Original Research Article

Evidence that Parent-of-Origin Affects Birth-Weight Reductions at High Altitude

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ABSTRACT Hypoxia exerts a profound depressant effect on fetal growth, lowering birth weight, and raising mortality risk. Multigenerational high-altitude populations are relatively protected from this birth-weight decline, leading us to hypothesize that genetic factors were involved. We asked if the amount of high- versus low-altitude ancestry influenced birth weight at high altitude and, specifically, whether such influences were affected by parent-of-origin effects (i.e., genomic imprinting). Medical records were reviewed from 1,343 consecutive, singleton deliveries in La Paz, Bolivia (3,600 m) of high- (Andean) or low- (European) altitude ancestry. Parental surnames were used to classify ancestry as Andean, European, Mestizo ("mixed") or some combination thereof. The effects of population ancestry on birth weight were determined by categorical, conditional linear regression. Babies born at altitude with two Andean parents weighed 252 g more than their European counterparts, with the protective effect being proportional to the amount of Andean parentage and independent of maternal parity, body size, smoking, or socioeconomic status. Paternal compared with maternal transmission raised birth weight 81 g for a given ancestry group. We concluded that indigenous high-altitude ancestry protected against hypoxia-associated fetal growth reduction in a dose-dependent fashion consistent with the involvement of genetic factors. Further, some of the genes involved appeared to be influenced by parent-of-origin effects, given that maternal transmission restricted and paternal transmission enhanced fetal growth. Am. J. Hum. Biol. 20:592–597, 2008.

Reduced birth weight raises the risk of mortality and morbidity during infancy as well as later in life (Barker et al., 1989). Populations residing at high altitude (>2,500 m) provide an experiment of nature for determining whether genetic factors influence hypoxia-associated reductions in birth weight. While a birth weight reduction has been seen in every population studied to date, the magnitude of decline varies such that babies born to populations who have resided at high altitudes for multiple generations (Andeans, Tibetans) are protected relative to those of low-altitude ancestry (Europeans, Han "Chinese") (Giussani et al., 2001; Haas, 1981; Jensen and Moore, 1997; Moore, 1990; Mortola et al., 2000). Such differences cannot be attributed to variation in maternal body size, parity, smoking behavior, gestational age, or the occurrence of pregnancy complications, but rather appear because of physiological factors regulating uterine blood flow and hence fetal growth (Moore et al., 2001; Wilson et al., 2007; Zamudio et al., 1993).

To test the hypothesis that genes influenced the hypoxia-associated reduction in birth weight, we asked if birth weight at high altitude varied in relation to the amount of high- versus low-altitude parentage. Birth weight and other data were examined for 1,343 consecutive deliveries in La Paz, Bolivia, the highest capital city in the world where large numbers of persons of high- (Andean) and/or low- (European) altitude ancestry reside. We used surnames to assess population ancestry since these afford good correlation with gene marker data and permitted us to examine whether the effects of ancestry were influenced by maternal versus paternal transmission (i.e., "parent-of-origin"). We considered that such information was of interest not only for improving our understanding of the role of genetic factors in the determination of birth weight, but also was of public health relevance for the 140 million persons living at high altitude and comprising the largest group worldwide at risk for fetal growth restriction (Krampl, 2002).

METHODS

Subjects and definitions

Medical records were examined for 1,520 consecutive, singleton deliveries at the two largest, public or private maternity units providing prenatal care in La Paz, Bolivia. All births to women with two or more prenatal visits were reviewed for the periods January–April 1998 in the public and January 1996–April 1999 in the private facilities, the longer sampling period being required to obtain similar-sized samples (n = 768 public and n = 752 private). The Colorado Multiple Institutional Review Board and the Colégio Medico, the ethical oversight groups for the institutions involved, reviewed study procedures and

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judged that informed consent was not required from the patients whose medical records were reviewed. The same persons evaluated and abstracted all medical records. Inclusion criteria were at least two prenatal visits and three of the baby's four parental surnames were present. Prenatal care was required to permit the diagnosis of preeclampsia for a related project (Keyes et al., 2003) and also allowed us to reduce the confounding effects of lack of prenatal care on birth weight. Excluded were women with known risk factors for fetal growth restriction (40 women with chronic hypertension, 12 of whom developed superimposed preeclampsia, and 4 women with gestational diabetes) and cases which lacked birth weight, sex, or gestational age information ($n = 133$), leaving 1,343 cases for the analyses reported here.

Information was tabulated concerning the mother's surnames, nationality, smoking behavior, health history, date of last menstrual period, age, gravidity, parity, education, BP, and body weight during pregnancy; father's surnames and nationality; infant sex, birth weight, and gestational age. Gestational age was calculated as weeks from the last menstrual period unless values differed by more than 2 weeks from those obtained by clinical exam, in which case the latter value was used. Babies born at less than 37 weeks were considered preterm. Small for gestational age (SGA) was defined as birth weights less than the 10th percentile for gestational age and sex using a large sea-level series that had been validated with perinatal mortality criteria (Williams et al., 1982). Preeclampsia was defined as reported previously (Keyes et al., 2003).

Surnames were used to classify each baby's mother's and father's ancestry. We employ "ancestry" rather than "ethnicity," or "race" since we had no knowledge of the person's cultural practices as required for assessing ethnicity, and conventional racial designations are not well suited for describing these study populations. In Bolivia each parent has two surnames, consisting of his/her mother's and father's paternal surnames, and these surnames do not change with marriage. While paternity was difficult to know with complete certainty, most unions were church-sanctioned "marriages" and therefore we can be reasonably confident of paternal classification. In 79% of the cases, all four surnames were present; the remainder had three surnames by study design. Surnames were considered Andean (A) when Aymára or Quechua in origin (i.e., the languages spoken by indigenous Andean residents), European (E) if non-Hispanic or nationality was foreign, and all others classified as "Mestizo" (M, mixed) (Schull and Rothhammer, 1977). Classification of population ancestry using surnames correlates closely with that obtained using genetic markers (Chakraborty et al., 1989).

Statistical analyses

Values are reported as mean ± standard error of the mean (SEM) unless specified otherwise. Comparisons among ancestry groups were performed using analysis of variance for continuous variables and χ^2 tests for categorical variables (SPSS, 2002). Nonparametric tests were used to evaluate the relationship between the mother's and father's ancestry. After confirming that birth weight demonstrated a normal distribution, the effects of parental ancestry on birth weight were examined by linear regression using the R statistical computing and graphics environment (R Development, 2005). Each parent's ancestry was coded in a categorical as well as a conditional way in order to take his/her spouse's ancestry into account. The resultant model was $y = -1749.90 + 126.14x_1 + 17.02x_2 + 16.75x_3 - 187.92x_4 - 73.53x_5$ where x_1 represented gestational age; x_2, x_3, and x_4 were "dummy" variables for the "other" parent's ancestry; and x_5 was an indicator for one parent being Mestizo. Gestational age, maternal age, parity, smoking, maternal education level, and week of first prenatal visit were included as covariates in some models. The final model was verified by examining residuals and other standard diagnostics as well as with a stepwise approach that included all the above terms as well as any interactions. Variables and individual coefficients in the model were assessed using traditional t test or F-test, and comparisons considered significant when $P < 0.05$.

FATHER \ MOTHER	AA, %	AM, %	MM, %	ME, %	AE, %	EE, %	Total, %
AA, %	5	5	3	0	0	0	13
AM, %	4	5	6	2	0	0	15
MM, %	4	6	41	6	0	2	59
ME, %	0	0	7	1	0	1	9
AE, %	0	0	0	0	0	0	1
EE, %	0	0	1	0	1	1	3
Total %	13	16	58	8	0	4	100

Fig. 1. Distribution of ancestry groups for mothers and fathers of 1,343 babies born at the two largest private or public maternity units in La Paz, Bolivia (elev 3,600 m). Parental surnames were classified as Andean (A, of Aymára or Quechua origin), European (E, non-Hispanic or European nationality), Mestizo (M, "mixed") and then used to define each parent's ancestry. Most unions occurred between two M persons, intermediate numbers took place between M and A or E, and very few involved A and E groups. Surname origin is ignored for heterogeneous groupings; that is, either the maternal or paternal surname could be Andean in AM cases. Cells with percent frequencies greater than 5% are highlighted for clarity.

RESULTS

Parental characteristics

Maternal and paternal ancestries were closely correlated ($r = 0.56$, $P < 0.001$), indicating positive assortative mating (see Fig. 1). The most common matings were between Mestizo-Mestizo (MM) men and women, followed by those involving Andean-Andean (AA), Andean-Mestizo (AM), Mestizo-Mestizo (MM), or Mestizo-European (ME) partners. There were very few Andean-European (AE) persons ($n = 14$ or 1%) and no marriages between AA and European-European (EE) individuals.

Women of AA or AM ancestry were slightly younger than those of MM, ME, or EE parentage, and of similar gravidity but of higher parity (Table 1). The higher parity together with similar gravidity suggested that prenatal mortality rose with increasing amounts of European ancestry. By study design all women received prenatal care, but those from the ME or EE groups began their care earlier than did the AA, AM, or MM women. Socioeconomic status, as judged by the proportion receiving a post-secondary education, was markedly lower in the AA or AM women compared with the other ancestry groups.

TABLE 1. Maternal and infant characteristics as classified by maternal ancestry group

Variable	Andean-Andean	Andean-Mestizo	Mestizo-Mestizo	Mestizo-European	European-European	*P*-value
Mat age (years)	27.8 ± 0.4* (170)	27.8 ± 0.4* (216)	30.1 ± 0.2† (792)	30.3 ± 0.5† (180)	30.3 ± 0.6† (62)	<0.0001
Parity, no. live births	2.6 ± 0.1* (170)	2.5 ± 0.1* (216)	2.2 ± 0.0† (792)	2.2 ± 0.1† (180)	1.9 ± 0.2† (62)	<0.0001
Gravidity, no. pregnancies	3.0 ± 0.1 (170)	2.8 ± 0.1 (217)	2.6 ± 0.1 (796)	2.7 ± 0.2 (107)	2.6 ± 0.3 (61)	NS
Smoking, % yes	0 [0, 0] (148)	0 [0, 0] (197)	5.4 [4, 7] (647)	10.0 [5, 17] (90)	8.9 [3, 20] (45)	<0.0001
1st prenatal visit (week)	19.3 ± 0.6* (170)	19.9 ± 0.5* (215)	15.0 ± 0.3† (716)	11.6 ± 0.6† (93)	12.6 ± 1.2† (48)	<0.0001
<Secondary high school education (%)	35 [28, 42] (166)	29 [23, 35] (215)	6 [1, 4] (644)	3 [1, 8] (74)	0 [0, 0] (43)	<0.0001
Mat wt at 1st visit (kg)	59.8 ± 0.7 (168)	59.5 ± 0.5 (213)	59.4 ± 0.4 (618)	59.7 ± 1.0 (73)	59.3 ± 1.4 (43)	NS
Mat wt at term (kg)	66.7 ± 0.7 (168)	66.4 ± 0.5 (217)	68.2 ± 0.3 (772)	68.2 ± 0.6 (104)	68.2 ± 1.2 (56)	NS[a]
Mat wt gain (kg)	6.9 ± 0.3 (166)	6.8 ± 0.3 (213)	8.4 ± 0.2 (595)	8.9 ± 0.6 (71)	9.9 ± 1.0 (36)	NS
Preeclampsia[b] (%)	20.1 [15, 26] (170)	17.2 [13, 23] (215)	17.3 [15, 20] (715)	22.6 [15, 32] (93)	22.9 [13, 36] (48)	<0.05
MAP at 1st visit (mm Hg)	79 ± 1* (170)	79 ± 1* (215)	77† ± 0 (715)	77 ± 1 (93)	76 ± 1 (48)	<0.01
MAP at term (mm Hg)	87 ± 1 (165)	88 ± 1 (212)	87 ± 0 (776)	89 ± 1 (107)	90 ± 2 (57)	NS
MAP max (mm Hg)	90 ± 1 (170)	90 ± 1 (215)	87 ± 0 (715)	86 ± 1 (93)	87 ± 2 (48)	NS
Baby birth weight (gm)	3,163 ± 36* (170)	3,145 ± 36* (217)	3081 ± 17 (785)	2978 ± 52 (103)	2907 ± 55† (61)	<0.001
Gestational age (weeks)	39.3 ± 0.1* (170)	39.2 ± 0.1* (217)	38.5 ± 0.1† (786)	38.1 ± 0.2† (107)	38.8 ± 0.2 (61)	<0.0001
Male sex (%)	51 [44, 59] (168)	49 [43, 56] (216)	54 [51, 58] (787)	49 [40, 59] (104)	57 [45, 69] (61)	NS
SGA (%)	10.6 [7, 16] (170)	17.0 [13, 23] (217)	15.4 [13, 18] (780)	19.6 [13, 28] (102)	32.8 [22, 45] (61)	<0.01
Preterm (%)	4.1 [2, 8] (170)	6.4 [4, 10] (217)	12.1 [10, 15] (786)	14.0 [8, 22] (107)	13.1 [6, 23] (61)	<0.05

Mat, maternal; no, number; wt, weight; MAP, mean arterial pressure; SGA, small for gestational age defined as <10th percentile for gestational age and sex compared with sea-level values (Vargas et al., 2007).
Values are mean ± SEM or 95% confidence intervals for proportions. Sample sizes are in parentheses. Different symbols indicate designate significant pair wise comparisons using Scheffé post-hoc tests.
[a]$0.05 < P < 0.10$.
[b]Both mild and severe disease; frequency of severe preeclampsia in AA = 0.6%, AM = 1.4%, MM = 0.7%, ME = 0%, EE = 2.1%, p = NS.

Only 19 (1.4%) of the women smoked—all of whom were from the MM, ME or EE groups—but nearly all (90%) smoked less than half a pack of cigarettes per day.

Weight at the first prenatal visit was similar among all ancestry groups whether or not the week of the first visit was taken into account (Table 1). Maternal body weight at term was also similar; hence, weight gain during pregnancy was equivalent in all groups. Maternal blood pressure (BP) at the first prenatal visit was slightly higher in the AM than MM women, but the frequency of preeclampsia, maximal BP during pregnancy, and BP at term did not differ among ancestry groups (Table 1).

Infant characteristics

Birth weights for all 1,343 babies born at 3,600 m averaged 3,086 ± 13 g (SD 490 g). Birth weight fell progressively with increasing European parentage (Fig. 2A). Babies with more European parentage were more often preterm but even after adjusting for gestational age, there were three times as many babies with EE mothers as babies with AA mothers who were small-for-gestational age (SGA, Table 1). Likewise, when only term infants were considered, birth weights of babies of EE mothers remained lower than AA values (2972 ± 51 g vs. 3186 ± 36 g respectively, $P = 0.0007$). Variation in other factors affecting birth weight could not account for these ancestry-group differences; using a model that incorporated both parent's ancestries and controlled for variation in gestational age, maternal age, parity, smoking, socioeconomic status, and onset of prenatal care, AA were 252 g heavier than EE babies ($P < 0.0001$). The more linear fall in birth weight that was seen when birth weight was classified by the mother's parentage supported the importance of ancestry-specific factors influencing maternal characteristics affecting fetal growth (Fig. 2A).

The overwhelming majority of babies had at least one Mestizo (MM) parent (Fig. 1). Since having one Mestizo parent was therefore common among all groups, we used a subset of 487 cases with one Mestizo parent and one parent of different ancestry to test for parent-of-origin effects. We excluded cases with two Mestizo parents as they provided redundant information. Baby weight declined with increasing European parentage (Fig. 2B), similar to what was seen for all babies (Fig. 2A). However when classified by the father's parentage, birth weights averaged 74 g higher than when classified by the mother's parentage, or 81 g higher if the effects of gestational age on birth weight were taken into account (both $P < 0.05$). Parental ancestry and gestational age were able to account for 27% of the overall variance in birth weight ($R^2 = 0.27$, $P < 0.0001$); no additional improvement in the model was observed if other variables (e.g., maternal age, parity, smoking, socioeconomic status, or week of first prenatal visit) were included. The effect of ancestry combined with that of parent-of-origin meant that women of EE ancestry had the absolutely lowest birth-weight babies, averaging ~2,900 g (Fig. 2B).

DISCUSSION

High altitude provides a natural laboratory for examining the mechanisms responsible for hypoxia-associated reductions fetal growth. The principal finding of the present study was that high-altitude ancestry protects against

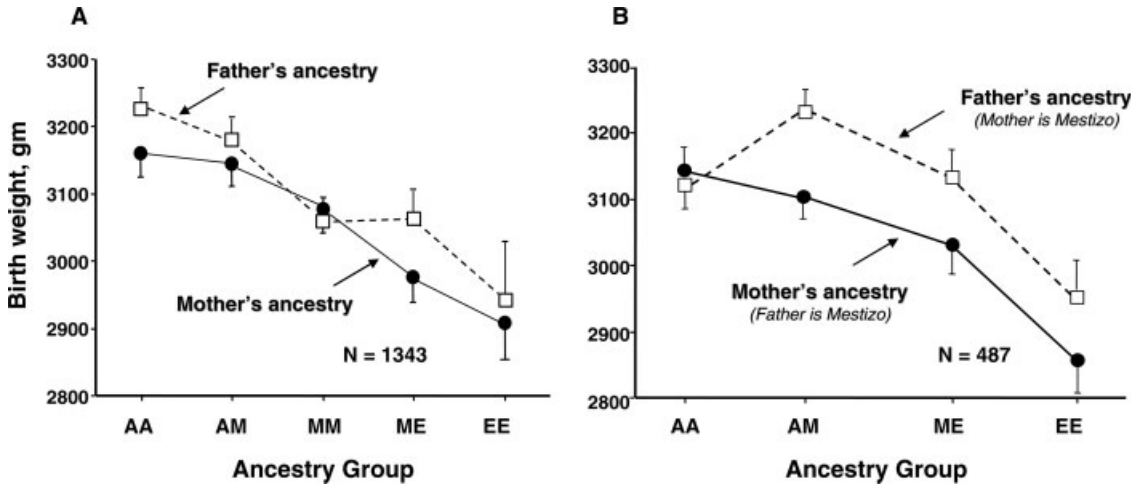

Fig. 2. Birth weights as classified by the mother's or the father's ancestry are shown for babies born at the two largest private or public maternity units in La Paz, Bolivia (elev 3,600 m). Panel A shows mean ± SEM birth weight values for 1,343 babies as classified either by their mother's or father's ancestry. Panel B shows birth weight values for the 487 babies with one Mestizo parent as classified by the "other" (non-Mestizo) parent's ancestry. Infant birth weight declines progressively with increasing European parentage. Father's ancestry is shown with open squares and dotted lines; mother's ancestry is depicted as filled circles and solid lines.

the hypoxia-associated fall in birth weight in a fashion that is consistent with the involvement of genetic factors. Three kinds of evidence supported this. First, the protective effect of high-altitude ancestry could not be attributed to confounding effects of gestational age, parity, maternal age, the week at which prenatal care began, smoking behavior, or socioeconomic status. Second, birth weight declined in proportion to the amount of high- (Andean) versus. low- (European) altitude ancestry. Third, parent-of-origin influenced the effect of ancestry in a manner consistent with maternal genes serving to restrict and paternal genes to enhance fetal growth. Alternatively, parental ethnicity could be affecting fetal growth independent of genetic mechanisms. We concluded that the depressant effect of chronic hypoxia on fetal growth acted, in part, through genetically-determined mechanisms.

Central to our study design was the availability of large numbers of persons who were descended from the indigenous, Aymára- or Quechua-speaking populations that have resided on the Andean altiplano ("high plains") for ~10,000 years (see Niermeyer et al., 2001 for original citations). Also needed were populations of low-altitude origin, provided in our case by the European-surnamed descendants of Spanish colonialists or other, more recent immigrants. To capture this population variation, we studied residents of the world's highest capital city (La Paz, Bolivia) who delivered in the two largest private and public facilities there. We selected facilities providing care to persons carrying health insurance in order to control for the lack of prenatal care and therefore limit other factors affecting birth weight. However, even though we had a larger sample size and data on a greater range of risk factors than earlier reports, we lacked information on the number of spontaneous abortions or miscarriages. As a result we could not determine whether greater prenatal mortality, frequency of twinning, or simply data-recording errors were responsible for the greater differences between gravidity and parity in the groups with more European ancestry.

In Bolivia, women (or men) do not change their surnames with marriage. Thus, four surnames are available for each newborn and can be used to judge population ancestry, given that surnames are distinctive for the indigenous Aymára- and Quechua-speaking residents of the Andean region. Since persons are known that have resided at high altitude for millennia and there are no permanent European settlements above 2,500 m (Niermeyer et al., 2001), it is clear that Andean populations have lived at high altitude for more generations than have Europeans. While surnames can be altered and hence are imperfect indications of population ancestry, it has previously been shown that surname-derived information correlates closely with that obtained from genetic markers in Bolivian as well as other populations (Bedoya et al., 2006; Chakraborty et al., 1989; Vargas et al., 2007).

The 3,163 g average birth weight value seen in the present study compares favorably to the ~3,200 g average reported previously for high-altitude residents of La Paz (Giussani et al., 2001; Haas, 1981) and is ~250 g lower than at low altitudes in Bolivia (Giussani et al., 2001; Haas, 1981; Keyes et al., 2003). While the causal factor linking lower birth weight with increased infant (or later in life) mortality continues to be debated (Wilcox, nd), a ~250 g fall in birth weight would be expected to raise the proportion of low birth weight (<2,500 g) babies by nearly 50% (from 12 to 18%). Such an increase would be expected to raise infant mortality markedly, especially under the conditions of limited medical care present in developing countries such as Bolivia.

The altitude-associated birth-weight decline is known to be due principally to chronic hypoxia acting to slow fetal growth, not shorten gestation (Giussani et al., 2001; Jensen and Moore, 1997; Lichty et al., 1957; Mortola et al., 2000). Has first noted that babies born to women of Andean ancestry are protected from this altitude-associated reduction in birth weight compared to those of European ancestry, and that this protection was independent of the duration of the woman's own residence at high alti-

tude (Haas, 1981). We reported similar findings on the Tibetan Plateau in western China, where increasing altitude from 2,800 to 4,800 m reduced birth weights to a lesser extent in Tibetans (−150 g/1,000 m) than in Han "Chinese" (−450 g/1,000 m) (Moore et al., 2001). We hypothesized that genetic factors were involved since there were no such these birth-weight differences present at low altitudes (Haas, 1981; Moore, 1990; Niermeyer et al., 2001; Zamudio et al., 1993); the population differences at high altitude could not be accounted for by variation in maternal body size, parity, smoking, or the altitude at which the mother herself had been born and raised; and genes are known to influence birth weight (Vlietinck et al., 1989). In terms of evolutionary process, we considered that the operation of natural selection over multiple generations of high-altitude residence could have preserved new genetic variants or increased the frequency of advantageous genes in the long- versus shorter-resident groups.

To test the hypothesis that genetic factors influence hypoxia-associated reductions in fetal growth, we asked if the amount of high- versus low-altitude ancestry and/or parent-of-origin were related to birth weight. We found that population ancestry exerted a "dose-dependent" effect on birth weight, with birth weight declining in proportion to the amount of European Andean parentage. This supported the involvement of genetic factors since these too would be so apportioned across such an ancestry gradient. Cultural factors affecting gestational age, maternal age, parity, infant sex, maternal smoking, socioeconomic status, or onset of prenatal care could not account for the ancestry-group differences observed. That is, birth weights remained heavier in babies of Andean versus European parentage using a model that incorporated both parental ancestries and controlled for these covariates plus gestational age. Cultural factors, however, were not unimportant; one of their clear influences was on the nature of marital unions. Positive assortative mating augmented the frequency of unions within the same or closely-related ancestry groups; this, in turn, would be expected to help preserve the effects of population ancestry.

Given previous physiological as well as genetic studies emphasizing the critical role of the maternal environment for provisioning the nutrients required for fetal growth (Karn and Penrose, 1957), including several conducted at high altitudes (Moore, 2003), we anticipated that maternal rather than paternal ancestry would exert a stronger effect on birth weight. Consistent with this was that the absolutely lowest birth weights occurred in babies born to EE women, either when all babies (Fig. 2A) or just those with one Mestizo parent (Fig. 2B) were considered. In addition, the mother's versus father's parentage exerted a more consistent effect on birth weight as demonstrated by the more linear slopes of the parentage lines in Figure 2A, suggesting that the genetic influences targeted the maternal determinants of fetal growth.

Finding that paternal versus maternal transmission of population ancestry raised birth weight 74 g, or 81 g if gestational age was also included in the model, was unexpected and suggested a role for an epigenetic mechanism such as genomic imprinting. Genomic imprinting refers to selective modification of gene expression through the addition of molecules such as methyl groups to specific genes affecting intrauterine growth, based upon parental origin. Genomic imprinting and other epigenetic modifications have been increasingly implicated in affecting interactions between environmental exposure, development, and disease susceptibility (Jirtle and Skinner, 2007).

Not all the effect of ancestry could be attributed to genomic imprinting, since the slopes of all lines declined with increasing European parentage, but the results observed were consistent with those of previous studies in which maternally-transmitted genes restricted and paternally-transmitted ones enhanced fetal growth (Moore and Haig, 1991). Since maternal surnames survive for only a few [two (Since it is only the mother's father's surname (and not mother's mother's surname) that is transmitted to her offspring, maternal surnames only survive two generations—her mother's and her's)] generations, parent-of-origin effects appear to occur over a relatively short time span, which is consistent with recent evidence indicating that the effects of genomic imprinting endure only for a few generations (Hitchins et al., 2007). The absence of any difference in birth weight for babies born to AA mothers or fathers further suggests that it is the non-Andean, rather than the Andean, component of paternal parentage that raises birth weight (Fig. 2B). We speculate that the selective pressure would be greater on non-Andean babies, as they are on average smaller, so imprinting modifications might operate more strongly here and less so in the Andean case. This could partially explain why differences in birth weight based upon parental ancestral contribution are greater for the non-Andean groups.

In conclusion, the dose-dependent nature of the protective effect of high-altitude ancestry and presence of parent-of-origin effects are consistent with the possibility that genetic factors and specifically, imprinted genes, protect long-resident high-altitude populations from hypoxia-associated reductions in birth weight. Since a finite (but growing) number of genes are imprinted, the involvement of genomic imprinting should facilitate the identification of such genes. Additional studies are therefore warranted to examine whether imprinted genes are differentially expressed in SGA babies and to identify the specific genes responsible for protecting long-resident high-altitude populations from hypoxia-induced fetal growth restriction, still a significant contributor to neonatal and infant mortality in the developed and especially the developing world.

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