Diagnosing Deep Roots of Development: Genetic, Disease, and Environmental Factors*

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Abstract

Recent research explores "deep roots" of economic development such as climate, geography, and genetic diversity. Using new data about the country-level frequencies of ACP1 genes and a novel identification strategy, this paper shows how historic genetic adaptations to disease and ultraviolet exposure have strong causal effects on per capita income today. The results are robust to controlling for reversal of fortunes, migration, and a range of other factors held to be relevant in the economics literature. The results have policy implications including protecting from ultraviolet radiation, control of tropical diseases, and the use of specific nutritional supplements.

KEYWORDS: deep roots of development, acid phosphatase locus 1, economic growth

JEL Codes: O1, O4, I15, I18.

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1 Introduction

We explore the impact of a "deep root" of development. The fundamental proposition is that geography influences the distribution and intensity of disease prevalence, which in turn leads to genetic adaptation in human populations, and these genetic adaptations in turn affect economic development.

Over centuries and millennia, climate, geography, and human genetic characteristics have interacted in ways that may have implications for development outcomes today. For example, many infectious diseases are more prevalent in hot, humid climates. These diseases affect human populations through attrition, migration, and adaptation (genetic and sociocultural). The coevolution of geography-climate-gene-culture complexes can modify physiological traits, such as skin pigmentation or the ability to breathe easily at high altitudes. They may also modify psychological traits, social interactions, and cultural repertoires; and these in turn may affect development outcomes. Understanding these relationships could be important for practice as well as theory.

A number of papers have explored the links between geography and development, and diseases and development. These studies have tested the associations between indicators of geography and development, or diseases and development, without considering the mechanism of genetic adaptation to location and disease, and its consequences for growth. Using newly available data on a specific genetic adaptation mechanism that represents a direct response of human biology to the disease environment due to its geographic location, we are able to correct this omission.

To our knowledge this paper is the first to explore the link of a specific genetic marker to development. The markers for the genetic adaptation we explore are the prevalence of acid phosphatase locus 1 ($ACP1$) A, B and C alleles in human populations. The assembled data on the frequencies of $ACP1*A$, $ACP1*B$, and $ACP1*C$ alleles is a compilation of $153,090$ global genotypes (the largest such genetic undertaking ever), in the populations of 121 countries.

The specific mechanism we propose rests on three mutually reinforcing linkages. Ultra-violet radiation (UVR) exposure lowers folate, increases oxidative stress, and increases immune suppression (switch from pro- to anti-inflammatory immune system). Lower folates raise $ACP1*B$, which in turn combats oxidative stress (by raising glutathione reductase) and strengthens the switch from pro- to anti-inflammatory immune system. In order to defend against DNA and tissue damage, equatorial populations have been under substantial selection

pressure. Alleles that increase pro-inflammatory responses were positively selected for, while anti-inflammatory alleles were selected against, with considerable behavioral and reproductive cost. Specifically, studies have noted that while genetic adaptations may resist certain diseases, they also cause side effects that affect drivers of development ranging from energy to learning ability to values and preferred modes of social organization (Thornhill and Fincher 2014).

This paper presents three important innovations.

The mechanism we propose and test, while a variant of the geography-environment-development association, is a major advance in hypothesizing a specific genetic adaptation in the *ACP1* gene as critical to the human adaptation mechanism that influences the developmental outcome. The focus on a single polymorphism has considerable analytical advantages, since it forces the identification of a specific mechanism, linking environment to genetic adaptation to developmental outcomes directly. The specific geography - disease - genetic adaptation mechanism proposed here allows for more direct and empirically transparent testing of the linkages, and a wide range of robustness checks.

Our work reinforces three policy prescriptions. Amelioration of UVR exposure is the most immediate inference. The results underscore the importance of reducing the burden of tropical diseases.[1] In the presence of folate deficiency due to high UVR exposure and in the absence of good dietary standards, folate acid (a vitamin B member) treatment is an intervention that stands to raise cognitive ability with likely positive consequences for economic performance.[2] Thus the deep root we explore does not imply developmental predestination. On the contrary, they may prove useful in identifying mechanisms that are open to treatments readily accessible to policy makers, benevolent, and without denying that other things also matter for developmental outcomes.

Recent literature on economic development has moved beyond proximate to primordial determinants of

[1] Eppig et al (2010) demonstrated a profound correlation between global infectious disease rates and IQ, concluding that in disease-endemic regions heightened demands on the immune system during pregnancy and early childhood divert metabolic energy away from brain development to combat disease. Additionally, many infections cause intestinal malabsorption, reducing the child's ability to retain nutrients and further contributing to cognitive impairment (Vavricka and Rogler, 2012). Finally, UVR directly induces folate deficiency. This produces maternal-fetal complications and is a major cause of neural tube defects and stunted cognitive growth (Borradale et al 2012).

[2] The studies on micronutrient supplementation or fortification that show only modest or negligible effects on cognitive performance (McNeill et al 2011), have largely been conducted on urban children in developed countries with relatively good diets, while diets of rural children in developing countries show large deficits in micronutrient intake, particularly of folic acid, riboflavin and iron (Swaminathan et al 2013). In poorer populations folate status has been found to be a significant predictor of cognitive performance,and the use of maternal micronutrient supplements in poor populations has been found to produce significant improvements in motor and cognitive abilities of offspring for at least 3.5 years of follow-up (Strand et al 2013, and Prado et al. 2012). A short term but economical solution to ensure adequate micronutrient intakes during pregnancy and childhood could be accomplished through fortification of staple cereals (Swaminathan et al 2013, Mitchell et al 2014, and Zinck and MacFarlane 2014).

growth. Traditional economic theory identified the determinants of economic growth as factor accumulation and technological progress in either exogenous of endogenous format, while more recent contributions have added institutions, policy, and openness to the explanation. Such explanations rest on factors that directly influence the incentives that economic agents face, through the productivity of factors of production, technologies, and the rate of return on production. Hence they fit neatly into the framework of economic analysis. Primordialist explanations have deeper and more ambitious reach. They identify geography, early technological adoption and subsequent persistence of technological differentials, early institutional dispensations, and the genetic make-up of populations as determinants of development, whose characteristics are established long ago in human history.[3] Identifying and including deep roots in the analysis may help reassess the importance of more proximate measures, including the exploration of interactions among policy choices and those deep roots.

Jointly considering deep roots and more proximate causes and conditions raises methodological complications, which are also a focus of this paper. Our approach is to test the robustness of the deep root proposed against the full range of methodological challenges identified by the literature, as well as to the inclusion of the full range of alternative deep roots identified in the literature, and a set of standard explanations of variation in per capita GDP that do not depend on the existence of deep roots.

Our discussion is structured as follows. Section 2 reviews in detail the mechanism we are exploring in the paper, and contrasts it to the alternatives found in the literature as well as introducing the set of methodological issues confronting any empirical testing of deep-roots mechanisms. Section 3 presents the new data we employ for the present study in rendering the location-disease-genetic selection mechanism explicit. Section 4 presents the estimation evidence, with section 4.1 and 4.2 reporting the direct results on the mechanism we propose, section 4.3 robustness checks against alternative deep roots, while section 4.3.6 presents robustness checks against standard drivers of economic growth from growth theory. Section 5 concludes.

[3] A useful survey of the literature can be found in Spolaore and Wacziarg (2013).

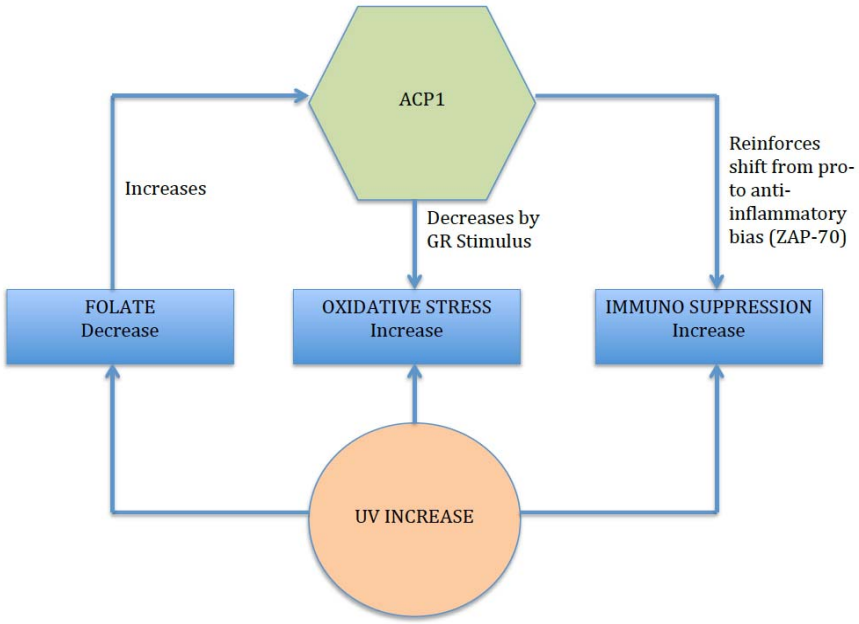


Figure 1:

2 The Geography-Disease-Genetic Adaptation Mechanism

Much recent work in fields from genetics to psychology,[4] and a little in economics,[5] examines how climates and geography create different disease environments, which in turn affect behavioral repertoires that can persist and affect economic development.

The specific mechanism we examine rests on three mutually reinforcing linkages. Ultra-violet radiation (UVR) exposure lowers folate, increases oxidative stress and increases immune suppression (switch from pro- to anti-inflammatory immune system). Lower folates raise *ACP1*, which in turn combats oxidative stress (by raising glutathione reductase(GR)), and strengthens the switch from pro- to anti-inflammatory immune system. Figure 1 illustrates.

The *ACP1* gene (gene map locus chr. 2p25, OMIM**171500) encodes the Low Molecular Weight-Protein Tyrosine Phosphatase that functions both as an acid phosphatase and a protein tyrosine phosphatase by hydrolyzing protein tyrosine phosphatase to protein tyrosine and orthophosphate. *ACP1* has three common codominant alleles, *ACP1*A*, *ACP1*B* and *ACP1*C*, with combinations defining six genotypes characterized

[4] See for instance Thornhill and Fincher (2014) and Fumagalli et al (2011).
[5] See for instance Acemoglu and Robinson (2007), Cook (2014) and Maseland (2013).

by different enzyme activity (from least to most active, A/A<B/A<(B/B, C/A)<C/B<C/C). As populations migrate out of equatorial regions to higher latitudes the compelling need for disease-resistance and defense against thermal stress gradually abates, and frequencies of the **B* allele decline from 0.85 in sub-Saharan Africa to 0.59 in Northern Europe, while frequencies of the **A* allele increase. Thus, a global view of *ACP1*A* and **B* allele frequencies is a reflection of the evolutionary trade-off between adaptation to thermal stress and disease endemicity, on the one hand, and a corollary sacrifice of behavioral plasticity on the other.

The high enzymatic activity *ACP1*B* allele is favored in tropical regions because it promotes thermal tolerance (Greene et al 2000) and confers greater immune resistance to the infectious diseases that are more common in the tropics (Bottini et al 2001). In such regions a robust pro-inflammatory immune response is needed to combat disease. This is facilitated by *ACP1*, which exerts regulatory influence over the balance between pro- vs. anti-inflammatory immune responses (Bottini et al 2005). *ACP1* interacts with the Interleukin-6 (*IL-6*) G-allele, a pleiotropic immune molecule that acts both as a pro-inflammatory cytokine to stimulate immune response during infection. In particular, *ACP1* and *IL6* may act synergistically in mediating the immunological responses to UVR exposure. Human and animal studies have established that UV exposure produces both local and systemic immunosuppression (Beissert and Schwarz 1999). To induce immune suppression, the electromagnetic energy of UVB is absorbed by an epidermal photoreceptor, trans-urocanic acid (UCA), and converted into a biologically recognizable signal, *cis*-UCA (Sreevidya et al. 2010). In turn, UVR-stimulated *cis*-UCA activates a cytokine cascade (*PGE2→IL-4*) which culminates in the activation of interleukin-10 (*IL-10*) (Grimbaldeston et al. 2007), and suppression of *IL-6* (Kreuter et al. 2006). Thus, by stimulating *IL-10* and inhibiting *IL-6*, UVB radiation initiates a shift from predominance of the pro-inflammatory immune system (*Th2*) to a predominance of anti-inflammatory (*Th1*) cytokines (Ulrich et al. 2004). Correspondingly, *ACP1* has been shown to act, through modulation of *ZAP-70* activity, to influence immune T-cell activity (Bottini et al 2002), and to mediate the shift from proinflammatory to anti-inflammatory bias (Gloria-Bottini et al 2007).

However, maintenance of a robust inflammatory response, associated with the *ACP1*B* allele, comes at a cost. Increased pro-inflammatory activity can cause tissue damage both in the periphery and in the brain. As a result, increased pro-inflammatory cytokines have been linked to a variety of cognitive deficits, including decrements in learning and memory (Sasayama et al 2012) and increased intellectual disability (Aureli et al

2014).

The human body needs folate to synthesize, repair, and methylate DNA. It is especially important in aiding rapid cell division and growth, such as in infancy and pregnancy. Folate is degraded by UVR (Jablonsky, 2012, Juzeniene et al 2013). As a result, folate levels are lowest near the equator and maximal at higher latitudes. In turn, folate is a general inhibitor of *ACP1* activity (Sensabaugh and Golden, 1978). Therefore, since UVR is positively associated with the level of *ACP1* activity, the expectation is that the high-activity *B*-allele predominates in equatorial regions and the low-activity *A*-allele predominates at higher latitudes. This has immediate implications for developmental prospects. Because of its impact on DNA instability, folic acid deficiency has been associated with a host of maladies ranging from birth defects to cancer (Duthie 1999). Low folate concentrations in blood are associated with poor cognitive performance in the general population (Durga et al 2006, 2007, Kerac et al, 2014), and folate pathway polymorphisms have been found to predict deficits in attention and processing speed. Treatment of patients with folate deficiency with folic acid therapy has been found to significantly improve performance in cognitive tests (Botez et al 1977).

UVR and *ACP1* are also linked by their association with oxidative stress, a measure of the imbalance between reactive oxygen species and a biological system's ability to detoxify or repair itself. UVR induces oxidative stress (Meng et al 2009). In turn, a critical molecule involved in resisting oxidative stress is glutathione reductase (GR), an important antioxidant enzyme. It has been shown that *ACP1* genotypes are inversely correlated with GR activity, with carriers of the low activity *AA* genotype showing the highest mean values of GR activity (Apelt et al 2009). As a result, carriers of the *ACP1*B* allele should be better able to resist the damaging effects of UVR-induced oxidative stress. Like folate, oxidative stress has been linked to a host of behavioral features, including reduction in learning and memory (Wang et al 2004) and the pathophysiology of schizophrenia (Flatow et al 2013; Bitanihirwe & Woo 2011).

In summary, the *ACP1* gene shares regulatory functions with UVR-related biological events. *ACP1* mediates the shift between pro- and anti-inflammatory immune processes, mediates disease susceptibility, is adapted to heat- and cold-stress, and exerts regulatory influence over fetal growth and development. As a result, across evolutionary time *ACP1* allele frequencies have become adapted to global variations in UV radiation and infectious diseases associated with the tropics. We emphasize that the links from UV radiation to folate decrease, oxidative stress, and immuno suppression, and associated personality characteristics and biological traits that

are important for individual-level economic outcomes are based on individual level studies in the biological and psychological sciences. Our interest lies in whether the individual level findings can be replicated at country mean level, and if so, assessing their theoretical and practical implications.

3 Our Data

In this paper we employ a number of data sets already established in the literature, including those of Ashraf and Galor (2013), Cook (2014), Comin et al (2010), Olsson and Hibbs (2005), Hibbs and Olsson (2004) and Putterman and Weil (2010). We add information about the acid phosphatase locus 1, soluble (*ACP1*) genetic polymorphism. We have assembled data on the frequencies of *ACP1*A*, *ACP1*B*, and *ACP1*C* alleles in the populations of 121 countries. The data is a compilation of 153,090 global genotypes (the largest such genetic undertaking ever). The data sources and compilation of the ACP1 measure is detailed in a separate file, and the detailed list of variables and their sources used for this study is listed in the Appendix of the paper. This is a new data set, and therefore this paper represents the first time country-level *ACP1* frequencies have been incorporated into studies of international development. Note that while data is available for 121 countries, individual country studies do not always guarantee a representative coverage of all ethnic groups.

Populations migrate over time, a tendency that has increased under colonialism and with falling transportation costs. The implication is that the genetic compositions of populations may come to change. It follows that to assess the importance of genetic roots, one has to take account of subgroups within a given country's population. Putterman and Weil (2010) and others carry out "ancestry adjustment" based on a country's ethnic groups, and we follow their example in estimating country frequencies of ACP1 alleles.

ACP1 is one of many genes that respond to the disease environment. In addition to *ACP1*, we have assembled new data on national frequencies of the Interleukin-6 (*IL-6*) G-allele. As noted above, though both *ACP1*B* and *IL-6* help people withstand pathogen stress and ultraviolet damage, both genetic markers have been shown to have negative effects on energy levels, cognitive ability, and some measures of mental and physical health. For the 68 countries for which we have *ACP1*B* and *IL-6* national data, the frequencies are correlated -0.77. In our empirical work, we use only *ACP1*, because 121 countries have such data, while information on *IL6* is much more restricted. But we believe that the coefficients we observe on *ACP1* are not

measuring the unique impact of this one gene. Rather, the coefficients indicate the effects of many correlated gene frequencies that respond to disease environments and subsequently have impact on traits and values that affect development outcomes.

Deep-roots data face a number of serious limitations. In some instances data points are inferred over prodigious time spans, rendering them subject to conceptual and empirical limitations.[6] Additional concerns surround the mapping of concepts into measurement, and the suitability of the resultant data to explore the causal links implicit in deep roots hypotheses. For some measures the number of countries with available data is small (well below 200, and all our measures have fewer than 200 observations), different measures have divergent country coverage, or the observations are the consequence of some imputation.[7] Even where we have data on a full complement of countries, sample size remains restricted at approximately 200 - so that all statistical inference has bounded statistical power.

4 Evidence

We briefly recap the mechanism we propose as a deep root of development. Geography, as measured by latitude, elevation, and precipitation is a determinant of disease prevalence. Disease prevalence and UVR damage bring about genetic adaptation in humans, to promote immunity to disease in order to deal with DNA damage, oxidative and heat stress. One crucial adaptation involves the *ACP1*A*, *ACP1*B*, and *ACP1*C* alleles. The *ACP1*B* allele is particularly geared toward the combating of the intense diseases of the tropics, but generates intensive energy (calorific) requirements that carry negative consequences for the ability of humans to devote resources to other, including cognitive activities. *ACP1*A* by contrast is better suited to resisting UVR induced oxidative stress, and is selected for where UVR induced folate degradation is low. Because of its effects on behavior and health, the *ACP1*A* allele should be positively related to economic productivity measures, while the *ACP1*B* allele should be negatively associated. The impact of ACP1 on productivity may be both directly on the productivity of producers, as well as indirect via socio-cultural adaptation.

[6] Coverage in some instances is as far back as 1000 BC and 0 AD for a large number of countries, including those with a relative paucity of historical records. This involves creative and sometimes heroic efforts to measure a level of development long ago, in a geographical area corresponding to today's national boundaries, and we add that the authors are at pains to be transparent about the associated data difficulties - see for instance Comin et al (2010).

[7] For instance, Ashraf and Galor (2013) employ genetic diversity as their deep root, but strictly have single observations for only 21 countries. They increase sample size by using migratory distance from East Africa to increase their sample size from 21 to 145.

4.1 The Geography - Disease - Genetic Adaptation Mechanism

At the core of our mechanism is that UVR varies with latitude, and that this causes genetic adaptation in the *ACP1*A* and *ACP1*B* alleles of humans.

To explore this we consider the World Health Organization-derived Ultraviolet (B) damage rating.[8] Across 184 countries for which data are available, the average of this rating is 202.0 and the standard deviation is 76.8, with a minimum of 31.8 (Iceland) and a maximum of 298.5 (Ethiopia). The distribution of countries is not uniform across latitude, with a strong density of country mean observations located at low latitudes, confirming a high exposure to UVR for a significant proportion of the world population - see Figure 2.

Figure 3 reports the association between ultraviolet radiation damage and absolute latitude in our data set. The evidence strongly confirms the strong association between UVR and latitude, with UVR declining in higher latitudes. Indeed, the correlation is so strong ($r = -0.96$) as to render them statistical substitutes. Panels A and B of Figure 3 provide graphic representation of annual averages and coefficients of variation during the year.

The frequencies of *ACP1*A* and *ACP1*B* also vary precisely as predicted in UVR and latitude - see Figure 4. Thus *ACP1*A* prevalence declines in rising UVR or as geographical location approaches the equator. Conversely, *ACP1*B* prevalence increases in rising UVR or at lower latitudes.[9] In Table 1 we confirm the association between *ACP1* and UVR damage. The association of Figure 4 is strongly confirmed. This is true both for the full sample of countries for which we have *ACP1* data (columns 1, 3, 5), as well as a sub-sample of countries for which our *ACP1* data is representative of at least 75% of the population (P>0.75: columns 2, 4, 6).

The variations in the *ACP1* gene in UVR that underlie our proposed mechanism are thus strongly borne out empirically.

[8] The rating reflects biological damage per square meter (BD/m2), with the continuous measure scaled by dividing each averaged Ultraviolet radiation (UVR) dose by half of the interquartile range (Herman et al., 1999). To confirm the salience of their measure of UVdamage, we compared this measure with an annual average ultraviolet index for countries based on NASA satellite recordings. For the 23 countries for which both measures are available, the correlation between them is 0.907.

[9] The *ACP1*C* allele mirrors the *ACP1*A* allele's association with UVR and latitude, though with less precision - and we suppress for presentational parsimony.

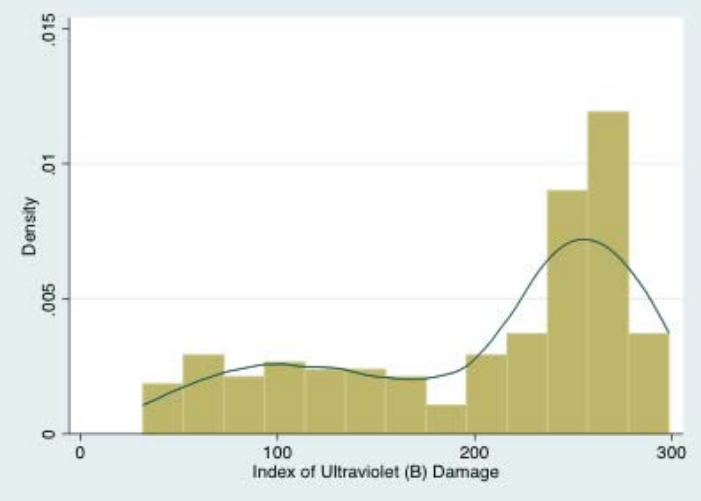
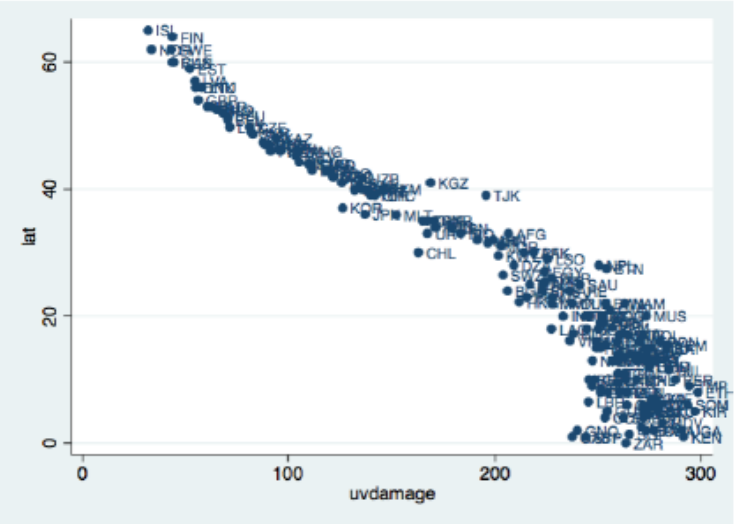


Figure 2: Histrogram of Ultraviolet Radiation Damage



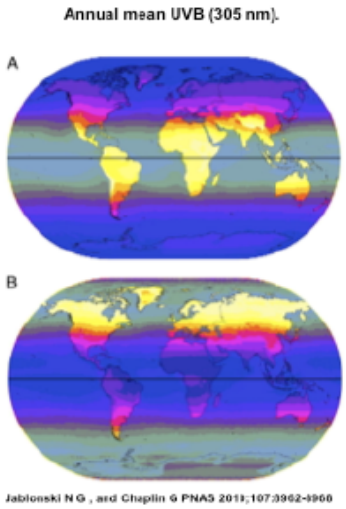


Figure 3: Ultraviolet Radiation Damage and Latitude

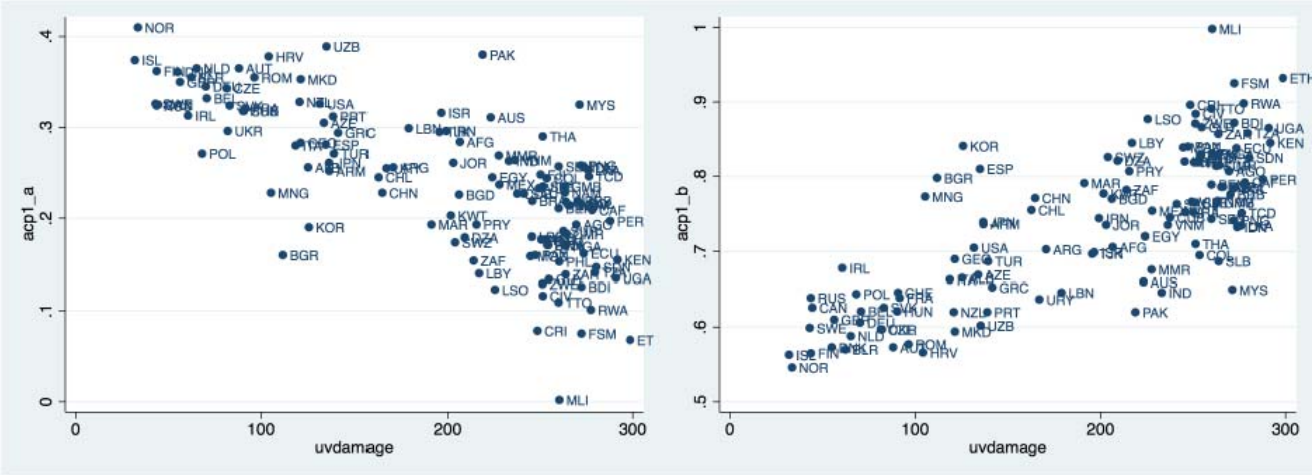


Figure 4: ACP1 and Ultraviolet Radiation Damage

	(1)	(2)	(3)	(4)	(5)	(6)
Dep. Var.:	ACP1*A	ACP1*A	ACP1*B	ACP1*B	ACP1*C	ACP1*C
Sample:	Full	P>0.75	Full	P>0.75	Full	P>0.75
Estimator:	OLS	OLS	OLS	OLS	OLS	OLS
uvdamage	-0.001^{***}	-0.001^{***}	0.001^{***}	0.001^{***}	-0.0003^{***}	-0.0003^{***}
	(0.000)	(0.000)	(0.000)	(0.000)	(0.0000)	(0.0000)
const.	0.39^{***}	0.39^{***}	0.55^{***}	0.55^{***}	0.07^{***}	0.07^{***}
	(0.01)	(0.01)	(0.02)	(0.02)	(0.004)	(0.004)
N	119	89	119	89	119	89
adj-R^2	0.53	0.60	0.58	0.61	0.61	0.57

Figures in round parentheses denote standard errors

***, **, * denotes significance at the 1%, 5% and 10% levels respectively

Table 1: ACP1 and UVR Damage

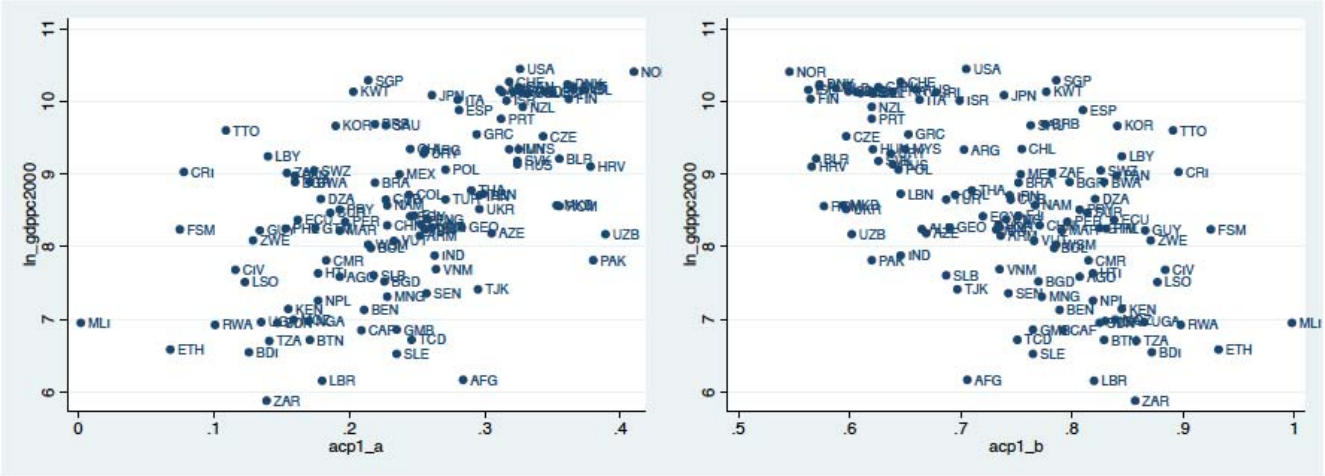


Figure 5: ACP1 and Real per Capita GDP in 2000

4.2 Real GDP per Capita and the *ACP1* Gene

Our core interest lies in whether the *ACP1* genetic markers are robustly associated with measures of development. Figure 5 reports the association between the *ACP1* alleles and real per capita GDP in 2000. The predicted positive association between the A allele and GDP, and the negative association between the B allele and GDP is evident from the data (the C allele mirrors the A allele).

Estimation results are reported in Table 2, where we consider the association between the log of real per capita GDP in 2000 and the three *ACP1* alleles. Given the perfect collinearity between the three allele measures, we can control for the A, B and C alleles only singly. Results consistently report a positive association between real per capita GDP and the *ACP1*A* and *ACP1*C* alleles, while the association is negative with respect to the *ACP1*B* allele. This is true regardless of whether we consider the full sample (columns 1 - 3) or the restricted sample of countries for which we have coverage of at least 75% of the population (columns 4 - 6). Regardless of specification, the *ACP1* alleles maintain significance at the 1% level.[10]

A persistent challenge faced by deep roots explanations comes from the observation of countries experiencing reversals of fortune. The argument here is that if the determinants of development are indeed deep, then their impact should be invariant in time. In the case of geography, for instance, this is argued to be empirically false, and that this points to the importance of institutions, human capital transfers, and innovation incentives in

[10] For a set of Asian, particularly East Asian countries, the association we report comes to be inverted. We do not have an explanation for this. We note only that the general result is not sensitive to controlling for the East Asian inversion, and that the inversion may be relevant for future research.

	(1)	(2)	(3)	(4)	(5)	(6)
Dep. Var.:	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc
Sample:	Full	Full	Full	P>0.75	P>0.75	P>0.75
Estimator:	OLS	OLS	OLS	OLS	OLS	OLS
ACP1*A	7.89***			9.41***		
	(1.09)			(1.28)		
ACP1*B		−6.50***			−7.12***	
		(0.89)			(1.04)	
ACP1*C			25.81***			24.63***
			(3.41)			(3.74)
const.	6.66***	−6.50***	8.00***	6.29***	13.82***	8.04***
	(0.28)	(0.66)	(0.11)	(0.34)	(0.75)	(0.14)
N	118	118	118	89	89	89
adj-R^2	0.31	0.31	0.32	0.38	0.34	0.32

	(7)	(8)	(9)	(10)	(11)	(12)
Dep. Var.:	lnpd1	lnpd1500	lnpd1	lnpd1500	lnpd1	lnpd1500
Sample:	Full	Full	Full	Full	Full	Full
Estimator:	OLS	OLS	OLS	OLS	OLS	OLS
ACP1*A	7.22***	4.58**				
	(1.95)	(1.83)				
ACP1*B			−6.11***	−3.57**		
			(1.59)	(1.49)		
ACP1*C					20.09***	12.52**
					(5.96)	(5.72)
const.	−1.82***	−0.19	4.43***	3.55***	−0.48**	0.65
	(0.51)	(0.47)	(1.17)	(1.11)	(0.21)	(0.19)
N	101	117	101	117	101	117
adj-R^2	0.11	0.04	0.12	0.04	0.09	0.03

Figures in round parentheses denote standard errors

***, **, * denotes significance at the 1%, 5% and 10% levels respectively

Table 2: Real per Capita GDP in 2000 and ACP1

being able to reverse initial fortunes.[11] Given the concerns raised by reversals of fortune, testing for an impact of deep roots includes tests for the impact of the deep root at an early historical stage, as well as for associations with the current level of development. We do so in columns 7-12 of Table 2, by testing whether the *ACP1* gene is associated with population density in 1 AD (lnpd1) and 1500 AD (lnpd1500). The use of population density is due both to the absence of reliable GDP measures prior to 1800, and since the Malthusian trap eroded any gain in per capita income through accelerated population growth prior to the industrial revolution. Population density captures the Malthusian response.[12] Results are consistent across all specifications. They confirm the statistically significant positive association between all of the population density measures and the *ACP1*A* and *ACP1*C* alleles, and the significant negative association between the *ACP1*B* allele and the early measures of economic development. The inference is thus that the association between the *ACP1* gene and development is invariant in time, and hence survives the reversal of fortune challenge.[13]

A more fundamental concern is that our genetic markers may be subject to endogeneity. This is particularly true of the genetic variables. If populations are subject to significant migration over time, then the process of economic development may select for specific genetic types, generating reverse causality in any specification with development measures as the outcome, and genetic variables as the determining variables.

One means of correcting for this is by the ancestry adjustment to which our genetic marker variables have already been subjected as per Putterman and Weil (2010). But this solution is only partial, since potentially the selection effect could already be under way by the 1500 AD date for which Putterman and Weil (2010) adjust, and secondly since this would not correct for any latent factor not controlled for in the specification that determines both the genetic composition and the development outcome. Given that our genetic marker variables do not have time variation, the only feasible recourse is instrumental variables estimation. This in turn raises the general concern with the strength and validity of instruments,[14] which has found repeated

[11] See for instance Acemoglu et al (2002), Engerman and Sokoloff (1997), Glaeser et al (2004), Galor and Weil (2000), Galor et al (2009), and Easterly and Levine (2012). Note though that Michalopoulos and Papaioannou (2010) question the impact of institutions across homogeneous ethnic groups separated by arbitrary national boundaries in Africa, showing no difference in economic performance, thus suggesting the relevance of long-term features of the population rather than institutions.

[12] See Ashraf and Galor (2013), Comin et al (2010), Kremer (1993), Galor (2005) and Ashraf and Galor (2011a).

[13] The reversal of fortune argument is in any event potentially misleading. Strictly only the historically deep roots need to answer the call to account for the reversal of fortunes, since their claim is that early events came to induce a path dependence to development, with leaders and laggards maintaining their relative position in the distribution of development. By contrast, roots that are deep in a pre-behavioral sense (eg. genetic markers) are robust to reversals of fortune, since the qualities that may be important for development may vary with time. Agricultural and industrial production may favour different traits, for instance. This would render the fact that the pre-behavioral conditions or qualities are not associated with levels of economic development at all times irrelevant. Thus, since deep roots interact with both progress and policy, the impact of deep roots need not be invariant across time.

[14] See Murray (2006).

echoes in relation to growth regressions.[15]

In a context in which we consider deep determinants of development, an additional concern is that any instrument that is utilized, no matter how historically remote or deeply buried in pre-behavioral (that is falling outside the scope of choice theory) aspects of human activity, is subject to the suspicion that it itself may exercise an influence on the measure of development. If so, this would violate the exclusion restriction of IV estimation and thus confidence in any causal claims attached to the endogenous genetic regressor. This has become a particularly stringent concern influencing assessments of the statistical legitimacy of deep roots determinants of development.[16] In our approach to dealing with endogeneity, we pay particular attention to whether the exclusion restriction is plausibly satisfied.

For our case, the hypothesized theoretical mechanism surrounding *ACP1* lends itself directly to an instrumentation strategy. Since the *ACP1* gene responds to variations in UVR damage, which is itself an expression of geographic location, we have an exogenous instrument at our disposal in the form of the UVR damage measure. As we have seen, the UVR measure has a strong association with *ACP1*, and thus is a good candidate for an instrument.

We report the IV estimation results in Table 3, restricted to the *ACP1*A* and *ACP1*B* alleles for the sake of parsimony. As reported in columns 1 and 4, the predicted positive and negative associations between the *ACP1*A* and *ACP1*B* alleles and real per capita GDP are confirmed under instrumentation. What is more, Wu-Hausman statistics confirm the endogeneity of the *ACP1* variables.

4.2.1 Validity of Instrumentation Strategy

While compelling, the IV results remain subject to standard concerns regarding the validity of the instrumentation strategy. Of particular concern is that the exclusion restriction on UVR damage exercising a direct influence on our measure of economic development may be violated - a pervasive concern attaching to all deep roots testing strategies. In what follows, we advance reasons why we believe concerns about violation of the exclusion restriction are insufficient to overturn our reported result.

To aid the discussion, we refer to Table 4, adapted from the discussion of the validity of instrumentation

[15] See Brock and Durlauf (2001), Dollar and Kraay (2003), Glaeser et al (2004), Durlauf et al (2005), Hauk and Wacziarg (2009), Bazzi and Clemens (2013), and Albouy (2012).

[16] See the discussion in Alesina and Giuliano (2014) and Tabellini (2010).

	(1)	(2)	(3)	(4)	(5)	(6)
Dep. Var.:	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc
Sample:	Full	Full	Full	Full	Full	Full
Estimator:	IV: 2SLS	IV: 2SLS	IV: 2SLS	IV: 2SLS	IV: 2SLS	IV: 2SLS
ACP1*A	12.46*** (1.58)	10.94** (4.96)	3.21** (1.31)			
ACP1*B				−9.69*** (1.20)	−9.80*** (4.32)	−2.61** (1.11)
const.	5.56*** (0.39)	6.67*** (1.20)	−1.44 (0.92)	15.71*** (0.89)	16.64*** (3.25)	1.44 (1.84)
Wu-Hausman	24.51***	6.38**	0.11	22.21***	6.04**	0.78
IV:	uvdamage	uvdamage	uvdamage	uvdamage	uvdamage	uvdamage
Exclusion Test:	None	Curr.Disease	LifeExp.1940	None	Curr.Disease	LifeExp.1940
N	118	74	66	118	74	66
adj-R^2	0.21	0.47	0.75	0.24	0.50	0.73

Figures in round parentheses denote standard errors

***, **, * denotes significance at the 1%, 5% and 10% levels respectively

Table 3: Real per Capita GDP in 2000 and ACP1: IV Results

of Angrist et al (1996), and illustrated for the case of *ACP1*B*.[17] Angrist et al (1996) point out that a causal interpretation of the IV estimand becomes compromised in the presence of any mechanism noncompliance, which may arise for three distinct logical reasons. The first is mechanism defiance, in which the postulated association between the instrument (selection) and endogenous regressor (treatment) is reversed. This concern is readily dismissed in our case, since the results of Figure 4 and Table 1 demonstrate a close association between UVR damage and the *ACP1* adaptation advanced by our mechanism. In effect our data satisfies the Angrist et al (1996) monotinicity requirement. Of greater concern in our context is the possibility of partial mechanism non-compliance, in which we may observe that for some countries there is a low observed *ACP1*B* frequency despite the fact that UVR radiation is high (the Non-Compliance I case), or a high observed *ACP1*B* frequency despite the fact that UVR radiation is low (the Non-Compliance II case). Given the pervasiveness of human migration and legacy effects of the colonial era, such aberrations are certainly plausible despite our efforts to purge such effects through ancestry adjustment of our data. Only when the diagonal element cases of mechanism non-compliance are excluded (the exclusion restriction), and mechanism defiance is excluded (monotinicity), will the average causal effect of the instrument on the dependent variable be proportional to the average causal effect of the endogenous (instrumented) variable on the dependent variable, providing a straightforward causal interpretation of the IV coefficients.

[17] The Angrist et al (1996) discussion is illustrated in terms of a selection process (a lottery) which serves as an instrument for an endogenous treatment (military service), in relation to a fianl health outcome measure. As such instrument and treatment are both binary. In our case the selection (instrument: UVR damage) and the treatment (endogenous regressor: *ACP1*), are continuous, but for ease of exposition we illustrate in terms of a simple high/low binary classfication.

		UVR (LOW)	
	ACP1*B	LOW	HIGH
UVR (HIGH)	LOW	Mechanism Non-Compliance I: UVR (LOW) → ACP1*B (LOW) UVR (HIGH) → ACP1*B (LOW)	Mechanism Defiance: UVR (LOW) → ACP1*B (HIGH) UVR (HIGH) → ACP1*B (LOW)
	HIGH	Mechanism Compliance: UVR (LOW) → ACP1*B (LOW) UVR (HIGH) → ACP1*B (HIGH)	Mechanism Non-Compliance II: UVR (LOW) → ACP1*B (HIGH) UVR (HIGH) → ACP1*B (HIGH)

Table 4: Potential Sources of Concern with Instrumentation

The ancestry adjustment of our data is one means of minimizing the chances of non-compliance. But we present two additional considerations to suggest that the exclusion restriction can be taken to be adequately met. First, the results of Figure 4 and Table 1 demonstrate a close association between UVR damage and the *ACP1* adaptation, with reported adj-R^2 coefficients of approximately 0.6. There is thus evidence in support of the "strength" of the instrument, thus reducing the odds of non-compliance and hence violation of the exclusion restriction (Angrist et al, 1996:451).

Second, the structure suggested by our theoretical priors provides us with a means of providing an indirect test of the exclusion restriction. The mechanism suggests that disease burdens vary systematically with geographical location. The mechanism hypothesizes the *ACP1* allele frequencies to be genetic adaptations to the differential disease burdens faced under distinct geographical conditions. It follows that disease burden incidence should therefore covary closely with our instrument, UVR damage.

An indirect test of the exclusion restriction is therefore to estimate the association between real per capita GDP and the *ACP1* allele markers, instrumenting on UVR damage, and then testing for the robustness of the association between GDP and *ACP1* by including the covariants of UVR damage provided by the disease burden measures in the specification. Survival of the statistical significance of the *ACP1* measures would provide support for the satisfaction of the exclusion restriction.

Which measures of disease are appropriate? One approach would be to employ measures of disease burden that are currently reported. Examples of such measures might be provided by the incidence of tuberculosis, sexually transmitted diseases, HIV-AIDS, diarrhea, childhood diseases, malaria, tropical diseases, and intestinal diseases. The advantage of such measures is their multiplicity, their ready availability, and the relative quality of measurement with which current health indicators are collected.

The difficulty is that measures of disease burden that are contemporaneous with real per capita GDP in 2000

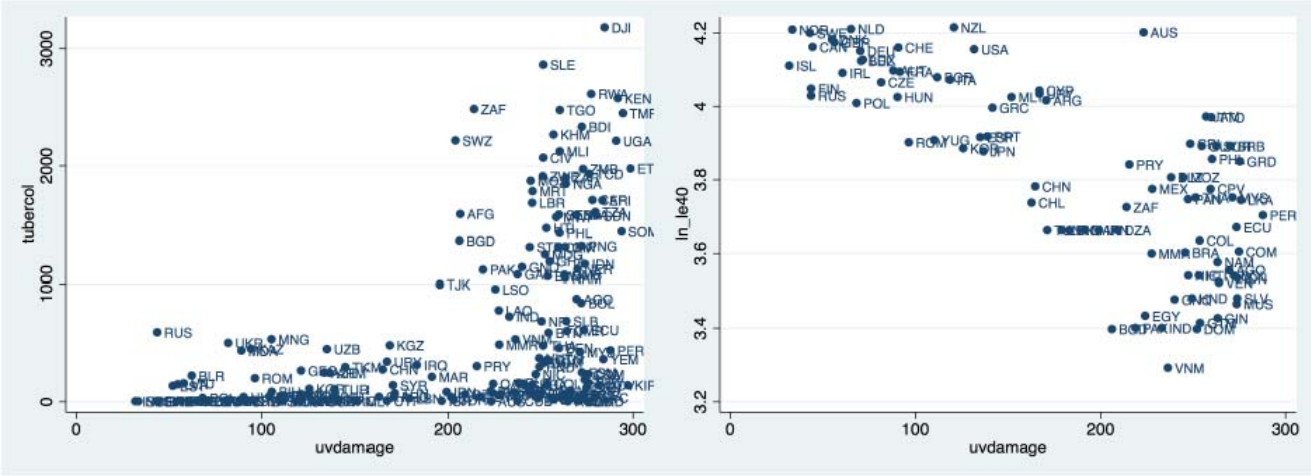


Figure 6: Incidence of Tuberculosis, Life Expectancy in 1940, and UVR damage

are subject to the epidemiological transition, which has significantly reduced the impact of infectious diseases on mortality and life expectancy through relevant policy interventions, potentially rendering the measures of disease burden unreliable as indicators of true underlying unfavorable UVR conditions. Given the paucity of records on historical disease burdens prior to the epidemiological transition, an alternative measure is therefore a measure of life expectancy from 1940, which predates the transition. While life expectancy does not capture the disease burden directly, it does capture the net effect of disease on human health.

In conducting our test, we therefore employ both the measures of current disease burdens, and the measure of life expectancy in 1940 obtained from Cook (2014).

Note that the strong covariance between UVR damage and disease burden, and life expectancy in 1940, and UVR damage is borne out by the evidence - as illustrated in Figure 6. Note that the association that is reported for the incidence of tuberculosis extends to all of our measures of disease burden.[18]

We then reestimated our IV specification, including our full set of contemporaneous disease burden measures as the indirect test of the exclusion restriction, reported in columns 2 and 5 of Table 3. The statistical significance and pattern of association between the instrumented *ACP1* allele markers and real per capita

[18] In additional estimations we confirmed the presence of robust statistical association between our measures of disease and measures of absolute latitude, elevation above sea level, and precipitation. We also confirmed a consistent association between the measures of disease and our *ACP1* allele measures. Given that over over sufficiently long time periods, there is a genetic adaptation response to the disease environment to improve immunity, the disease markers again are rendered potentially endogenous. For this reason we explored the link between disease and the *ACP1* allele both under OLS and IV estimation, employing the three geographical variables as instruments. The *ACP1*A* and *ACP1*C* alleles are negatively associated with all disease measures. The *ACP1*B* allele is positively associated with all disease measures. All disease measures are statistically significant, regardless of whether we estimate under OLS or IV, and the impact of the disease measures is enhanced under instrumentation.

GDP is robust to the inclusion of the disease measures, while Wu-Hausman statistics continue to confirm the endogeneity of the *ACP1* variables.

In columns 3 and 6 of Table 3, we repeat the indirect test of the exclusion restriction, using life expectancy in 1940. The statistical significance and pattern of association between the instrumented *ACP1* allele markers and real per capita GDP is once again robust to the inclusion of the life expectancy measure robust to the timing of the epidemiological transition, though the coefficient size is lower and here Wu-Hausman statistics do not support the endogeneity of the *ACP1* variables.

Third, we employ a stringent definition of mechanism non-compliance as falling outside a one standard deviation confidence interval about the conditional mean obtained from Table 1 results, as illustrated in Figure **??**. We then interacted this definition of non-compliance with reported *ACP1* frequencies, and controlled for the interaction terms in estimation. In the presence of mechanism noncompliance, we might expect countries that non-comply by reporting *ACP1*A* (*ACP1*B*) frequencies above the upper bound would have lower (higher) observed developmental outcomes, while those that non-comply by reporting *ACP1*A* (*ACP1*B*) frequencies below the lowery bound would have higher (lower) observed developmental outcomes.

Finally, we also considered additional evidence on the impact of any mechanism violation on the estimated instrumented relationship. Specifically, we employ a stringent definition of mechanism non-compliance as falling outside a one standard deviation confidence interval about the conditional mean obtained from Table 1 results. We then interacted this definition of non-compliance with reported *ACP1* frequencies, and controlled for the interaction terms in the IV estimation. Our finding is that the impact of the *ACP1*A* and *ACP1*B* alleles is unaffected in terms of both statistical and substantive significance. This remains true under mechanism non-compliance bands defined by 1.5 and 2 standard deviation bands.

Our predicted association between the *ACP1* gene and development thus appears robust to adjusting for the potential endogeneity of the genetic measure. As always, no test of robustness can be definitive. Nonetheless, we have presented at least three considerations (strength of instruments, an indirect test of the exclusion restriction, and controlling for mechanism violation) that lend support to the IV strategy we employ. This suggests that at least part of the relation between development and *ACP1* is caused by *ACP1* affecting development, and that the estimated effect is not simply a spurious result of selection effects due to some latent trait, or reverse causality from development to genetic traits.

4.3 Robustness

Thus far we have considered whether there exists a statistical association between our *ACP1* markers and real per capita GDP, and whether this is robust across time and to the possibility of endogeneity of genetic adaptation to economic development.

The question now is whether this association is robust to the inclusion of other potential determinants of development.

4.3.1 More Genes?

Our modelling approach has been to explore the possibility of whether there is a robust statistical association between a single gene, and a measure of economic development. While we have already pointed out that *ACP1* is part of a group of genes, which includes *IL6* and *IL10*, that are likely to act together, nonetheless, given the very large number of genes that make up the human genome, this approach is radical. The immediate and obvious question is therefore whether there is nothing to be gained from employing not a single genetic marker, but a more aggregate measure of the genetic composition of populations.

In an influential paper, Ashraf and Galor (2013), developed and tested several measures of genetic heterozygosity in countries. Their key variable is predicted genetic diversity adjusted for ancestry. Conceptually, it measures the expected heterozygosity between two randomly selected people in the country in question, after adjusting for ancestry. It is based on two sources. The first comes from data about heterozygosity in 53 ethnic groups in the HGDP-CEPH Human Genome Diversity Cell Line Panel in a sample of 21 countries. Second, Ashraf-Galor build on work by Ramachandran et al. (2005), which shows that this heterozygosity is highly correlated with the migratory distance of these 53 groups from East Africa ($r = 0.92$). This robust association between genetic diversity and migratory distance before the Common Era is used in order to obtain predicted values of genetic diversity for an extended sample of 145 countries. The hypothesis in Ashraf and Galor (2013) is that increased genetic diversity stimulates innovation, but beyond a certain point also raises distrust and the propensity for conflict due to falling trust, with the net result being a hump-shaped association between the measure of genetic diversity and economic development, and they present extensive evidence in support.[19]

[19] An alternative genetic mechanism focusses on the genetic *distance* between populations, as a measure of the ease of diffusion of technology and human capital between societies. See for instance Spolaore and Wacziarg (2009), based on the measures of genetic distance reported in Cavalli-Sforza et al (1994).

An alternative proposal by Cook (2014) also uses a measure of genetic diversity, given by the human leukocyte antigen (HLA) system a highly polymorphic genetic cluster located on the sixth chromosome, responsible for the location of foreign proteins in order to direct an immune response to identified pathogens. The hypothesis is that increased HLA diversity improves disease resistance. Cook reports a strong positive association between HLA diversity and country-level health outcomes in periods prior to the epidemiological transition, with a weakening of the association in subsequent periods with the advent of improved medical and health system technology.

These deep roots of development share with ours a reliance on pre-behavioral human conditioning to environment. They differ in that they use an aggregated summary measure of the genetic information humans carry, while we are exploring the impact of a specific gene. For this reason, we explore closely the robustness of our results to controlling for the two alternative diversity measures.

We proceed by including the Ashraf-Galor measure of ancestry adjusted genetic diversity in their favoured non-linear specification, and the Cook measure of HLA genetic diversity, both singly and jointly, while controlling for *ACP1*A* and *ACP1*B*. We also consider the possibility that the *ACP1* measures may be endogenous to development, by instrumenting on UVR damage.[20]

Results are reported in Table 5.

Our findings are that the *ACP1* prove robust to controlling for genetic diversity, either in the form of the Ashraf-Galor measure, or the Cook HLA measure, or both. *ACP1*A* and *ACP1*B* consistently remain statistically significantly associated with real per capita GDP, with positive (columns 1 - 3) and negative (columns 5 - 7) sign respectively. Allowing for the possibility of endogeneity by instrumenting on UVR damage for the *ACP1* alleles strengthens rather than dissipates the association (columns 4 and 8).

Our specific *ACP1* genetic markers are thus robust to controlling for the more aggregated measures of human genetic composition. Once again, while we are not suggesting that ACP1 is the only gene that matters, nor that ACP1 exerts its influence alone, our results are suggestive of the fruitfulness and feasibility of exploring the association between the biological consequences of adaptation to climate and disease and long-run

[20] We conducted extensive additional testing using the measures of genetic diversity. In particular, we replicated the full modeling strategy of Ashraf and Galor (2013), testing with predicted genetic diversity both ancestry adjusted and unadjusted, controlling for the timing of the Neolithic transition, latitude, the proportion of land that is arable, suitable for agriculture, and population density in AD 1500. In addition, we followed the full non-linear instrumentation strategy of Ashraf and Galor. In none of the resultant specifications do the *ACP1* variables ever lose statistical significance. By contrast, the measures of genetic diversity do not prove robust to the inclusion of *ACP1* - as in Table 5.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Dep. Var.:	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc
Sample:	Full	Full	Full	Full	Full	Full	Full	Full
Estimator:	OLS	OLS	OLS	IV: 2SLS	OLS	OLS	OLS	IV: 2SLS
ACP1*A	6.59***	6.74***	5.30***	9.15***				
	(1.16)	(1.16)	(1.07)	(1.64)				
ACP1*B					−5.90***	−5.52***	−4.46***	−7.14***
					(0.96)	(0.94)	(0.86)	(1.25)
pdiv_aa	294.81**		−3.63	−94.98	286.76**		10.33	−56.86
	(129.11)		(127.16)	(135.06)	(126.44)		(125.57)	(130.21)
pdiv_aa_sqr	−213.33**		−14.20	52.27	−208.39**		−24.28	24.66
	(91.26)		(89.52)	(95.23)	(89.33)		(88.37)	(91.73)
ln_HLA_div		2.24**	10.35***	8.78***		2.16**	9.96***	8.43***
		(0.96)	(1.65)	(1.78)		(0.96)	(1.65)	(1.76)
const.	9.56***	9.56***	29.23	57.72	−85.30*	15.16***	28.53	51.69
	(1.22)	(1.22)	(45.78)	(48.35)	(44.94)	(1.10)	(45.38)	(47.00)
Wu-Hausman				12.16***				10.54***
IV:				uvdamage				uvdamage
N	111	110	104	104	111	110	104	104
adj-R^2	0.36	0.32	0.51	0.47	0.38	0.32	0.52	0.49

Figures in round parentheses denote standard errors

***, **, * denotes significance at the 1%, 5% and 10% levels respectively

Table 5: Incorporating Genetic Deiversity

developmental outcomes.

4.3.2 Geography

Geography is a deep root of development of long provenance in the literature, with a range of authors observing variation in productivity with geographical variables. The specific mechanism associated with geography has covered climate and temperature,[21] the disease environment,[22] natural resources,[23] and transport conditions (being landlocked in particular).[24]

The impact of geography can be viewed as direct, by lowering agricultural productivity or by raising the high burden of disease. It can also be indirect, with geographical and biological conditions determining the onset and spread of agriculture and animal domestication,[25] or with the distribution of crops and germs determining the onset and extent of European settlements during the age of colonization and thereby the transfer of human capital, institutions and technology.[26] In the context of any proposed geography - disease - development nexus,

[21] See for instance Myrdal (1968), Kamarck (1976), Masters and Macmillan (2001) and Sachs (2001).
[22] See Bloom and Sachs (1998), Sachs, et al (2001), and Sachs and Malaney (2002).
[23] See Sachs and Warner (2001).
[24] See Rappaport and Sachs (2003).
[25] This is the famous argument of Diamond (1997) - and see the empirical results in Olssen and Hibbs (2005) and Hibbs and Olssen (2004) confirming the mechanism. Note, however, that Ashraf and Galor (2011b), while confirming that climate, continental size and orientation, and biogeographic conditions determine the timing of the neolithic transition (adoption of agriculture), do not find an impact on modern development outcomes.
[26] See Engerman and Sokoloff (1997, 2002), Acemoglu, Johnson and Robinson (2001, 2002), Easterly and Levine (2003) and Glaeser et al (2004).

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Dep. Var.:	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc
Sample:	Full	Full	Full	Full	Full	Full	Full	Full
Estimator:	OLS	OLS	OLS	IV: 2SLS	OLS	OLS	OLS	IV: 2SLS
ACP1*A	4.82***	5.21***	3.59**	19.84**				
	(1.21)	(1.67)	(1.55)	(7.82)				
ACP1*B					−4.01***	−4.32***	−3.20***	−12.40***
					(1.02)	(1.31)	(1.22)	(4.05)
const.	5.70***	7.09***	6.53***	4.54***	9.84	11.52	9.82***	18.00***
	(0.39)	(0.39)	(0.57)	(1.26)	(1.06)	(1.10)	(1.21)	(3.67)
Physical Controls:	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Diamond Controls:	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Wu-Hausman				12.69***				11.09***
IV:				uvdamage				uvdamage
N	109	83	78	78	109	83	78	78
adj-R^2	0.54	0.48	0.61	0.11	0.53	0.48	0.62	0.39

Figures in round parentheses denote standard errors

***, **, * denotes significance at the 1%, 5% and 10% levels respectively

Table 6: Incorporating Geography

it is worth noting that Easterly and Levine (2003) examined the impact of the endowment of tropics, germs, and crops on development, finding no direct impact on economic development, only an indirect impact via institutional quality. In their analysis they lacked access to the specific *ACP1* genetic adaptation and the associated data that we employ here. As we show in what follows, inclusion of specific genetic adaptation increases the precision with which the impact of environment on development can be captured.

We consider two separate sets of geographical variables. The first relates to the physical characteristics of countries. These include the log transforms of absolute latitude, the percentage of land area that is arable, a measure of soil fertility, and the mean distance to the nearest waterway. The second set of variables control for the Diamond (1997) hypothesis concerning the importance of continental orientation, size, and the availability of domesticable plants and animals. To control for these additional deep roots we employ the variables proposed by Olsson and Hibbs (2005) and Hibbs and Olsson (2004): the axis and size of the continent on which a country is located, and the number of plants and animals suitable to domestication.

It is also worth noting that since some geographical measures covary closely with UVR damage, the inclusion of geography markers in the estimation is yet another indirect test of the exclusion restriction where estimation instruments on UVR damage.

Results are reported in Table 6. The findings are straightforward: the statistical significance and sign of the association between the *ACP1* alleles and real per capita GDP is robust to the inclusion of the geographical

controls. The association between *ACP1*A* and real per capita GDP remains positive and statistically significant throughout (columns 1 - 3), that between *ACP1*B* and development negative and significant (columns 5 - 6). This remains true if we allow for the potential endogeneity of the genetic markers by instrumenting on UVR damage (columns 4 and 8).[27] The anticipated form and statistical significance between the *ACP1* alleles and real per capita GDP is thus robust to controlling for other geographical deep roots.

4.3.3 Technology

A further deep root of development has been identified with the role of technology. Here development is held to rest on an "early" adoption of crucial technologies by 1000 BC, 0 AD and 1500 AD in agriculture, transportation, communications, writing and military dimensions. A more radical suggestion is that the deep root of development may lie as early as the timing of the Neolithic transition (adoption of agriculture).

The mechanism suggested is that where new technology adoption is a function of both the strength of complementarity to old technology, and the return from adopting new technology, having significant stocks of old technology can significantly lower the cost of new technology adoption, giving a persistent developmental advantage over time.[28] Early adoption of specific technologies in agriculture, by increasing population density and through animal husbandry, has also been associated with increased exposure to disease, with resultant improvements in disease resistance over time.[29]

To test the robustness of our mechanism, we therefore control for the summary "average" technology measure across agriculture, communications, transportation, military and industry, for the 1000 BC, 0 AD and 1500 AD time points. In addition, we control for the timing of the Neolithic transition. Results are reported in Table 7.

The finding to emerge from the results is again that the association between economic development and *ACP1* proves robust to the impact of early technological adoption. Irrespective of the timing of early technology

[27] We also tested under the presence of the disease environment that we have proposed as underlying *ACP1* adaptation over time. We have already shown these variables are statistically associated with the *ACP1* alleles. In estimations between real per capita GDP and *ACP1*, that also control for the full set of disease measures, the *ACP1* alleles maintain their statistically significant association and their expected sign with real per capita GDP.

[28] The central argument here is presented by Comin et al (2010). Note that the claim is not that early technological adoption is sufficient to explain current development. For instance Mokyr (1990) and Rosenberg and Birdzell (1986) show that technological advantage is not sufficient to explain European industrialization, given earlier Chinese technological leads - though Greene (2000) demurs and favours European exceptionalism. All that the claim amounts to is that early technological adoption matters - other things likely do too, such as institutions and human capital.

[29] See Diamond (1997), but also the discussion surrounding the impact of the timing of the neolithic revolution - Galor and Moav (2007).

	(1)	(2)	(3)	(4)	(5)	(6)
Dep. Var.:	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc
Sample:	Full	Full	Full	Full	Full	Full
Estimator:	OLS	OLS	OLS	OLS	OLS	IV: 2SLS
ACP1*A	9.42^{***}	8.50^{***}	7.69^{***}	7.58^{***}	7.63^{***}	14.68^{***}
	(1.26)	(1.21)	(1.52)	(1.25)	(1.52)	(2.75)
const.	6.66^{***}	6.92^{***}	6.63^{***}	6.93^{***}	10.74^{***}	8.65^{***}
	(0.30)	(0.37)	(0.31)	(1.43)	(2.06)	(2.36)
Tech in 1000 BC	Yes	No	No	No	No	No
Tech in 0 AD	No	Yes	No	No	No	No
Tech in 1500 AD	No	No	Yes	No	Yes	Yes
Neolithic Transition	No	No	No	Yes	Yes	Yes
Wu-Hausman						14.96^{***}
IV:						uvdamage
N	80	92	82	99	81	81
adj-R^2	0.41	0.34	0.35	0.29	0.39	0.24

	(7)	(8)	(9)	(10)	(11)	(12)
Dep. Var.:	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc
Sample:	Full	Full	Full	Full	Full	Full
Estimator:	OLS	OLS	OLS	OLS	OLS	IV: 2SLS
ACP1*B	-7.80^{***}	-7.05^{***}	-6.67^{***}	-6.47^{***}	-6.54^{***}	-10.57^{***}
	(0.95)	(0.94)	(1.18)	(0.97)	(1.18)	(1.83)
const.	14.66^{***}	14.15^{***}	13.45^{***}	13.69^{***}	17.04^{***}	19.52^{***}
	(0.79)	(0.79)	(1.00)	(1.84)	(2.09)	(2.34)
Tech in 1000 BC	Yes	No	No	No	No	No
Tech in 0 AD	No	Yes	No	No	No	No
Tech in 1500 AD	No	No	Yes	No	Yes	Yes
Neolithic Transition	No	No	No	Yes	Yes	Yes
Wu-Hausman						10.96^{***}
IV:						uvdamage
N	80	92	82	99	81	81
adj-R^2	0.46	0.38	0.39	0.33	0.42	0.35

Figures in round parentheses denote standard errors

***, **, * denotes significance at the 1%, 5% and 10% levels respectively

Table 7: Incorporating Early Technology Adoption

adoption, the sign and statistical significance of the association between real per capita GDP in 2000 and the *ACP1* allele measures is fully robust in both sign and statistical significance, with *ACP1*A* and *ACP1*B* consistently reporting positive and negative association with real per capita GDP. Columns 1 - 3, and 7 - 9 control for technology adoption in 1000 BC, 0 AD and 1500 AD respectively. The same robustness is true once we control for the timing of the Neolithic revolution (columns 4 and 10), and where we control for both forms of early technology adoption simultaneously (columns 5 and 11). Finally, allowing for the endogeneity of the *ACP1* alleles by instrumenting on UVR damage (columns 6 and 12), again does not affect the robustness of the result.[30]

4.3.4 Institutions

That the quality of institutions is of fundamental significance to the growth performance of countries has found widespread support in the literature.[31] A radicalization of this hypothesis is the suggestion that it is not just current institutions that matter, but that the presence of state-level political institutions from 1 AD through 1950 AD matters for the current level of development and economic growth.[32] Since early state formation is non-randomly distributed, with higher frequencies occurring at high latitudes, an additional concern with our reported association between the *ACP1* measures and development, is that it is spurious since the *ACP1* measures are simply serving as proxies for the early adoption of good institutions.

To explore this possibility, we follow the suggestion that the presence of state-level political institutions from 1 AD through 1950 AD matters for the current level of development and economic growth. We employ the summary measures of institutional presence over the two millennia, developed by Bockstette et al (2002), developed further in Chanda and Putterman (2005, 2007), and used in the results of Putterman and Weil (2010), and control for them in our specification linking GDP to the *ACP1* measures.

One of the perennial debates surrounding the evidence that has accumulated on the impact of institutions has focussed on whether the evidence isolates the impact of institutions, or some other dimension such as

[30] We also undertook a supplementary estimation exercise in which we controledd for the individual technology measures in agriculture, communications, transportation, military and industry. Our results remain unaffected. Similarly if we also add the Diamond geographical measures to the measures of early technological adoption, our results remain robust.

[31] This hypothesis has roots with the multiple contributions of Douglass North - see for instance North (1990), in which institutions are conceived of as the rules of the game governing interactions within society. Empirically the link has been prolifically explored in the work of Acemoglu, Johnson and Robinson (2001, 2005, by way of example). See also Rodrik et al (2004). Glaeser et al (2004) dissent, and argue that that the more plausible mechanism rests on human capital and its transfer.

[32] See Bockstette et al (2002), Chanda and Putterman (2005, 2007), Iliev and Putterman, (2007), Cinyabuguma and Putterman (2011) and Putterman and Weil (2010).

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Dep. Var.:	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc
Sample:	Full	Full	Full	Full	Full	Full	Full	Full
Estimator:	OLS	OLS	OLS	IV: 2SLS	OLS	OLS	OLS	IV: 2SLS
ACP1*A	8.24***	3.51***	3.21**	7.81***				
	(1.35)	(1.29)	(1.28)	(2.79)				
ACP1*B					−7.15***	−2.93***	−2.77***	−6.73***
					(1.04)	(1.14)	(1.11)	(2.40)
const.	6.76***	7.25***	7.17***	6.52***	14.01***	10.28***	10.00***	13.41***
	(0.33)	(0.28)	(0.26)	(0.44)	(0.88)	(0.93)	(0.97)	(2.08)
Early State Form - 5%	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Prop. European	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Wu-Hausman				4.20**				4.21**
IV:				uvdamage				uvdamage
N	71	98	70	70	71	98	70	70
adj-R^2	0.38	0.44	0.63	0.58	0.43	0.44	0.63	0.58

Figures in round parentheses denote standard errors

***, **, * denotes significance at the 1%, 5% and 10% levels respectively

Table 8: Incorporating Early Institutional Quality

human capital - for instance see Glaeser et al (2004). For this reason, we also follow the agnostic approach of Easterly and Levine (2012), in controlling simply for the European proportion of the population, leaving moot the question of whether the Europeans were transferring institutional, educational, technological, cultural or simply economic outcomes.

Estimation results are reported in Table 8.[33]

The results are again unambiguous. Controlling for early institutions does not affect either the sign or the statistical significance of the *ACP1* alleles, with *ACP1*A* maintaining positive association, *ACP1*B* its negative association with the measure of development (columns 1 and 5). In addition, the direction and statistical significance of the *ACP1* alleles is also robust to the introduction of the European proportion of the population (columns 2 and 6), and the inclusion of both early state formation and European population proportions (columns 3 and 7) Finally, allowing for endogeneity of the genetic markers also does not alter the findings (columns 4 and 8).

Once again, therefore, our mechanism remains robust to controlling for an institutional deep root.

4.3.5 All Deep Roots Together

As a final check we control for all the deep roots simultaneously. Results are reported in Table 9.

[33]Here we report only results under the assumption of a 5% discount rate on institutions - results under the full array of depcreciation rates are invariant to the depreciation rate adopted.

	(1)	(2)	(3)	(4)
Dep. Var.:	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc
Sample:	Full	Full	Full	Full
Estimator:	OLS	OLS	IV: 2SLS	IV: 2SLS
ACP1*A	3.59**		18.30***	
	(1.49)		(6.75)	
ACP1*B		−3.52***		−15.23***
		(1.21)		(5.38)
const.	−111.03**	−109.88**	−155.30*	142.11*
	(48.47)	(47.00)	(79.87)	(75.42)
Full Set Deep Roots	Yes	Yes	Yes	Yes
Wu-Hausman			21.33***	20.41***
IV:			uvdamage	uvdamage
N	53	53	53	53
adj-R^2	0.73	0.75	0.30	0.36
Figures in round parentheses denote standard errors				
***, **, * denotes significance at the 1%, 5% and 10% levels respectively				

Table 9: Incorporating All Deep Roots

Deep roots included include latitude, proportion of land arable, soil suitability, distance from navigable waterways, axis and size of continental landmass, number of domesticable plants and animals, the early technology adoption measure in for 1500 AD, early state formation, and the measures of ancestry adjusted genetic diversity.

Notably for our purposes, the form and statistical significance of the association between real per capita GDP in 2000 and the *ACP1* allele measures is fully robust to controlling for all of the other deep roots simultaneously. Specifically, the positive and statistically significant association between *ACP1*A* and real per capita GDP is present (column 1), matched by the significant negative association between GDP and *ACP1*B* (column 2). Finally, under a 2SLS IV estimator the statistical significance and the nature of the impact of the *ACP1* variables is similarly robust (see column 3 and 4).

4.3.6 Other Determinants of Development

As a final step, we also examine whether the Geography-Disease-Genetic adaptation mechanism is robust to the inclusion of a range of variables that the literature has identified as of significance to the growth performance of countries. To do so, we control for measures of physical capital, human capital and current institutions (as opposed to deep-roots institutions).

Capital stock figures are derived by means of the perpetual inventory method from World Bank Development Indicator investment series. The human capital measures include male and female literacy, as well as

	(1)	(2)	(3)	(4)	(5)	(6)
Dep. Var.:	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc	lnGDPpc
Sample:	Full	Full	Full	Full	Full	Full
Estimator:	OLS	OLS	OLS	OLS	OLS	OLS
ACP1*A	4.60*** (0.89)	1.83* (1.09)	4.17*** (1.08)			
ACP1*B				−4.09** (0.68)	−1.70* (0.91)	−3.63*** (0.88)
const.	0.17 (0.75)	6.30*** (0.78)	7.18*** (0.37)	4.39*** (1.08)	8.00*** (1.18)	10.87*** (0.81)
Phy. Capital	Yes	No	No	Yes	No	No
Human Cap.	No	Yes	No	No	Yes	No
Institutions	No	No	Yes	No	No	Yes
N	85	83	99	85	83	99
adj-R^2	0.69	0.71	0.53	0.71	0.71	0.54

Table 10: Incorporating Physical, Human and Institutional Capital

an average years of schooling measure. Finally, for institutions we employ the POLITY-IV democracy and executive constraints measures.

Results are reported in Table 10.

The impact of the *ACP1* alleles on real per capita GDP is not affected by the inclusion of the capital stock measure or of the institutional measures (columns 3 and 6), though particularly the capital stock measure improves goodness of fit considerably (columns 1 and 4). Specifically *ACP1*A* maintains its positive and significant, *ACP1*B* its negative and significant impact on real per capita GDP.

The inclusion of human capital in estimation marginally weakens the statistical significance of *ACP1*. The decrease in significance is due to the inclusion of the schooling variable. The issue is the relatively high collinearity between the schooling and the *ACP1* allele measures biases standard errors in estimation upward. However, the nature of the impact of the *ACP1* alleles is unaffected by the inclusion of the human capital variables - *ACP1*A* maintain its positive, *ACP1*B* its negative impact on real per capita GDP (columns 2 and 5).

The impact of the *ACP1* alleles on real per capita GDP is thus robust to the inclusion of standard drivers of economic growth.

5 Conclusions and Policy Considerations

We have examined a theory linking climate, geography, disease, genetic adaptation, and economic development. Our inspiration comes from individual-level studies that find a link between the *ACP1* gene and various

development, psychological and health outcomes. We explore this link using aggregate country-level data. Using new data we have assembled data on the *ACP1* genetic polymorphism across countries, we show that different distributions of *ACP1* alleles have seemed to respond to particular disease and geographical conditions. Moreover, the distributions of *ACP1* alleles have a robust predictive relationship with levels of GDP per capita. Figure 7 summarizes the statistically significant relationships between the *ACP1*A* and **B* alleles and GDP per capita, controlling for a variety of other variables. The coefficients are consistent in sign and statistical significance through all specifications. Correcting for potential endogeneity of the *ACP1* alleles does not reduce the association between the genetic marker and real per capita GDP.

We quickly reiterate a point stated throughout the paper: *ACP1* is a marker of a number of correlated genetic adaptations to climate and disease, rather than being a sole genetic determinant of development. Thus, *ACP1* is a proxy for many genetic adaptations to hostile climates and disease environments. *ACP1* frequencies are also a proxy for psychological, social and cultural adaptations of pathogen-rich environments, including collectivism, uncertainty avoidance, out-group intolerance, punitive childrearing, and more. Do these orientations persist when the disease environment changes, either through public health measures or people migrating to places with different disease profiles? Thornhill and Fincher (2014) conclude that they do. While we do not yet have enough national-level data on the frequencies of other genes that similarly react and then have subsequent effects on psychology, health, and perhaps social behavior, our limited data on IL-6 and IL-10 support the conjecture that the coefficient on *ACP1* is picking up the effects of these genetic adaptations as well.

Nevertheless, the positive associations between the *ACP1*A* and *ACP1*C* alleles and real per capita GDP, and a negative association in the case of the *ACP1*B* allele, are robust to reversal of fortunes, migration, and the potential endogeneity of the *ACP1* genetic polymorphism. The results are also robust to controlling for other deep roots of development in the literature, including genetic heterozygosity, geography, early adoption of technology, the timing of the Neolithic transition, early state formation, and European population proportions. Finally, the association stands up to the inclusion of measures of physical, human and institutional capital. Our results add another deep root to the literature on economic development.

The impact of *ACP1* on real per capita GDP is substantively significant. Under the coefficients estimated under inclusion of all deep roots, the inference is that a one standard deviation increase in *ACP1*A* would

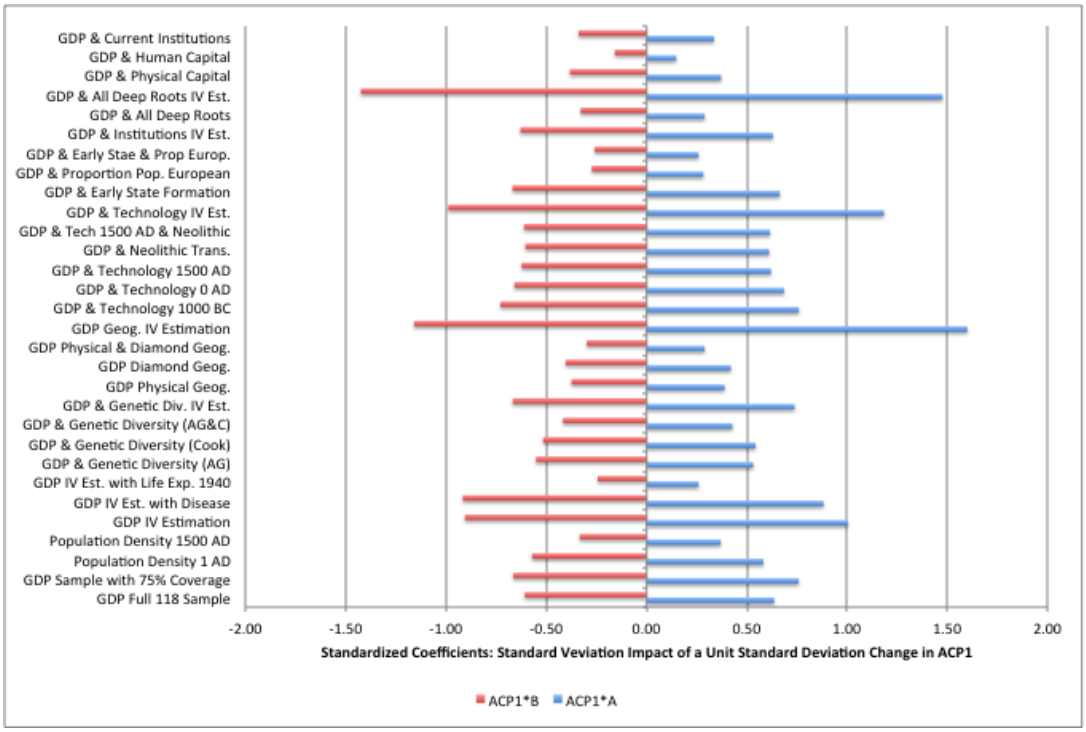


Figure 7: Estimated standardized ACP1*A and ACP1*B coefficients across specifications. Note: presence of a bar indicates both estimated standardized impact and statistical significance.

be associated with a 0.29 standard deviation increase in real per capita GDP, while a one standard deviation increase in *ACP1*B* would be associated with a 0.33 standard deviation decrease in real per capita GDP. These impacts would be associated with changes in real per capita GDP roughly equivalent to a move from Thailand to South Africa, Spain to Canada, or Nepal to Angola. These are not overwhelming impacts, but nor are they trivial.

Methodologically, it is worth noting the issue of endogeneity. Our modeling approach begins with a theory of geography - disease - genetic adaptation, which provides a structure to guide instrumental variables estimation. We exploit the theory by instrumenting genetic adaptation on ultraviolet radiation damage, a variable that is exogenous to economic development outcomes. In common with all studies that explore deep roots of development, however, this still leaves unanswered concerns regarding the satisfaction of the exclusion restriction on the instrument. Here, too, the geography - disease - genetic adaptation mechanism proves helpful. It serves to identify a set of variables that are strong covariates of the ultraviolet radiation damage instrument, in the form of disease incidence and life expectancy measures (ideally measured prior to the epidemiological

transition). These variables can then be introduced in the IV regression which incorporates the instrumented *ACP1* measure, to provide an indirect test of the exclusion restriction. Our measures of the *ACP1* genetic polymorphism survive this test of the exclusion mechanism throughout, suggesting that *ACP1* measure does not simply control for UVR damage.

Exploration of genetic information in relation to developmental outcomes is a large, promising and essentially unexamined field for future research. Our data on the country-level distributions of *ACP1* alleles is a harbinger. The rapid growth of genome wide association studies will lead to data on the distributions of many genetic characteristics across countries. At the level of individuals, genetic factors have been linked with health, psychology, education, political behavior, and more. At the level of countries, however, only recently are data emerging that would enable comparative studies. With the advent of genome-wide association studies and the subsequent amalgamation of genetic data, we expect more and more research to focus on variables like *ACP1*. Our research suggests ways to do this, and we report a statistically robust and practically important association. Moreover, our results may have policy relevance as well. Note that some of the disadvantages associated with *ACP1*B* have their impact in the presence of infectious disease, ultraviolet damage, and folate deficiency. These are potentially treatable.

Specifically, while our results isolate a deep "pre-behavioral" root of development, they lead to the identification of clear and implementable policy interventions: protection against UVR (to mitigate the negative impacts on folate), the combat of tropical diseases, and micronutrient supplementation and folic acid therapy. Much work remains to be done to clarify the conditions under which folate and nutrient supplements will be effective, and circumstances in which these interventions are contra-indicated.[34] Nonetheless the identification of a concrete policy intervention in the form of folate and nutrient supplements, is in sharp contrast to an interpretation of deep roots in general, and genetic variations in particular, as condemning developmental laggards to eternal followership.

Effective policies and programs can adapt to genetic distributions, so that deep roots of development do not necessarily imply developmental predestination.

[34] See for instance the discussion in Horton et al (2009).

References

[1] Acemoglu, D., Johnson, S., and Robinson, J., 2001, The Colonial Origins of Comparative Development: An Empirical Investigation, *American Economic Review*, 91(5), 1369-401.

[2] Acemoglu, D., Johnson, S., and Robinson, J., 2002, Reversal of Fortune: Geography and Institutions in the Making of the Modern World Income Distribution, *Quarterly Journal of Economics*, 117(4), 1231-94.

[3] Acemoglu, D., Johnson, S., and Robinson, J., 2005, The Rise of Europe: Atlantic Trade, Institutional Change, and Economic Growth, *American Economic Review*, 95(3), 546-79.

[4] Acemoglu, D., and Johnson, S., 2007, Disease and development: The effect of life expectancy on economic growth, *Journal of Political Economy*, 115(61), 925-985.

[5] Albouy, D.Y., 2012, The Colonial Origins of Comparative Development: An Empirical Investigation: Comment, *American Economic Review*, 106(6), 3059-76.

[6] Alesina, A., and Giuliano, P., 2015, Culture and Institutions, *Journal of Economic Literature*, 53(4), 898-944.

[7] Angrist, J.D., Imbens, G.W., and Rubin, D.B., 1996, Identification of Causal Effects unsing Instrumental Variables, *Journal of the American Statistical Association*, 91(434), 444-55.

[8] Apelt, N., da Silva, A.P., Ferreira, J., Alho, I., Monteiro, C., Marinho, C., Teixeira, P., Sardinha, L., Laires, M.J., Mascarenhas, M.R., Bicho, M.P., 2009, *ACP1* genotype, glutathione reductase activity, and riboflavin uptake affect cardiovascular risk in the obese, *Metabolism.*, 58(10), 1415-23.

[9] Ashraf, Q., and Galor, O., 2011a, Dynamics and Stagnation in the Malthusian Epoch, *American Economic Review*, 101(5), 2003-41.

[10] Ashraf, Q., and Galor, O., 2011b, Cultural Diversity, Geographical Isolation, and the Origin of the Wealth of Nations, NBER Working Paper No. 17640.

[11] Ashraf, Q., and Galor, O., 2013, The "Out of Africa" Hypothesis, Human Genetic Diversity, and Comparative Economic Development, *American Economic Review*, 103(1), 1-46.

[12] Aureli, A., Sebastiani, P., Del Beato, T., Marimpietri, A.E., Graziani, A., Sechi, E., Di Loreto, S., 2014, Involvement of IL-6 and IL-1 receptor antagonist on intellectual disability, *Immunol Lett.* Aug 11.

[13] Bazzi, S., and Clemens, M.A., 2013, Blunt Instruments: Avoiding Common Pitfalls in Identifying the Causes of Economic Growth, *American Economic Journal: Macroeconomics*, 5(2), 152-86.

[14] Beissert, S., Schwarz, T., 1999, Mechanisms involved in ultraviolet light-induced immunosuppression. *J Investig Dermatol Symp Proc.,* 4(1), 61-4.

[15] Bitanihirwe, B.K., and Woo, T.U., 2011, Oxidative stress in schizophrenia: an integrated approach, *Neurosci Biobehav Rev.,* 35(3), 878-93.

[16] Bloom, D.E. and Sachs, J.D., 1998, Geography, Demography and Economic Growth in Africa, *Brookings Papers on Economic Activity*, 2, 207-95.

[17] Bockstette, V., Chanda, A., and Putterman, L., 2002, States and Markets: The Advantage of an Early Start, *Journal of Economic Growth*, 7, 347-69.

[18] Botez, M.I., Fontaine, F., Botez, T., Bachevalier, J., 1977, Folate-responsive neurological and mental disorders: report of 16 cases. Neuropsychological correlates of computerized transaxial tomography and radionuclide cisternography in folic acid deficiencies, *Eur Neurol.,* 16(1-6), 230-46.

[19] Bottini, E., Palmarino, R., Lucarelli, P., Lista, F., and Bottini, N., 2001, ACP1 and human adaptability: association with past malarial morbidity in the Sardinian population, *Am J Hum Biol.,* 13(6), 753-60.

[20] Bottini, N., Stefanini, L., Williams, S., Alonso, A., Jascur, T., Abraham, R.T., Couture, C., Mustelin, T., 2002, Activation of ZAP-70 through specific dephosphorylation at the inhibitory Tyr-292 by the low molecular weight phosphotyrosine phosphatase (LMPTP), *J Biol Chem.,* 277(27), 24220-4.

[21] Bottini, N., Gloria-Bottini, F., Amante, A., Saccucci, P., and Bottini, E., 2005, Genetic polymorphism and TH1/TH2 orientation, *Int Arch Allergy Immunol.,* 138(4), 328-33.

[22] Borradale, D.C., and Kimlin, M.G., 2012, Folate degradation due to ultraviolet radiation: possible implications for human health and nutrition, *Nutr Rev.,* 70(7), 414-22.

[23] Brock, W.A., and Durlauf, S.N., 2001, Growth Empirics and Reality, *World Bank Economic Review*, 15(2), 229-72.

[24] Cavalli-Sforza, L.L., Menozzi, P., and Piazza, A., 1994, *The History and Geography of Human Genes*, Princeton: University Press.

[25] Chanda, A., and Putterman, L., 2005, State Effectiveness, Economic Growth, and the Age of States, in M.Lange and D.Rueschemeyer (eds.), *States and Development: Historical Antecedents of Stagnation and Advance*, Basingstoke: Palgrave Macmillan.

[26] Chanda, A., and Putterman, L., 2007, Early Starts, Reversals and Catch-Up in the Process of Economic Development, *Scandinavian Journal of Economics*, 109, 387-4.

[27] Cinyabuguma, M. and Putterman, L., 2011, Sub-Saharan Growth Surprises: Being Heterogeneous, Inland and Close to the Equator Does not Slow Growth within Africa, *Journal of African Economies,* 20 (2), 217 – 62.

[28] Comin, D., Easterly, W., and Gong, E., 2010, Was the Wealth of nations Determined in 1000 BC? *American Economic Journal: Macroeconomics*, 2, 65-97.

[29] Cook, C.J. 2014, The Natural Selection of Infectious Disease Resistance and Its Effect on Contemporary Health, *Review of Economics and Statistics*, forthcoming.

[30] Diamond, J., 1997, *Guns, Germs and Steel*, W.W.Norton.

[31] Dollar, D., and Kraay, A., 2003, Institutions, Trade and Growth, *Journal of Monetary Economics*, 50(1), 133-62.

[32] Durga, J., van Boxtel, M.P., Schouten, E.G., Bots, M.L., Kok, F.J., Verhoef, P., 2006, Folate and the methylenetetrahydrofolate reductase 677C–>T mutation correlate with cognitive performance, *Neurobiol Aging.,* 27(2), 334-43.

[33] Durga, J., van Boxtel, M.P., Schouten, E.G., Kok, F.J., Jolles, J., Katan, M.B., Verhoef, P., 2007, Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial, *Lancet*, 369(9557), 208-16.

[34] Durlauf, S.N., Johnson, P.A., and Temple, J.R.W., 2005, Growth Econometrics, in P.Aghion and S.N.Durlauf (eds.), *Handbook of Economic Growth*, North-Holland, 555-678.

[35] Duthie, S.J., 1999, Folic acid deficiency and cancer: mechanisms of DNA instability, *Br Med Bull.,* 55(3), 578-92.

[36] Easterly, W., and Levine, R., 2003, Tropics, Germs, and Crops: How Endowments Influence Economic Development, *Journal of Monetary Economics*, 50(1), 3-39.

[37] Easterly, W., and Levine, R., 2012, The European Origins of Economic Development, NBER Working Paper No. 18162.

[38] Engerman, S.L., and Sokoloff, K.L., 1997, Factor Endowments, Institutions, and Differential Paths of Growth among New World Economies: A View from Economic Historians of the United States, in S.Haber (ed.), *How Latin America Fell Behind: Essays on the Economic Histories of Brazil and Mexico, 1800-1914*, Stanford: University Press.

[39] Engerman, S.L., and Sokoloff, K.L., 2002, Factor Endowments, Inequality, and Paths of Development among New World Economies, *Economia: Journal of the Latin American and Caribbean Economic Association*, 3(1), 41-88.

[40] Eppig, C., Fincher, C.L., and Thornhill, R., 2010, Parasite prevalence and the worldwide distribution of cognitive ability, *Proc Biol Sci.,* 277(1701), 3801-8.

[41] Flatow, J., Buckley, P., and Miller, B.J., 2013, Meta-analysis of oxidative stress in schizophrenia, *Biol Psychiatry.*, Sep 15, 74(6):400-9.

[42] Fumagalli, M., Sironi, M., Pozzoli, U., Ferrer-Admettla, A., Pattini L., and Nielsen, R., 2011, Signatures of environmental adaptation pinpoint pathogens as the main selective pressure through human evolution, *PLoS Genetics,* 7: e1002355.

[43] Galor, O., 2005, From Stagnation to Growth: Unified Growth Theory, in P.Aghion and S.Durlauf (eds.), *Handbook of Economic Growth*, Vol 1A, Amsterdam and Boston: North-Holland, 171-294.

[44] Galor, O., and Moav, O., 2007, The Neolithic Revolution and Contemporary Variations in Life Expectancy, Working Papers 2007-14, Brown University, Department of Economics.

[45] Galor, O., Moav, O.,and Vollrath, D., 2009, Inequality in Landownership, the Emergence of Human-Capital Promoting Institutions, and the Great Divergence, *Review of Economic Studies*, 76(1), 143-79.

[46] Galor, O., and Weil, D.N., 2000, Population, Technology, and Growth: From Malthusian Stagnation to the Demographic Transition and Beyond, *American Economic Review*, 90(4), 806-28.

[47] Glaeser, E.L., La Porta, R., Lopez-de-Silanes, F., and Shleifer, A., 2004, Do Institutions Cause Growth? *Journal of Economic Growth*, 9(3), 271-303.

[48] Gloria-Bottini, F., Bottini, N., Renzetti, G., Bottini, E., 2007, ACP1 and Th class of immunological disease: evidence of interaction with gender., *Int Arch Allergy Immunol.*, 143(3), 170-6.

[49] Greene, K., 2000, Technological Innovation and Economic Progress in the Ancient World: M.I.Finley Re-considered, *Economic History Review*, 53(1), 29-59.

[50] Greene, L.S., Bottini, Nunzio, Borgiani, P., Gloria-Bottini, Fulvia, 2000, Acid phosphatase locus 1 (*ACP1*): Possible relationship of allelic variation to body size and human population adaptation to thermal stress-A theoretical perspective., *Am. J. Hum. Biol.,* 12, 688-701.

[51] Grimbaldeston, M.A., Nakae, S., Kalesnikoff, J., Tsai, M., Galli, S.J., 2007, Mast cell-derived interleukin 10 limits skin pathology in contact dermatitis and chronic irradiation with ultraviolet, *B. Nat Immunol.,* 8(10), 1095-104.

[52] Hauk, W.R.Jr., and Wacziarg, R., 2009, A Monte Carlo Study of Growth Regressions, *Journal of Economic Growth*, 14(2), 103-47.

[53] Herman, J. R., Krotkov, N., Celarier, E., Larko, D., and Labow, G., 1999, Distribution of UV radiation at the Earth's surface from TOMS-measured UV-backscattered radiances, *J. Geophys. Res.*, 104, 12,059–12,076.

[54] Hibbs, D.A., and Olsson, O., 2004, Geography, Biogeography, and Why Some Countries Are Rich and Others Are Poor, *Proceedings of the National Academy of Sciences*, 101, 3715-20.

[55] Horton, S., Alderman, H., and Rivera, J.A., 2009, Hunger and Malnutrition, in Lomborg, B., ed., 2009, *Global Crises, Global Solutions*, 2'nd ed. Cambridge: University Press, 305-333.

[56] Iliev, P. and Putterman, L., 2007, Social Capability, History and the Economies of Communist and Post-Communist States, *Studies in Comparative International Development*, 42 (1), 36-66.

[57] Jablonski, N.G., 2012, The evolution of human skin colouration and its relevance to health in the modern world, *J R Coll Physicians Edinb.,* 42(1), 58-63.

[58] Juzeniene, A., Thu Tam, T.T., Iani, V., Moan, J., 2013, The action spectrum for folic acid photodegradation in aqueous solutions, *J Photochem Photobiol B.,* Sep 5;126:11-6.

[59] Kamarck, A.M., 1976, *The Tropics and Economic Development*, Baltimore and London: Johns Hopkins Press.

[60] Kerac, M., Postels, D.G., Mallewa, M., Alusine Jalloh, A., Voskuijl, W.P., Groce, N., Gladstone, M., and Molyneux, E., 2014, The interaction of malnutrition and neurologic disability in Africa, *Semin Pediatr Neurol.,* 21(1), 42-9.

[61] Kremer, M., 1993, Population Growth and Technological Change: One Millon B.C. to 1990, *Quarterly Journal of Economics*, 108(3), 681-716.

[62] Kreuter, A., Hyun, J., Skrygan, M., Sommer, A., Bastian, A., Altmeyer, P., Gambichler, T., 2006, Ultraviolet A1-induced downregulation of human beta-defensins and interleukin-6 and interleukin-8 correlates with clinical improvement in localized scleroderma, *Br J Dermatol.,* 155(3), 600-7.

[63] Maseland, R., 2013, Parasytical Cultures? The cultural origins of institutions and development, *Journal of Economic Growth*, 18, 109-36.

[64] Masters, W.A., and McMillan, M.S., 2001, Climate and Scale in Economic Growth, *Journal of Economic Growth*, 6(3), 167-86.

[65] McNeill, G., Jia, X., Whalley, L.J., Fox, H.C., Corley, J., Gow, A.J., Brett, C.E., Starr, J.M., Deary,JJ., 2011, Antioxidant and B vitamin intake in relation to cognitive function in later life in the Lothian Birth Cohort 1936, *Eur J Clin Nutr.,* 65(5), 619-26.

[66] Meng, J.Y., Zhang, C.Y., Zhu, F., Wang, X.P., Lei, C.L., 2009, Ultraviolet light-induced oxidative stress: effects on antioxidant response of Helicoverpa armigera adults, *J Insect Physiol.,* 55(6), 588-92.

[67] Michalopoulos, S., and Papaioannou, E., 2010, Divide and Rule of the Rule of the Divided? Evidence from Africa, CEPR Discussion Paper 8088.

[68] Mitchell, E.S., Conus, N., and Kaput, J, 2014, B vitamin polymorphisms and behavior: Evidence of associations with neurodevelopment, depression, schizophrenia, bipolar disorder and cognitive decline, *Neurosci Biobehav Rev.*, pii: S0149-7634(14)00204-8. doi: 10.1016/j.neubiorev.2014.08.006. [Epub ahead of print].

[69] Mokyr, J., 1990, *The Lever of Riches: Technological Creativity and Economic Progress*, Oxford: University Press.

[70] Murray, M.P. 2006, Avoiding Invalid Instruments and Coping with Weak Instruments, *Journal of Economic Perspectives*, 20(4), 111-32.

[71] Myrdal, G., 1968, *Asian Drama: An Inquiry Into the Poverty of Nations*, New York: Twentieth Century Fund.

[72] North, D.C., 1990, *Institutions, Institutional Change and Economic Performance*, New York: Cambridge University Press.

[73] Olsson, O., and Hibbs, D.A., 2005, Biogeography and Long-Run Economic Development, *European Economic Review*, 49(4), 909-38.

[74] Prado, C., Contreras, F., González, H., Díaz, P., Elgueta, D., Barrientos, M., Herrada, A.A., Lladser, Á., Bernales, S., Pacheco, R., 2012, Stimulation of dopamine receptor D5 expressed on dendritic cells potentiates Th17-mediated immunity, *J Immunol.,* 188(7), 3062-70.

[75] Putterman, L., and Weil, D.N., 2010, Post-1500 Population Flows and The Long-Run Determinants of Economic Growth and Inequality, *Quarterly Journal of Economics*, 125(4), 1627-82.

[76] Ramachandran, Sohini et al., 2005, Support from the Relationship of Genetic and Geographic Distance in Human Populations for a Serial Founder Effect Originating in Africa, *Proceedings of the National Academy of Sciences,* 102(44), 15942-47.

[77] Rappaport, J., and Sachs, J.D., 2003, The United States as a Coastal Nation, *Journal of Economic Growth*, 8(1), 5-46.

[78] Rodrick, D., Subramanian, A., and Trebbi, F., 2004, Institutions Rule: The Primacy of Institutions Over Geography and Integration in Economic Development, *Journal of Economic Growth*, 9, 131-65.

[79] Rosenberg, N., and Birdzell, L.E., 1986, *How the West Grew Rich: The Economic Transformation of the Industrial World*, New York: Basic Books.

[80] Sachs, J.D., 2001, Tropical Underdevelopment, NBER Working Paper No. 8119.

[81] Sachs, J.D., and Malaney, P., 2002, The Economic and Social Burden of Malaria, *Nature*, 415(6872), 680-85.

[82] Sachs, J.D., Mellinger, A.D., and Gallup, J.L., 2001, The Geography of Poverty and Wealth, *Scientific American*, March, 71-4.

[83] Sachs, J.D., and Warner, A.M., 2001, The Curse of Natural Resources, *European Economic Review*, 45(4-6), 827-38.

[84] Sasayama, D., Hori, H., Teraishi, T., Hattori, K., Ota, M., Matsuo, J., Kawamoto, Y., Kinoshita, Y., Amano, N., and Kunugi, H., 2012, Association of cognitive performance with interleukin-6 receptor Asp358Ala polymorphism in healthy adults, *J Neural Transm.,* 119(3), 313-8.

[85] Sensabaugh, G.F., and Golden, V.L., 1978, Phenotype dependence in the inhibition of red cell acid phosphatase (ACP) by folates, *Am J Hum Genet.,* 30(5), 553-60.

[86] Spolaore, E., and Wacziarg, R., 2013, How Deep Are the Roots of Economic Development? *Journal of Economic Literature*, 51(2), 325-69.

[87] Strand, T.A., Taneja, S., Ueland, P.M., Refsum, H., Bahl, R., Schneede, J., Sommerfelt, H., and Bhandari, N., 2013, Cobalamin and folate status predicts mental development scores in North Indian children 12-18 mo of age, *Am J Clin Nutr.,* 97(2), 310-7.

[88] Sreevidya, C.S., Fukunaga, A., Khaskhely, N.M., Masaki, T., Ono, R., Nishigori, C., Ullrich, S.E., 2010, Agents that reverse UV-Induced immune suppression and photocarcinogenesis affect DNA repair, *J Invest Dermatol.,* 130(5),1428-37, doi: 10.1038/jid.2009.329.

[89] Swaminathan, S., Edward, B.S., and Kurpad, A.V., 2013, Micronutrient deficiency and cognitive and physical performance in Indian children, *Eur J Clin Nutr.,* 67(5), 467-74.

[90] Tabellini, G., 2010, Culture and Institutions: Economic Development in the Regions of Europe, *Journal of the European Economic Association*, 8(4), 677-716.

[91] Thornhill, R., and Fincher, C.J., 2014, *The Parasite-Stress Theory of Value and Sociality: Infectious Disease, History, and Human Values Worldwide*, New York: Springer.

[92] Ulrich, C., Schmook, T., Sachse, M.M., Sterry, W., Stockfleth, E., 2004, Comparative epidemiology and pathogenic factors for nonmelanoma skin cancer in organ transplant patients, *Dermatol Surg.*, 30(4 Pt 2), 622-7.

[93] Vavricka, S.R., and Rogler, G., 2012, Intestinal absorption and vitamin levels: is a new focus needed? *Dig Dis.* 30 Suppl 3, 73-80.

[94] Wang, J., Ge, Y., Ning, H., and Wang, S., 2004, Effects of High Fluoride and Low Iodine on Oxidative Stress and Antioxidant Defense of the Brain in Offspring Rats, *Fluoride*, 37(4), 264–270.

[95] Zinck, J.W.R. and MacFarlane, A.J., 2014, Approaches for the identification of genetic modifiers of nutrient dependent phenotypes: examples from folate, *Front. Nutr.*, doi: 10.3389/fnut.2014.00008.