomes associated with LP?

Currently there exists reasonable evidence related to question (1), although much of it comes from contemporary, rather than early dairying populations. As **Figures 1a and 1b**

indicate, countries with high frequencies of LP individuals are also those with the highest per capita milk intake among adults (see also Durham, 1991; Wiley, 2007). Multiple studies show that people with LP tend to drink more milk than those with LNP (e.g. Almon et al., 2013; Baadkar et al., 2012; Fernández and Flores, 2014; Hartwig et al., 2016; Laaksonen et al., 2009). For example, in a Danish study, LP adults consumed 5 glasses of milk/week compared to 2 glasses among LNP individuals (Bergholdt et al., 2018). It should be noted, however, that historical materials indicate that milk intake increased dramatically in Europe and the United States in the 19th century (Atkins, 2010; DuPuis, 2002; Wiley, 2015), and systematic data on earlier patterns of milk or non-fermented whey intake are lacking. In prehistoric dairying populations in Europe and Africa, archaeological materials indicate the presence of milk fat in sieves and pottery (Evershed et al., 2008; Ranciaro et al., 2014; Salque et al., 2013), while analysis of human dental calculus from Bronze Age skeletons from European regions with high LP allele frequencies identified the presence of β-lactoglobulin, a whey protein found in bovine and caprine milk (Warinner et al., 2014). The latter evidence is particularly important because β-lactoglobulin partitions with lactose when milk is separated (as in cheese-making), and hence represents a good marker of lactose, rather than dairy consumption more generally.

There are at least three hypotheses proposed to answer question (2): culture-historical, calcium assimilation, and hydration, and these are described in the next section. At present there is scant evidence for question (3). LP frequency has been positively correlated with pre-colonial population density (as a rough proxy for fitness) in Europe and Asia (Cook, 2014), but the mechanism by which LP contributes to fitness has not been demonstrated.

For most humans – like most other mammalian species – lactase production is a life history trait, as it corresponds roughly to the period of nursing. Considering lactase persistence and (non-human) milk consumption as related life history traits offers a new opportunity for developing and testing hypotheses about the spread of LP alleles in dairying populations. Life history traits are those that describe or differentiate stages of the lifespan, and impact individual survival and reproduction (Stearns, 1976). They are descriptors of individuals in a given life stage or they mark transitions between life history stages. For example, larger body size at a given age may reduce mortality, while earlier sexual maturation may enhance lifetime fertility. There are also well-described trade-offs in life history: prolonged growth and larger adult body size may reduce the window of time for reproduction. In general, these trade-offs are considered to occur along a "fast-slow" axis. Organisms with fast life histories grow rapidly, are small as adults, produce many small offspring, and die young compared to those with slow life histories (Promislow and Harvey, 1990), although more recent evidence suggests that the fast-slow axis does not adequately capture variability in fertility and mortality schedules across taxa (Jones et al., 2013b). Changes in the life history may reflect species-wide adaptations to a given set of environmental circumstances or result from individual- or population-level plasticity in the face of variable environments.

Much current work in life history theory revolves around understanding the mechanisms that underpin life history traits and their timing. Life history traits are choreographed, with changes in one influencing others, and there have been efforts to ascertain whether there is a common pathway through which environmental cues are translated into changes in life history parameters. While steroid hormones such as estrogen, progesterone, or testosterone have been the focus of research in humans (Bribiescas, 2001; Vitzthum, 2009),

Ben Dantzer and Eli Swanson (2012) suggested insulin-like growth factor I (IGF-I) as a potential candidate mechanism. IGF-I is produced in the liver as well as in in many somatic and reproductive tissues. It is regulated by pituitary growth hormone (GH), responsive to diet, and involved in the regulation of both growth and reproductive function (Bartke et al., 2013; Livingstone, 2013).

IGF-I is relevant to the evolution of lactase persistence for two reasons: milk is a source of IGF-I (Oftedal and Iverson, 1995), and milk consumption is associated with increases in circulating IGF-I (Qin et al., 2009). It is not clear whether milk IGF-I is absorbed intact from milk, or, if milk's components stimulate endogenous production (Holmes et al., 2002; Juskevich and Guyer, 1990; Rich-Edwards et al., 2007). An experimental protocol involving consumption of radioactively-labeled recombinant IGF-I found that IGF-I is not absorbed intact in humans (Mero et al., 2002), although absorption has been demonstrated in some (but not all) studies of neonatal pigs and calves (Hoeflich and Meyer, 2017). Of particular importance to the discussion of the evolution of LP is that IGF-I in milk is degraded in the process of fermentation but stable in the context of heat treatment or drying (Kang et al., 2006). Furthermore, circulating IGF-I concentrations appear to be more responsive to fresh milk consumption than dairy products such as cheese or yogurt (Esterle et al., 2009; Holmes et al., 2002; Norat et al., 2007).

Milk is an unusual food. It is produced by mammalian mothers to meet a wide range of infant needs (e.g. nutritional, immunological, hormonal) while nursing. Among other components, it contains a variety of growth factors including IGF-I that support infant growth and development. It would seem to follow that human consumption of milk from species with different life histories, along with consumption of such milk after the traditional life history

stage for nursing, would likely impact human life history parameters in ways that are mediated by IGF-I. Indeed, the extension of lactase activity beyond the weaning age represents a major life history modification.

In this paper I propose a novel hypothesis for the evolution of lactase persistence in dairying populations that links selection for LP alleles with milk consumption, higher circulating IGF-I levels, and fitness-enhancing life history alterations. In particular, higher IGF-I levels may be associated with more rapid growth and larger adult body size, early sexual maturation, or have fitness-enhancing effects on other physiological systems. There may also be negative pleiotropic effects on later life survival. Importantly, this proposal does not supplant existing hypotheses, but rather adds a new dimension to them by describing a mechanism by which milk consumption could enhance fitness among ancestral dairying populations.

I start with an overview of our current understanding of the evolution of LP and population variation in LP alleles and their relationship to dairying and milk consumption, and then consider existing evolutionary hypotheses proposed to account for this pattern of variation. I outline a justification for considering the milk consumption-IGF-I relationship and provide a brief overview of IGF-I and its role in the life history. Next I consider milk and other dairy consumption in relation to IGF-I, and review evidence linking milk consumption, IGF-I, and life history changes. This is followed by a discussion of predictions that follow from the hypotheses and potential data sources to test them. "Milk" here refers primarily to cow's milk, because almost all research relating current dairy intake to human IGF-I has referred to cow's milk and its products. Other mammals are kept for their milk, including goats, sheep, horses, camels, and water buffalo, but we know little about how consumption of

these forms of milk impacts human life history parameters or might have effects that are different from cow's milk. Information on IGF- concentrations in the milk of other dairy animals can be found in Meyer et al (2017).

Evolution of Lactase Persistence

Lactase (also known as lactase-phlorizin hydrolase [LPH]) is a small intestine ß-galactosidase that cleaves lactose into glucose and galactose. Lactose is found only in mammalian milk, and lactase likely co-evolved to allow nursing infants to digest this dietary carbohydrate, as mammals whose milk does not contain lactose (e.g. the pinnipeds) do not produce lactase (Kretchmer, 1972). For most mammals lactase activity peaks early in life and declines around the time of weaning (Kretchmer, 1989). Approximately 65% of contemporary *Homo sapiens* retain the ancestral mammalian alleles associated with lactase non-persistence (LNP), the phenotype of declining lactase production in childhood and low/no lactase production in adulthood (Itan et al., 2010). Evolution of the alleles associated with lactase persistence (LP) is unique to some human populations, and has been documented best in European and African dairying populations (Bersaglieri et al., 2004; Ranciaro et al., 2014; Tishkoff et al., 2007), with more limited evidence of LP alleles in Asia (Gallego Romero et al., 2011; Heyer et al., 2011). Multiple alleles contribute to the LP phenotype across human populations, and these mutations occur in promotor regions around the lactase gene (LCT). Five mutations conferring LP are best described: *–13907*G*, *–13910*T*, *–13915*G*, *–14010*C*, and *–14009*G* (Ségurel and Bon, 2017). Additional mutations associated with LP across the Old World are described in Liebert et al (2017). LP alleles have not been identified

among indigenous populations in the New World, where there were no dairying traditions prior to European contact.

There is a strong positive correlation between LP alleles and lactose digestion capacity (Ingram et al., 2009; Itan et al., 2010). In a Finnish study, *–13910*T* perfectly corresponded to biochemically-confirmed lactase persistence (Enattah et al., 2002), while *-14010*C*, *-13915*G*, and *-13907*G* accounted for about 45% of the phenotypic variance among populations in East Africa (Ranciaro et al., 2014). In Ethiopia, *-14009*G* was significantly more frequent among the lactose digesters vs. non-digesters (Jones et al., 2013a). Although *-13910*T* is considered dominant to *-13910*C*, heterozygotes do show intermediate lactose digestion phenotypes (Dzialanski et al., 2016; Enattah et al., 2007). It is important to note that LP allele status, phenotypic expression of lactase digestion, and individual reports of symptoms of lactose intolerance do not always correspond, and there is much individual variability in symptomatology that is not well understood, but may be related to colonic microbiota fermentation of lactose (Ségurel and Bon, 2017).

Evidence from genomic studies of contemporary human populations indicates that LP alleles appears after the adoption of dairying, with age ranges for the origins of the *-13910*T* allele roughly between 5,000-10,000 BP (Burger et al., 2007; Ingram et al., 2009), and more recent dates in East Africa for *-14010*C* (2,700–6,800 BP, Ranciaro et al., 2014). Ancient DNA (aDNA) analyses thus far indicate the earliest evidence of *-13910*T* around 4,000-5,000 BP (see Liebert et al., 2017 for a summary). LP alleles spread rapidly in both regions, and Bersaglieri and colleagues (2004) established that LP variants display the strongest signals of selection ever documented in the human genome (selection coefficients between 0.014 and

0.19). In some northern European populations LP allele frequencies can be greater than ninety percent (Itan et al., 2010).

Three major hypotheses have been proposed to account for the strong selection for LP alleles: the cultural-historical hypothesis, first outlined by Frederick Simoons (1970)and Robert McCracken (1971), the calcium assimilation hypothesis proposed by Flatz and Rotthauwe (1973), and the hydration hypothesis (Cook and al-Torki, 1975). LP mutations spread in dairying populations living quite distant from one another and in different environments, indicating convergent evolution (Itan et al., 2010; Tishkoff et al., 2007), and it may be unreasonable to expect that there was one universal selective force to explain the high rates of LP across them.

Cultural Historical Hypothesis

In two seminal papers, geographer Frederick Simoons reviewed what was known about the biology and genetics of lactose digestion in humans, population variation in lactose digestion, and traditions of dairying across human populations (Simoons, 1969; Simoons, 1970). Noting a strong correspondence between the presence of dairying and the ability to digest milk in adulthood, as well as absence of a dairying tradition and a high frequency of lactose intolerance, he proposed a culture-historical hypothesis. LP alleles were selected for in dairying populations that did not process milk into low lactose products (e.g. yogurt or cheese) "but that had other foods inadequate in amount and quality…Under these conditions, the lactase-aberrant [i.e. LP] adults would enjoy greater health and vigor, would better multiply, and would more successfully defend their families against others. And in their numerous descendants, high levels of adult lactase activity would come to prevail" (Simoons, 1970:700). Later he added that LP individuals

would "benefit nutritionally as a result, and would enjoy increased prospects of survival, well-being, and of bearing progeny and supporting them," (Simoons, 1981:29).

Working at the same time, Robert McCracken assembled a dataset of human populations with different levels of milk production and frequencies of "lactase deficiency," and proposed a similar hypothesis: " in a preindustrial society in which a large variety of foods is not available to most individuals, the introduction of new and more efficient dietary items, requiring unique genetic-based traits for assimilation, will give rise to selective pressures which favor those with the trait over those in whom it is absent. In this case, the lactose-tolerant are favored over the lactose-intolerant," (McCracken, 1971:495).

Both Simoons and McCracken are credited with a modern understanding of LP as the result of gene-culture co-evolution. That is, a cultural shift in subsistence to include dairying created new selective forces in dairying populations, leading to selection for LP alleles and evidence of high frequencies of these alleles in extant populations descended from those with longstanding dairying traditions. But the exact selective forces were not well-specified. Both posited unspecified health and reproductive advantages to individuals in dairying populations who had a genetically-encoded trait that allowed them to made use of milk (or other "lactose-rich" dairy products) and digest lactose in adulthood. Furthermore, they each stipulated an additional condition that must be present along with dairying: a scarcity of other high quality food resources. This is rarely considered; it is easier to posit in populations relying heavily on pastoralism, but less compelling in the European context, where mixed agro-pastoralism was the norm (Zvelebil, 2001). That said, famines from crop failures were common in European history (Gráda and Gráda, 2010).

Calcium Assimilation

In contrast to the generalized health benefits posited by Simoons and McCracken, Gerhard Flatz and Hans Rotthauwe (1973) proposed a very specific hypothesis to account for the high frequencies of LP alleles found among northern Europeans. They argued that LP alleles would have been selected for in high latitude regions characterized by low annual UV-B light. UV-B is necessary for conversion of epidermal 7-dehydrocholesterol to pre-Vitamin D_3, which isomerizes to Vitamin D_3 and then is converted in the liver and kidneys to 1,25-dihydroxycholecalciferol, the biologically active form of Vitamin D (Wacker and Holick, 2013). Low Vitamin D levels are a well-known cause of bone deformities such as rickets and osteomalacia, due to Vitamin D's role in calcium absorption and deposition into bone; compromise of these functions would have been a threat to individual survival and reproduction (Wacker and Holick, 2013). Importantly, lactose can act as a substitute for Vitamin D in the absorption of calcium in the small intestine (Cámara-Martos and Amaro-López, 2002; Lee et al., 1990), and given that infants cannot produce Vitamin D, this may explain the presence of lactose in most mammalian milks (Wacker and Holick, 2013). Thus according to this hypothesis, the ability to tolerate lactose in the gut would enhance calcium absorption and protect against bone malformities in the context of insufficient UV-B light to synthesize Vitamin D. This would further help explain why some southern European dairying populations have low frequencies of LP alleles and make extensive use of low-lactose dairy products. Durham (1991) tested this hypothesis using data on latitude, fresh milk and other dairy product intake, and reports on LP frequency across populations, and concluded that fresh milk consumption was highest among high latitude populations, with a separate clustering among African pastoralist populations.

More recent reviews have found only limited support for the calcium assimilation hypothesis, and it sheds little light on the evolution of LP alleles and milk consumption among low latitude pastoralist populations. Simoons (2001) challenged the existence of rickets as a widespread problem in ancient Europe and reviewed evidence indicating that LNP individuals are able to efficiently absorb calcium. Simulations of the evolution of LP have provided mixed results. Sverrisdóttir and colleagues (2014) found that selection was necessary to explain LP alleles in southwestern Europe, where Vitamin D production from UVB is not significantly constrained. Itan et al (2009) did not find that selection for LP alleles increased with latitude in Europe, but in a simulation model allowing for variation in selection intensity across time and space, Gerbault and colleagues (2009) reported that latitude did play a role in the evolution of LP alleles.

Hydration

Among low latitude pastoralist groups who often inhabit arid environments where plant-based agriculture poses significant challenges, Cook and El-Torki(1975) argued for the critical role of fresh milk consumption in meeting both caloric and hydration needs of pastoralists. In their view, fresh milk consumption, facilitated by LP alleles, would have been prevented dehydration and undernutrition in arid environments, where diarrheal disease would have been particularly deleterious.

Holden and Mace (2009) tested these three hypotheses using a global sample of human populations and adjusting for phylogenetic relationships, UV radiation, measures of aridity and degree of dependence on pastoralism. Their analysis supported the culture historical hypothesis, but not the calcium assimilation or hydration hypotheses, to account for the distribution of LP

alleles across human populations. They further confirmed that dairying most likely preceded the spread of LP alleles.

Other hypotheses

Other hypotheses advanced to account for LP alleles in dairying populations have included the benefits of milk as an uncontaminated source of fluid and protection from diarrheal disease (independent of arid environments) or as a buffer against other food scarcity (see Ségurel and Bon, 2017 for a summary of these). However, milk is also a well-known source of bacterial disease (such as tuberculosis, World Health Organization, 2017), and crop failures and lack of forage for animals may co-occur. Another hypothesis for LP alleles among pastoralist populations recognizes that fresh milk or whey provides a source of glucose from milk lactose, and glucose is a limited nutrient in the diet of groups relying heavily on animal products (Wiley, 2015).

One last hypothesis contends that LP alleles arose prior to the animal domestication and dairying. As the ancestral allele in humans, LP would have supported prolonged breastfeeding (Anderson and Vullo, 1994). However, when malaria became a major selective force in some human populations, prolonged milk consumption would have been deleterious as milk is a rich source of the B-vitamin riboflavin. Evidence suggests that malarial parasites are impaired by moderate riboflavin deficiency, and thus the inability to drink milk would have conferred some protection against malaria. However, given the ubiquity of LNP among mammals and humans, and recent evidence for the timing of the emergence and spread of LP alleles, it is not tenable to consider LP as the ancestral condition for humans. Furthermore, Meloni and colleagues found no evidence of covariance between LP/LNP frequencies and malaria exposure in southern

Europe (Meloni et al., 1998) and Lokki and colleagues (2011) found that there was no significant difference in falciparum malaria parasite number between those with LP compared to LNP among the Fulani of West Africa.

While researchers agree that LP alleles show signals of strong selection, other evolutionary processes such as migration and genetic drift could also contribute to its rapid spread. In an evolutionary simulation of LP alleles in Europe, Gerbault et al (2009) found the genetic drift alone could explain the distribution of LP alleles in southern Europe (contra Sverrisdóttir et al., 2014), while selection was required to account for LP frequencies in northwestern Europe. Furthermore, there is evidence that LP alleles spread with demographic diffusion across the continent. In Africa and Asia, admixture between pastoralist and non-pastoralist populations may also contribute to lower-than-expected frequencies of LP alleles among pastoralists (Ségurel and Bon, 2017). Gene flow has certainly contributed to the current geographical distribution of both LP and milk drinking (see Figures 1a and 1b), as Europeans colonized regions such as Australia, New Zealand and the Americas, where indigenous groups had no dairying traditions and LP alleles were absent.

In sum, current evidence indicates that LP constitutes a genetic adaptation to dairying and use of lactose-rich milk products, insofar as LP would have allowed individuals with the trait to make use of milk components. What remains at issue is whether those with LNP would have been disadvantaged, given the ease with which milk can be converted into lactose-reduced products such as yogurt or cheese, and that many LNP individuals appear to be able to ingest milk in small quantities without developing symptoms of lactose intolerance (Shaukat et al., 2010). In addition, it remains unclear which qualities of milk might make LP advantageous; neither lactose (to facilitate calcium absorption) nor water (as a source of fluid) seem to account

for the geographic patterning of LP frequencies across the globe. At very least it seems that LP confers the ability to tolerate substantial quantities of lactose beyond infancy, which would mean fresh milk or whey consumption post-weaning. Below I consider one particular aspect of milk consumption – its ability to generate a rise in circulating IGF-I – that has heretofore not been considered in hypotheses for the spread of LP alleles in dairying populations. This new hypothesis does require consumption of milk, as opposed to dairy products, or the scarcity of other foods, and may be independent of ecological conditions.

Insulin-like Growth Factor I (IGF-I)

IGF-I is a small peptide made up of 70 amino acids that is structurally similar to insulin. Vertebrates share a set of three related peptides: insulin, IGF-I, and IGF-II, which overlap in structure, function, and receptor affinity. IGF-I's cellular actions are initiated when it binds to the tyrosine kinase receptor IGF-IR. It will also bind with weaker affinity to insulin receptors, and both insulin and IGF-I enhance glucose and protein uptake (Livingstone, 2013). IGF-I is a potent mitogen, stimulates DNA and protein synthesis, and inhibits apoptosis, and thus plays key role in cellular growth in many tissues throughout the life cycle (Livingstone, 2013. Among humans, IGF-II is primarily active during gestation {Fowden, 2006 #3281).

IGF-I is produced in the liver and goes into circulation, where ~99% is bound to one of 6 binding proteins, of which IGFBP-3 is the most common in humans. The binding proteins serve to regulate IGF-I's biological activities and provide a reservoir of circulating IGF-I. IGF-I is also produced by most tissues. Hepatic IGF-I is regulated by pituitary GH and insulin, and both hepatic and tissue-specific IGF-I are responsive to nutrition, especially during infancy when growth hormone signaling is not fully established but energy and protein needs for growth are high (Livingstone, 2013). This is partially through insulin's positive effect on

IGF-I synthesis in the liver, and its inhibitory effects on IGF-I's binding proteins. In this way, insulin enhances both IGF-I levels and bioactivity, and these related molecules collectively serve as an energy-sensing mechanism linking nutrition and growth (Arafat et al., 2009). When protein and energy intake is below what is required, serum IGF-I levels diminish, binding proteins are elevated, and the liver becomes insensitive to GH.

IGF-I is the most abundant growth factor in bone and important mediator of both muscle and bone growth through its ability to stimulate protein synthesis and its involvement in calcium and phosphate metabolism (Kelly et al., 2003). In the brain, IGF-I promotes neuronal development and survival. It is also produced by, and acts on immune cells with IGF-I receptors (Weigent, 2013). Serum IGF-I rises during puberty and likely directs reproductive maturation as well as further growth in body mass. It plays numerous roles in female and male fertility, including ovarian maturation, ovulation, pregnancy, and spermatogenesis (Chandrashekar et al., 2004).

IGF-I: life history activities

As part of the endocrine system, IGF-I has the potential to translate environmental cues into adaptive biological responses, including those that shape the life history. Dantzer and Swanson (2012) proposed IGF-I as a common mediator of life history parameters across a wide array of species. The key ways in which IGF-I may affect life history parameters are illustrated in **Figure 2**.

In a phylogenetically-adjusted principal component analysis of mammalian species, Swanson and Dantzer (2014) found a suite of "fast" life history parameters that explained 66% of the variation in serum IGF-I levels across 41 mammalian species: body mass, maximum lifespan, age at sexual maturity, neonatal mass, gestation length and lactation length were each

negatively associated with circulating IGF-I concentration, while litter size was positively associated with IGF-I. The second component, which explained 12% of the variance, indicated higher IGF-I among species (including primates) with fewer offspring, small size at birth, prolonged post-natal development, and larger adult body size relative to their lifespan. Overall, their analysis indicated that IGF-I was more closely related to adult body size (negative correlation), growth rate, and basal metabolic rate (positive correlation) than the fast-slow life history axis itself. Analysis of another sample of mammals also found a negative association between adult IGF-I and body size, independent of lifespan, although this trend was not found among when the sample was restricted to primates (Stuart and Page, 2010).

In contrast to the inter-species comparisons, within species IGF-I is generally positively associated with greater body size at a given age (Bernstein et al., 2007; Dantzer and Swanson, 2012; Juul et al., 1994). Higher IGF-I is also associated with more rapid sexual maturation among females (Swanson and Dantzer, 2014), possibly via both stimulation of the gonadal steroid hormones and its direct effects on follicular and oocyte maturation (Hiney et al., 1991). In a longitudinal study of wild spotted hyenas, Lewin et al (2017) found that higher IGF-I among juvenile females was associated with both greater weight and earlier age at first birth, and the latter was associated with greater lifetime reproductive output. The likelihood of survival to reproductive maturity was higher among those with higher IGF-I concentrations, but post-reproduction survival probability was lower, indicating negative pleiotropic effects of early life IGF-I. Thus IGF-I may have the capacity to stimulate more rapid growth and maturation and greater body size-for-age within species and thereby alter trade-offs between growth and reproductive effort.

IGF-I in the human life history

Figure 3 shows changes in serum IGF-I concentration over the human lifespan, although it should be recognized that most of the samples on which these measures are based are from European populations (Bidlingmaier et al., 2014; Brabant et al., 2003). Reference values recently published for Chinese adults show a similar pattern, with some differences in absolute age values (Zhu et al., 2017). IGF-I is low at birth and increases gradually until the pubertal period when it rises more rapidly, reaching its peak around age 15 y for girls and boys. Following this peak there is a rapid drop off into the 20s, after which there is a gradual decline through the aging process. Thus IGF-I production tracks important life history events, especially during growth and the transition from somatic growth to reproductive maturation, as well as senescence.

In the prenatal period, maternal IGF-I levels rise throughout pregnancy, most likely to mobilize energy for supporting tissues (Caufriez et al., 1993). Importantly, maternal IGF-I does not cross the placenta, but may bind to IGF-I receptors on the maternal side to increase nutrient uptake (Boyne et al., 2003). The fetus also produces IGF-I, and studies show a positive association between umbilical cord blood IGF-I and birth weight (Geary et al., 2003; Hung et al., 2008; Vatten et al., 2002), ponderal index (weight/length^3, Roberfroid et al., 2010; Vatten et al., 2002), neonatal adiposity (Wiley et al., 2016), and placental weight (Boyne et al., 2003). Females have higher average IGF-I concentrations than males at birth (Geary et al., 2003; Vatten et al., 2002), suggesting that fetal IGF-I may contribute to differences in body composition including greater adiposity among females.

During later infancy IGF-I concentrations are consistently positively associated with length (Hoppe et al., 2004b; Ong et al., 2009; Wang et al., 2013) and are higher among infants

who experienced more rapid gains in weight or length, or catch up growth (*z*-score change ≥0.67, Chellakooty et al., 2006; Madsen et al., 2011; Ong et al., 2002). Throughout childhood IGF-I concentration remains positively correlated with height (Alberti et al., 2011; Thankamony et al., 2012). Indeed, IGF-I and GH are prescribed for children with very short stature (Grimberg et al., 2016). IGF-I concentrations have been found to be higher among children who grew rapidly in the past or who experienced catch up growth (Fall et al., 1995; Garnett et al., 1999; Wiley et al., 2018). Higher prepubertal circulating IGF-I concentrations are also associated with greater subsequent growth in height (Juul et al., 1994; Rogers et al., 2006b).

In adulthood associations between height and IGF-I are less consistent. Some studies show positive associations among men but not women (Crowe et al., 2010; DeLellis et al., 2004), while others find no relationship (Goodman-Gruen and Barrett-Connor, 1997; Gunnell et al., 2004), or variation by ethnicity (Faupel-Badger et al., 2009; Gapstur et al., 2004). In addition, researchers have demonstrated an inverse relationship between birth weight and IGF-I in early childhood (Chellakooty et al., 2006; Fall et al., 1995; Madsen et al., 2011; Wiley et al., 2018) and between IGF-I in infancy and early adulthood (Larnkjaer et al., 2009). So, IGF-I appears to be more closely associated with growth itself, and after circulating concentrations decline in adolescence, they no longer closely track body size in adulthood.

With regard to sexual maturation, high IGF-I levels at 8 y independently predicted both larger body size and earlier onset of menarche among a sample of girls in the United Kingdom (Thankamony et al., 2012), while higher IGF-I was also found among women with earlier ages at menarche in a Singapore cohort (Probst-Hensch et al., 2003). Similarly, among males, those who matured earlier (measured as age at peak growth velocity) had higher IGF-I in their

seventh decade of life, which remained after adjustment for height (Sandhu et al., 2006). In a test of associations between serum IGF-I and measures of fertility among British adults, Rickard (2012) found that while IGF-I contributed to variation in these measures in men and women, there were no consistent correlations between IGF-I and measures of reproductive success. IGF-I was negatively associated with time to pregnancy (i.e. months of having unprotected sex before conception) among women, and pubertal age among men, two variables less subject to behavioral modification than others measured in the study.

As Figure 2 indicates, IGF-I levels gradually decline during the aging process. Overall, there is evidence that higher IGF-I at older ages is associated with a decreased risk of cardiovascular mortality but an increased risk of various forms of cancer. A meta-analysis concluded that there was increased risk at both the high and low end of the IGF-I range for both causes of mortality (Burgers et al., 2011). At the same time, low IGF-I may contribute to greater longevity; among individuals who were 90+ years of age, lower IGF-I was associated with longer life expectancies (Milman et al., 2014). It has been suggested that IGF-I acts to enhance organisms' fitness but has longer term costs in terms of shortened lifespan (Junnila et al., 2013; Milman et al., 2014), most likely through increased risk of cancer (Kasprzak et al., 2017).

In sum, evidence indicates that IGF-I is involved in major life history transitions, and that within human populations, higher IGF-I is involved in more rapid growth, earlier sexual maturation, and larger body size in childhood. Furthermore, it also shows expected trade-offs between investment in growth and reproduction and longevity such that high IGF-I in the early decades of life may enhance fitness, while it is likely to be associated with reduced survival at

older post-reproductive ages, especially from diseases stemming from dysregulation of cell division.

IGF-I and milk consumption

Among dietary practices, consumption of dairy products, particularly milk, is most consistently linked to higher circulating IGF-I levels across the lifespan in humans, and serum levels of IGF-I rise after milk consumption (Cadogan et al., 1997; Crowe et al., 2009; Esterle et al., 2009; Giovannucci et al., 2003; Harrison et al., 2017; Holmes et al., 2002; Hoppe et al., 2004b; Young et al., 2012; Zhu et al., 2004). Beasley et al (2014) reported that a 3 serving increase in milk consumption was associated with an 18.6% increase in free IGF-I in circulation. In a test of milk vs. meat's impact on IGF-I among 8-year old boys, Hoppe et al (2004a) found a positive IGF-I response to milk but not meat. Both major cow's milk proteins have been shown to stimulate IGF-I and insulin signaling. Circulating IGF-I was more responsive to casein, while whey generated a stronger rise in insulin (Hoppe et al., 2009). One mechanism by which milk consumption might generate a rise in circulating IGF-I is through its insulinogenic actions (Nilsson et al., 2004).

Mammalian milk contains IGF-I as part of a suite of other growth and development-promoting milk components found in both the casein and whey portions. But given that IGF-I is produced by the fetus, neonate and infant, the function of IGF-I in milk is not clear. In pigs and cows, milk IGF-I has been demonstrated to promote growth and development of the neonatal gastrointestinal tract, and stimulate lactase activity (Blum and Baumrucker, 2008). Its effects on the gut appear to be most evident in the musculature and in the distal regions of the small intestine and colon (Cummins and Thompson, 2002), although other positive effects on

intestinal function, including gut maturation and nutrient transport, have been reported (Hoeflich and Meyer, 2017).

IGF-I's amino acid sequence is highly conserved across mammals and is identical in humans and cows (Stuart and Page, 2010). IGF-I concentrations in bovine milk are within the human range or higher, but much higher in bovine than human colostrum (Chatterton et al., 2013). The two species' milks are calorically similar, but bovine milk has about three times as much protein, four times as much calcium, and overall more minerals (except iron) than human milk (Patton, 2004). About 80% of protein in bovine milk is casein, compared to only 40% in human milk (Chatterton et al., 2013). Bovine milk also contains more short chain fatty acids, but less lactose (5 vs 7 g/100 ml) than human milk (Prentice, 1996). Cow's milk (and that of other ruminants) contains β-lactoglobulin, a whey protein not found in human milk. The differences in milk composition in part reflect species' variation in growth patterns during infancy. Cows grow rapidly in skeletal size and body weight, gaining 0.7–0.8 kg per day throughout lactation in the first year of life (Marlowe and Gaines, 1958; Reynolds et al., 1978), compared to breastfed human infants, who gain about 0.02 kg per day (World Health Organization, 2007).

IGF-I, bovine milk, and human life history parameters

Given evidence indicating that variation in IGF-I is associated with variability in critical human life history parameters, and that bovine milk consumption is associated with higher circulating levels of IGF-I, the question arises as to whether milk consumption alters the human life history in ways that would enhance fitness of milk drinkers, thereby facilitating the spread of LP alleles. Below I review evidence indicating ways that milk consumption is

associated with both circulating IGF-I and life history parameters, focusing on growth in height, sexual maturation, and aging.

Although the focus here is on IGF-I as part of the protein fraction of milk, it is important to keep in mind that milk contains many components that can affect growth and development. Milk is – like other foods – primarily a source of calories. Bovine milk is also very high in calcium, and because it is a major component of skeletal tissue, it has long been assumed that calcium would be the nutrient responsible for any relationship between milk and skeletal growth. However, studies have generally found that calcium intake itself has little or no relationship to growth in height (Bonjour et al., 1997; Bonjour et al., 2001; Dibba et al., 2000; Lee et al., 1995; Lee et al., 1994). Furthermore, a recent meta-analysis indicated calcium supplementation's effects on bone density were unlikely to reduce fracture risk (Tai et al., 2015).

Pertinent to the evolution of LP is that milk and dairy products may have quite different relationships to IGF-I or life history parameters. Several studies have found that consumption of dairy products (e.g. cheese, yogurt) have less strong, or no relationship to IGF-I or indices of growth and development (Holmes et al., 2002; Norat et al., 2007; Esterle, 2009 #2698, see meta-analysis by Qin et al., 2009; Rogers et al., 2006b; Wiley, 2010; Wiley et al., 2016). It has long been noted that the ease with which milk can be transformed into dairy products with little or no lactose in them poses a challenge for nutrition-related hypotheses for the evolution of LP alleles (Durham, 1991; Ségurel and Bon, 2017). Genetic evolution is relatively slow compared to change in cultural behaviors such as culinary traditions that include milk fermentation or separation for making yogurt or cheese. The fact that consumption of dairy products seems to

have less of an impact on IGF-I or life history parameters lends support to the hypothesis that fluid milk's effects on IGF-I might contribute to the spread of LP alleles.

Prenatal growth

Multiple studies have shown that maternal milk intake is positively associated with fetal growth (Heppe et al., 2011; Kanade et al., 2008; Ludvigsson and Ludvigsson, 2004; Mannion et al., 2006; Olsen et al., 2007; Xue et al., 2008) and placental weight (Godfrey et al., 1996; Olsen et al., 2007) after controlling for a variety of confounders. In an Indian cohort, maternal milk, but not dairy product intake in the third trimester of pregnancy was positively related to IGF-I in cord blood, independent of neonatal size (Wiley et al., 2016), but there is no published research on the relationships between maternal milk intake, maternal IGF-I and fetal IGF-I.

The pathways by which maternal milk intake might contribute to fetal growth via IGF-I are unclear, and any relationship between maternal milk intake, IGF-I and fetal growth likely only occurs through alterations in placental size or function (Boyne et al., 2003). Maternal IGF-I has been positively correlated with placental weight and birth weight in some studies (Boyne et al., 2003), but not in others (Holmes et al., 1998; Orbak et al., 2001; Pathmaperum et al., 2007).

Infancy

Cow's milk consumption is not generally recommended for infants below one year of age due to the allergenicity of cow's milk proteins and its low iron content (Michaelsen et al., 2007; Ziegler, 2007). Despite this, many infants are given cow's milk well before their first birthday. In a survey of European countries, researchers reported that 18% of infants were receiving cow's milk as their only milk source by 9 months of age, while 33% had received

some along with other source of milk or formula. By 12 months, 31% were consuming cow's milk as their primary milk and 50% were receiving some (Freeman et al., 2000). In the National Health and Examination Survey, a representative sample of U.S. children in 1999-2002, 34% of infants were drinking milk daily by their first birthday (Wiley, 2009).

Infant formula is more commonly given to infants who are not being breastfed, or whose nursing is being supplemented. Most formula is based on cow's milk, and the protein content is greatly reduced compared to plain cow's milk and more closely aligned with that of breastmilk. Formula fed infants grow faster and to heavier weights and greater lengths than breastfed infants, especially in the first six months of life (Agostoni et al., 1999; Chellakooty et al., 2006; Dewey et al., 1995; Michaelsen et al., 1994; Ong et al., 2002). They also have higher levels of IGF-I than breastfed infants (Chellakooty et al., 2006; Ong et al., 2002). Infants consuming plain cow's milk have been found to have higher IGF-I than those consuming formula (Larnkjaer et al., 2009).

Child growth in height

A number of studies have evaluated the relationship between milk consumption and growth in height among children, and some also measured IGF-I. Milk supplementation studies have been mixed in their results, and none have been able to distinguish which components of milk might be responsible for any differences in height between those who received a milk supplement and those who did not (see Wiley, 2012 for a review). Very few studies compared milk consumption to supplements of other nutrient-rich foods to ascertain whether milk has unique growth-enhancing properties that are seen at different periods of growth and development.

A meta-analysis of 12 studies from throughout the 20th century that considered the effects of milk supplementation on growth in height and that met specific quality criteria concluded that, on balance, these studies show a modest positive effect on growth in height among children 2-18 years of age (de Beer, 2012). The effect was around 0.4 cm per year per additional serving of milk, and greater when children were undernourished at the study's inception, or among adolescents (see **Table 1**). All of the studies were of relatively short duration, and longer supplementation periods were associated with declining annual rates of growth, so the long-term consequences of increased milk intake are not clear. Other reviews suggest that milk may contribute to greater height during periods of rapid growth such as early childhood and adolescence (Wiley, 2012).

Among observational studies, Hoppe et al (2006) found that IGF-I levels were positively correlated with both milk intake and height among 2 yr-old Danish boys, while a study of 7-8 yr olds in the United Kingdom (Rogers et al., 2006a) found a positive correlation between milk consumption, leg length, and IGF-I levels among boys, but not among girls. In a study of a cohort of U.S. girls followed from the ages of 9 to 11 through adolescence, those who drank more milk at baseline or during adolescence grew taller (Berkey et al., 2009). Importantly, their growth spurt stopped at the same time as that of the girls who drank less milk, but they grew faster and the net effect was greater height (2.5-5.0 cm) among those who drank more milk in adolescence (>3 glasses/day vs. <1 glass/day)

LP alleles (esp. *-13910*T*) themselves appear to have mixed associations with different aspects of body size and composition. In a Swedish sample, Almon and colleagues found that *-13910*T* and milk consumption were independently and positively associated with height (Almon et al., 2011). However other studies have found that associations between LP and

height in European populations can be explained by population stratification (Campbell et al., 2005). A meta-analysis of studies relating LP status (*-13910*T*) to body mass index (BMI) in European adults found greater BMI among LP individuals, independent of population structure (Kettunen et al., 2010). There are currently no published data on IGF-I concentrations and LP status specifically, and relationships between LP status and body size may reflect greater intake of milk and dairy products and thus overall nutrient intake and greater IGF-I signaling.

Sexual maturation

Studies of the relationship between childhood milk consumption and age at menarche have shown that higher milk intake is associated with a lower age at menarche or risk of early menarche (Ramezani Tehrani et al., 2013; Wiley, 2011), although other studies have not found significant relationships (Carwile et al., 2015; Zhu et al., 2004). Kwok et al (2012) found no association between milk consumption in early childhood and pubertal onset in boys and girls in a Hong Kong cohort. Berkey et al (2000) and Sanchez et al (1981) reported that girls with greater animal protein intake had lower ages at menarche, although other studies did not find this association (Moisan et al., 1990; Petridou et al., 1996). Increased animal fat (Colditz et al., 1987) and calcium intake (Chevalley et al., 2005) have also been associated with decreased age at menarche, and are both related to milk consumption. In the Tehran Lipid and Glucose study, only consumption of milk (rather than other dairy products such as cheese or yogurt) was associated with early menarcheal age (Ramezani Tehrani et al., 2013). Formula-fed female infants appear to have earlier menarche than those who were breastfed, possibly because of the association of formula feeding with more rapid growth and weight gain in infancy (Novotny et al., 2003). In sum, at this point, evidence for links between milk intake in childhood and sexual maturation remains inconclusive.

Milk, IGF-I and later life morbidity and mortality

The relationship between cow's milk consumption, IGF-I and early life history parameters is important not only in the short term, but over the life course these may alter the risk of bone fractures and osteoporosis, some types of cancer, and cardiovascular disease (CVD). The most frequently cited long-term benefit of childhood cow's milk consumption is its positive effect on bone health and decreased risk of fracture, both during childhood and at older ages (Heaney, 2000). Milk consumption is positively related to IGF-I, and IGF-I in turn is positively associated with bone mineral density (Boonen et al., 1996; Esterle et al., 2009). However, studies of the relationship between milk consumption and bone density in childhood do not reveal consistent relationships (see reviews in Dror and Allen, 2014; Lanou et al., 2005). Likewise, there is mixed evidence that milk consumption in childhood is positively correlated with reduced risk of fractures in adulthood (Feskanich et al., 2014; Kalkwarf et al., 2003), or between milk intake (rather than dairy product intake), bone density, or risk of fracture (see systematic review and meta-analysis in Bian et al., 2018). Across populations osteoporosis and related fractures are, paradoxically, highest among countries with the greatest milk and dairy intake (Kanis et al., 2012), indicating the importance of other environmental and behavioral factors in these outcomes.

Milk consumption has been linked to chronic diseases including various cancers and cardiovascular disease, increasing the risk of some and decreasing the risk of others (Aune et al., 2015; Elwood et al., 2010; Huth and Park, 2012; Moorman and Terry, 2004). In terms of overall mortality risk, a recent population-based study of two adult cohorts in Sweden (average age at baseline in late 50s) found that the risk of all-cause mortality increased with greater milk intake (adjusted hazard ratio 1.15 for each glass of milk). Mortality from cardiovascular disease and

cancer each showed a similar pattern (hazard ratio: 1.15, 1.07, for each glass of milk, respectively). Fracture risk also rose with increasing milk intake for women. Among men, the pattern was less pronounced, and there was no relationship between milk intake and fracture risk (Michaëlsson et al., 2014). Interestingly, fermented milk products or cheese did not show this same pattern, and another study that found positive associations between milk consumption and mortality reported similar protective effects of fermented milk products (Tognon et al., 2017). Milk intake was also positively associated with various markers of oxidative stress and inflammation. The authors argued for a causative role of D-galactose, one of the two sugars that comprise lactose, which has been associated with oxidative stress, inflammation, and premature aging in animal models (Michaëlsson et al., 2014). The authors re-analyzed the data controlling for fruit and vegetable intake and total anti-oxidant intake (which should mitigate this potential effect of D-galactose), and found that the positive relationship between milk intake and mortality remained, and was especially pronounced among women (Michaëlsson et al., 2017). This suggests that other components of milk, such as IGF-I (which contributes to oxidative stress), might be contributing to increased older-age mortality (Bartke et al., 2013). That said, other studies have not found a relationship between LP status or milk intake and mortality (Bergholdt et al., 2018), and earlier meta-analyses have indicated mostly neutral relationships between milk or dairy product intake, cardiovascular disease markers, and mortality (Drouin-Chartier et al., 2016; Guo et al., 2017)

Components of milk that may increase the risk of chronic diseases include saturated fat and IGF-I, while calcium has been posited as anticarcinogenic (Moorman and Terry, 2004). Most of the research linking dairy products to cancer has focused on IGF-I, citing its involvement in the unregulated growth of neoplastic cells (Ben-Shlomo et al., 2003; Gunnell et

al., 2001; Harrison et al., 2017; Ji et al., 2015). Adults who were taller during childhood have higher IGF-I levels than those who were shorter or who exhibited catch-down growth (Ben-Shlomo et al., 2003), and height itself is positively associated with cancer risk at numerous sites (Ihira et al., 2018; Ong et al., 2018). At the same time there are reports that adults who drank more milk in early childhood or whose mothers consumed more milk during pregnancy exhibited lower IGF-I in adulthood, independent of current body size (Ben-Shlomo et al., 2005). Among females, greater dairy protein intake around puberty was associated with higher IGF-I in adulthood (Joslowski, 2013 #2736, although see Anette et al., 2001).

The links among cow's milk consumption, IGF-I and cancer risk are very complex, and dependent on numerous other factors. For example, if milk intake in childhood has the capacity to decrease the age at menarche, this could be a route by which milk increases the risk of reproductive cancers, as earlier age at menarche is linked to an increase in breast cancer risk (Berkey et al., 1999; Petridou et al., 1996). Additionally, lactose intake was associated with later menopause in the U.S. Nurses Health Study (Carwile et al., 2013), which is also a risk factor for breast cancer. In the Boyd-Orr cohort, childhood milk intake in the highest quartile was associated with a 3-fold increase in the risk of colo-rectal cancer compared to the lowest, but not cancer at other sites (van der Pols et al., 2007). However, in a study in New Zealand, participating in a school milk program reduced later life risk of colo-rectal cancer (Cox and Sneyd, 2011). Prostate cancer was three times more likely in an Icelandic cohort of men who drank milk daily during adolescence (compared to <1 glass day) (Torfadottir et al., 2012), while the risk of breast, lung and ovarian cancer was lower among those diagnosed with lactose intolerance in a Swedish population-based study (Ji et al., 2015). The literature on milk intake and cancer at various sites is too extensive to review here, but increasing attention

is being paid to diet prior to adulthood as a contributor to later life cancer risk (see Clarke and Joshu, 2017).

Predictions and future tests of the hypothesis

The hypothesis outlined here is that selection favored LP alleles in dairying populations due to the IGF-I promoting effects of fresh milk (or whey) consumption, which may, in turn, alter life history trajectories. The LP phenotype and the associated behavior of drinking the milk of other species well beyond typical weaning age constitutes a major life history change. Mammalian milk is both a source of nutrients and signaling molecules that guide infant development (cf. Hinde et al., 2015), and exposure to milk – especially from mammals with different life history trajectories - throughout life has the potential to send ongoing signals for growth and development. Current evidence suggests that LP and the ability to consume milk beyond a typical age of weaning (2-3 years in humans, Kennedy, 2005) accelerates and increases overall growth, but does not extend the period of growth. Evidence is inconclusive as to whether it also shortens the time reproductive maturation. In focusing on life history alterations, milk consumption throughout the period of growth and development is most critical, rather life-long milk intake. Among adults, milk drinking may provide a rich nutrient source to support both somatic and reproductive investment, but given the mitogenic potential of milk-driven IGF-I signaling, it may also increase the risk of cancer later in life. At this point it remains to be seen if childhood milk consumption and IGF-I is more closely related to these later life outcomes than adult milk consumption – limited current research suggests that it is.

Much more research is necessary to test the hypothesis. Different data sources can be used to test these predictions, and necessarily, most evidence will be indirect. For example, in

skeletal remains of prehistoric dairying populations, the hypothesis would predict that individuals with ß-lactoglobulin in dental calculus would have fewer indices of growth disruption (indicated by Harris lines on long bones or enamel hypoplasia) or greater adult height or evidence of earlier skeletal maturation compared with those without evidence of ß-lactoglobulin. Comparisons between dairying and non-dairying archaeological populations for these same outcomes are also possible but other ecological differences must be considered. Without a biomarker of IGF-I in skeletal materials, these data cannot determine a role for IGF-I specifically.

Comparisons between contemporary populations with high vs low frequencies of LP or within populations and between individuals with/without LP alleles could be used to test whether those with high frequencies of LP have greater serum IGF-I concentrations at pre-adult ages that are attributable to higher milk intake. Outcomes such as height, age at sexual maturation, and measures of fertility or chronic disease have complex etiologies, and any relationship with milk consumption risks being confounded by other covariates. Currently a natural experiment is ongoing, as fresh milk consumption is rising in populations with high rates of LNP, such as those in China and Southeast Asia (Wiley, 2015), and any evidence of increasing IGF-I, height, reduced age at sexual maturity, and adult cancer mortality in such populations would suggest life history alterations related to milk consumption. Given overall increases in food intake, especially animal source foods, concurrently in such populations, well-controlled and large-scale longitudinal studies are essential (Delgado, 2003). Clearly this current trend does not reflect the conditions that existed when LP alleles originally spread, but it offers potential insight into biological changes associated with greater milk consumption among individuals with ancestral LNP alleles. Furthermore, in any contemporary study of

milk consumption it is important to acknowledge that milk from commercial milk production may not accurately reflect its contributions to human life history parameters in the past. Researchers have highlighted the practice of milking cows in the latter part of pregnancy, when estrogen and progesterone levels are elevated, as possibly altering the hormonal constituents of milk, with physiological effects on consumers (Ganmaa and Sato, 2005).

Experimental protocols are also possible to test the hypothesis. While LP has only been demonstrated in humans, it is possible to use a mammalian model to explore the effects of milk consumption on IGF-I among organisms that are LNP. Organisms can also be given exogenous oral lactase to better understand how milk or dairy intake affects IGF-I and whether lactose alters such relationships. Data from domesticated mammals whose characteristics are carefully managed to achieve faster growth and higher reproductive rates may be particularly apt. It is also possible to observe the effects of life long milk intake on longevity in a model system and compare the outcomes associated with milk, whey, and dairy product intake.

Ultimately these any life history alterations related to ongoing milk consumption need to confer higher fitness. Children who drink milk tend to have greater IGF-I and height, which confers a survival advantage, as shorter height is associated with increased child mortality (Pelletier, 1994). Furthermore, among contemporary populations, height is consistently associated with greater fitness among men (Pawlowski et al., 2000), and among subsistence societies, this pattern is observed for women as well (Sear et al., 2004). Height is also positively correlated with income within and across countries (Deaton, 2007). As height is mediated by IGF-I during growth, it likely has negative later life impacts in terms of increased risk of cancer in particular, as studies have indicated (Ong et al., 2018). At present there is little evidence that reduction in fracture risk at any age is a consistent benefit associated with

milk consumption.

Summary and Conclusions

If individuals with the LP mutation were able to release the ancestral age constraint on milk consumption and make use of non-human milk well past the traditional time of weaning and into adulthood, they may have had some life history advantages such as more rapid growth and larger body size at a given age. Milk's positive effects on circulating IGF-I strongly implicate this molecule as a mediator of any life history consequences. Importantly, the IGF-I hypothesis is consistent with the culture historical hypothesis, and provides a mechanism by which the purported nutritional benefits of milk drinking might manifest physiologically. Given that only milk – rather than dairy products more broadly – seems to influence circulating IGF-I levels, it adds explanatory power to why LP alleles would have spread in dairying populations when conversion of milk into lactose reduced dairy products that are equally nutrient-rich is relatively easy.

Although this review has focused on easily-measurable life history traits such as body size and age at sexual maturation, it may also be that other targets of IGF-I itself are important, as it has general mitotic and anti-apoptotic effects in many tissues. Although there is currently little evidence for links between milk intake, IGF-I, and reproductive function, it has been suggested that milk consumption increases the risk of twin births in humans (Steinman, 2006) and cows selected for higher rates of twinning have higher circulating and follicular IGF-I (Echternkamp et al., 1990). Alternatively, given that zoonotic infections likely increased in populations that domesticated mammals (Armelagos et al., 1991), IGF-I's involvement in immune function may be important. Regardless, highlighting the relationship between lactose-

containing milk consumption and IGF-I offers new possibilities for developing and testing hypotheses to explain the rapid spread of LP alleles in diverse dairying populations.

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