RESEARCH NOTE

REVISED Evidence of polygenic selection on human stature
inferred from spatial distribution of allele frequencies
[version 3; peer review: 1 approved with reservations, 1 not
approved]

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V3 First published: 16 Jan 2015, 4:15
<https://doi.org/10.12688/f1000research.6002.1>
 Second version: 23 Dec 2015, 4:15
<https://doi.org/10.12688/f1000research.6002.2>
 Latest published: 25 Jan 2016, 4:15
<https://doi.org/10.12688/f1000research.6002.3>

Abstract

Spatial patterns of allele frequencies reveal a clear signal of natural (or sexual) selection on human height. The average frequency of all hits (N=693) and the top significant 66 common genetic variants (pruned for linkage disequilibrium) for 26 populations belonging to 5 sub-continental human groups were significantly correlated to average phenotypic population height. The method of correlated vectors provided additional evidence for a signal of natural selection in SNPs with higher significance. Factor analysis of the five top genome-wide association study (GWAS) hits revealed a clear factor indicating selection pressures on human height, peaking among northern Europeans and some African groups (Esan Nigeria) whilst reaching a nadir among South-East Asians. Finally, a new polygenic score is created to take into account overrepresentation of derived alleles among GWAS hits and population-level differences in derived allele frequencies.

Keywords

Height; Evolution; Polygenic Selection; Height

Open Peer Review**Approval Status** ? X

	1	2
version 3 (revision) 25 Jan 2016		X view
version 2 (revision) 23 Dec 2015		
version 1 16 Jan 2015	? view	

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Any reports and responses or comments on the article can be found at the end of the article.

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Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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How to cite this article: Piffer D. **Evidence of polygenic selection on human stature inferred from spatial distribution of allele frequencies [version 3; peer review: 1 approved with reservations, 1 not approved]** F1000Research 2016, 4:15

<https://doi.org/10.12688/f1000research.6002.3>

First published: 16 Jan 2015, 4:15 <https://doi.org/10.12688/f1000research.6002.1>

REVISED Amendments from Version 2

GWAS hits were divided according to derived or ancestral allele status. A paragraph was added to the introduction to justify this novel procedure. A new subsection titled "Controlling for population differences in derived allele frequencies" was added to the results section. Derived allele frequencies (DAF) differ between populations, thus a "DAF-corrected" polygenic score was computed. Two tables were added (6 and 7) to the results section, reporting the average DAF and the DAF, AAF (Ancestral allele frequency) for the alleles with a positive effect, respectively. [Table 7](#) also reports the DAF-corrected scores. A paragraph elaborating on these new findings was added to the Discussion. The abstract has a minor correction and a sentence was added.

See referee reports

Introduction

A recent GWAS ([Wood *et al.*, 2014](#)) based on a very large sample (N=250K) identified common variants responsible for normal variation in human height within populations.

Over the last few years, researchers have started moving away from the study of genetic evolution using a single-gene, Mendelian approach towards models that examine many genes together (polygenic). The more genes are involved in a given phenotype, the more the signal of natural selection will be "diluted" across different genomic regions (because each gene accounts for a tiny effect) making it difficult to detect it using approaches focused on a single gene ([Piffer, 2014a](#); [Pritchard *et al.*, 2010](#)). A first attempt at empirically identifying polygenic selection was made by [Turchin *et al.* \(2012\)](#) on two populations (Northern and Southern Europeans) and evidence for higher frequency of height increasing alleles (obtained from GWAS studies) among Northern Europeans was provided. A drawback of that study was the reliance on populations from a single continent and that crude pairwise comparisons (e.g. French vs. Italian) were used without correlating frequency differences to average population height. Moreover, the strength of selection was not determined.

Two different approaches to identify selection based on the correlation of allele frequencies across different populations have been recently developed by [Piffer \(2013\)](#) and [Berg & Coop \(2014\)](#).

Piffer's method uses factor analysis of trait increasing alleles (found by GWA studies) as a tool for finding a factor that represent the strength of selection on a phenotype and the underlying genetic variation ([Piffer, 2014a](#)). An additional methodology consists of computing the correlation between genetic frequencies and the average phenotypes of different populations; then, the resulting correlation coefficients are correlated with the corresponding alleles' genome-wide significance (p value). If the alleles contain selection signals, a positive correlation will be found, as alleles with high p value (more likely to be false positives) have a weaker correlation to average population phenotype ([Piffer, 2014a](#)).

Piffer's method ([Piffer, 2013](#); [Piffer, 2014a](#)) to identify signals of polygenic selection was used in this study and applied to the top five GWAS hits (ranked according to p value). [Piffer \(2014b\)](#) carried out a study on height SNPs but it was based on a smaller GWAS sample and an older version (phase 1) of the 1000 Genomes

data, containing data for only 14 populations. This paper uses the phase 3 1000 Genomes data and the GWAS meta-analysis was carried out on a much larger sample size, which produces more hits with better significance. The aim of this paper is to test the hypothesis that stature has undergone natural or sexual selection in populations after humans dispersed in different continents giving rise to distinct genetic clusters.

This study also exploits additional information provided by frequencies of derived and ancestral alleles. At a theoretical level, an ancestral allele is the allele that was carried by the last common ancestor between humans and other primates whereas an allele is derived when it arose in the human lineage after the split from other primates. In practice, this allele is usually ascertained via comparison with chimpanzees. One limitation of this procedure is that if a mutation arose in chimpanzees after the split from humans, then the ancestral allele is not the chimp allele. Thus, 1000 Genomes infers ancestral alleles via alignment with 6 primate species ([Ensembl, 2015](#)).

Derived allele frequencies (DAF) are not the same for all populations. Substantial DAF differences across populations have been found, largely due to random drift and population bottlenecks but in part also by different selection pressures ([Henn *et al.*, 2015](#)). Non-African populations tend to have higher frequencies of derived alleles, and DAF is positively correlated to distance from Africa ([Henn *et al.*, 2015](#)). If among the GWAS hits there is an overrepresentation of an allele type (more ancestral than derived alleles or vice versa), this could bias the polygenic score towards the populations with a higher background frequency of such an allele type. Thus, this study will take into account baseline differences in DAF to create an "unbiased" or "DAF-corrected" polygenic score.

Methods

Frequencies of alleles with a positive effect (height increasing) were obtained from 1000 Genomes (phase 3): <http://browser.1000genomes.org/index.html> comprising 26 populations belonging to five racial groups.

Average population height was obtained from the references listed at: http://en.wikipedia.org/wiki/Human_height, considering only statistics published after 2000 and young age groups (18–40). Only 11 populations met these criteria (see references in [Table 1](#)).

First, the entire sample of SNPs meeting genome-wide significance (N=697) was downloaded and the population frequencies for the alleles with a positive Beta in the 250k GWAS Meta-analysis were calculated. 4 SNPs could not be included because they were absent from 1000 Genomes.

For each chromosome, the three alleles with the highest p values were selected, and these were all unlinked (>500Kb apart from each other). Only unlinked alleles were used to avoid the confounding influence of linkage on cross-population allele frequency. Selection was restricted only to the alleles with the highest significance because these are less likely to be false positives. The same number of SNPs (3) from each chromosome was used to get a representative sample of the entire genome, to avoid bias due to chromosome location. The conventional nominal p-value <5×10⁻⁸ was used as significance threshold ([Barsh *et al.*, 2012](#)).

Table 1. Polygenic score and height.

Population	Polygenic Score (All Hits), %	Polygenic score (66 SNPs), %	Height (cm)	Reference (Height)
Afr.Car.Barbados	47.32	48.94		
US Blacks	47.65	48.71	178.00	McDowell <i>et al.</i> , 2008
Esan Nigeria	47.09	49.50		
Gambian	47.19	48.97		
Luhya Kenya	46.85	48.42		
Mende Sierra Leo	47.21	49.03		
Yoruba	46.98	48.52		
Colombian	48.32	46.05	170.60	Meisel & Vega, 2004
Mexican LA	47.88	46.95	170.6	McDowell <i>et al.</i> , 2008
Peruvian	47.40	46.48		
Puerto Rican	48.34	46.79		
Chinese Dai	46.75	44.88		
HanChineseBeijing	46.95	44.76	170.2	Yang <i>et al.</i> , 2005
HanChineseSouth	47.12	45.70	170.2	Yang <i>et al.</i> , 2005
Japanese	46.75	44.85	172.00	Ministry of Ed., 2004
Vietnam	46.98	44.76	165.70	Hung & Park, 2008
UtahWhites	50.22	47.62	178.9	McDowell <i>et al.</i> , 2008
Finns	49.61	48.09	180.70	National Institute for Health and Welfare, 2011
British	49.89	46.80	177.80	Moody (2013). Health Survey for England
Spanish	49.10	46.77		
TuscanItaly	49.17	47.11	177.00	Cacciari <i>et al.</i> , 2002*
Bengali Banglade	47.50	46.09		
Gujarati Ind. Tx	47.60	47.12		
Indian Telegu UK	47.76	47.62		
Punjabi Pakistan	48.08	47.21		
SriLankanUK	47.70	46.98		

*Not on Wikipedia. Region of a country, more specific statistics found elsewhere.

A polygenic score was calculated as the mean frequency of height increasing alleles (defined as those with a positive Beta coefficient in the meta-analysis).

Analyses were carried out using R.

Results

Dataset 1. All Hits

<http://dx.doi.org/10.5256/f1000research.6002.d109935>

This dataset reports the 693 SNPs having genome-wide significance. Data derived from 1000 Genomes, phase 3 data.

Dataset 2. Hits 1+2+3

<http://dx.doi.org/10.5256/f1000research.6002.d41833>

This dataset reports the frequencies of 66 height increasing alleles, 3 from each autosomal chromosome. Data derived from 1000 Genomes, phase 3 data.

Dataset 3. Method of correlated vectors (MCV) for the top 66 SNPs

<http://dx.doi.org/10.5256/f1000research.6002.d109933>

This dataset reports SNP names, p value and the correlation between p value with polygenic score (col.B) and average height (col.D), for the top 66 SNPs. Data derived from 1000 Genomes, phase 3 data.

Dataset 4. Method of correlated vectors (MCV) for all SNPs

<http://dx.doi.org/10.5256/f1000research.6002.d109934>

This dataset reports SNP names, p value and the correlation between p value with polygenic score (col.B) and average height (col.D), for all SNPs. Data derived from 1000 Genomes, phase 3 data.

Polygenic score

Polygenic score and average country height are reported in [Table 1](#). The Pearson correlation between polygenic score including all hits (N=693) and average country height was $r=0.79$ (N=11, $p=0.004$).

The correlation with the 66 hits polygenic score was $r=0.83$ ($N=11$, $p=0.002$). [Table 2](#) reports average frequencies by sub-continental populations.

Frequencies in descending order for the two (66 hits and all hits, respectively) polygenic scores are: 1) Africans (AFR); 2) Europeans (EUR); 3) South Asians (SAS); 4) Latin Americans/Hispanics (AMR); 5) East Asians (ASN). 1) Europeans; 2) Latin Americans/Hispanics; 3) South Asians; 4) Africans; 5) East Asians

Method of correlated vectors (MCV)

Spearman's rank order correlation between each allele's p value and its correlation with the polygenic score (66 hits) and with height were respectively -0.26 and -0.34 ($N=66$, $p=0.037$ and 0.0053). The "rcorr" and "cor" functions in R produced slightly different results due to differences in dealing with ties (equal values). "cor" produced slightly stronger coefficients (-0.28 and -0.37). The correlations using all hits were much smaller, but in the right direction ($N=693$; $r=-0.059$, $p=0.121$ and $r=-0.111$, $p=0.003$ for height and polygenic score, respectively).

Table 2. Frequencies of height increasing alleles for sub-continental populations.

Continent	66 Hits Polygenic score (%)	All hits Polygenic Score
AFR	47.69	47.10
AMR	45.92	48.07
ASN	45.52	46.98
EUR	46.65	49.63
SAS	46.549	47.79

This provides evidence for the hypothesis that more significant GWAS hits (alleles) are enriched with natural selection signal. A similar phenomenon was observed in a previous analysis of genes affecting human height ([Piffer, 2014b](#)).

Factor analysis of the top 5 hits

Factor analysis requires a satisfying cases to variable ratio, thus only a handful of SNPs could be used and these had necessarily to be those with the lowest p value, as they are more likely to be genuine hits (see previous section, MCV).

The top 5 alleles (i.e. those with the lowest p value) all correlated with the polygenic score and with average height in the expected direction (positively), as shown in [Table 3](#) (see [Dataset 3](#)). The average correlations were 0.58 and 0.69, respectively, which is a significant improvement compared to the average of the correlations with polygenic score and height of all the 66 alleles ($r=0.03$ and 0.04 , respectively; see [Dataset 2](#), cells BP38-39).

A factor analysis using minimum residuals was carried out. A single factor was extracted that explained 42% of the variance. Factor loadings are displayed in [Table 4](#). These are all positive (in the expected direction).

Factor scores were extracted with the Thurstone method ([Thurstone, 1947](#)), and are reported in [Table 5](#).

The Pearson correlation between average country height and the factor score was strongly positive ($r=0.88$, $N=11$, $p=0.001$). This factor was also significantly correlated to the 66 hits polygenic score ($r=0.78$, $N=26$, $p<0.001$) and to the 693 hits polygenic score ($r=0.545$, $N=26$, $p=0.004$).

Table 3. Top five SNPs. (p value and r with polygenic (pol) score).

SNP	rs724016.G	rs1812175.G	rs42039.T	rs143384.G	rs8756.C
GWAS p value	3.2E-158	2.1E-86	3.8E-88	1.2E-121	4.5E-90
r with pol. score	0.78	0.26	0.22	0.84	0.78
r with average pop. height	0.62	0.75	0.75	0.49	0.88

Table 4. Top 5 SNPs. Standardized loadings (pattern matrix) based upon correlation matrix.

Gen.coordinate	SNP ID	Factor loading
142.588.260 (Chr.3)	rs724016.G	0.62
145.794.294 (Chr.4)	rs1812175.G	0.33
92.082.358 (Chr.7)	rs42039.T	0.62
33.489.170 (Chr.20)	rs143384.G	0.48
64.646.019 (Chr.12)	rs8756.C	1

Table 5. Factor scores.

Population	Height Top 5 SNP factor	Height (cm)
Afr.Car.Barbados	1.08	
US Blacks	0.24	178.00
Esan Nigeria	1.29	
Gambian	0.73	
Luhya Kenya	0.38	
Mende Sierra Leo	0.38	
Yoruba	1.08	
Colombian	0.08	170.60
Mexican LA	-0.27	172.00
Peruvian	0.15	
Puerto Rican	0.44	
Chinese Dai	-1.76	
HanChineseBeijing	-1.41	172.10
HanChineseSouth	-1.62	172.10
Japanese	-1.41	172.00
Vietnam	-1.69	165.70
UtahWhites	1.43	179.00
Finns	1.29	180.70
British	1.01	177.80
Spanish	0.58	
TuscanItaly	0.72	177.00
Bengali Banglade	-0.41	
Gujarati Ind. Tx	-0.41	
Indian Telegu UK	-0.69	
Punjabi Pakistan	-0.48	
SriLankanUK	-0.70	

Table 6. Average frequency of derived alleles (DAF).

Population	DAF
Afr.Car.Barbados	0.298
US Blacks	0.309
Bengali Bangladesh	0.363
Chinese Dai	0.359
Utah Whites	0.382
Chinese, Beijing	0.365
Chinese, South	0.362
Colombian	0.372
Esan, Nigeria	0.286
Finland	0.385
British, GB	0.381
Gujarati Indian, Tx	0.365
Gambian	0.291
Iberian, Spain	0.378
Indian Telegu, UK	0.362
Japan	0.366
Vietnam	0.360
Luhya, Kenya	0.291
Mende, Sierra Leone	0.283
Mexican in L.A.	0.376
Peruvian, Lima	0.373
Punjabi, Pakistan	0.366
Puerto Rican	0.369
Sri Lankan, UK	0.362
Toscani, Italy	0.376
Yoruba, Nigeria	0.285

Controlling for population differences in derived allele frequencies

Allele status could be ascertained for 691 of the 697 SNPs. Among the alleles with a positive effect, there were 370 derived and 321 ancestral alleles, respectively. Since this is not an equal representation, it creates a potential confounding factor. The derived allele frequency (DAF) was computed including both positive and negative effect alleles, to verify that these varied among populations. Average DAF is reported in Table 6. These indeed confirmed previous findings that non-African populations have higher frequencies of derived alleles (Henn *et al.*, 2015). Since there are more derived alleles with a positive effect in this sample, the polygenic scores for African populations are lowered compared

to non-African populations. Correcting for this bias will thus increase the polygenic scores of African populations relative to the others.

Since the frequency of ancestral alleles is the inverse of DAF (1-DAF), a polygenic score was calculated that gives equal weight to the ancestral and derived alleles by averaging the mean frequencies of ancestral and derived alleles with a positive GWAS effect. This ensures that polygenic scores of populations with higher background DAF are not biased upwards. Table 7 reports the average frequencies of derived and ancestral alleles with a positive effect, sorted in descending order by their mean polygenic score.

Table 7. Average frequency of alleles with a positive effect. Average frequency of alleles with a positive effect. AA=Ancestral alleles; DA=Derived alleles. Mean (DAF-corrected) polygenic score sorted in descending order.

Population	DAF	AAF	Mean
Utah Whites	0.393	0.629	0.511
British, GB	0.389	0.627	0.508
Finland	0.389	0.620	0.505
Toscani, Italy	0.377	0.625	0.501
Iberian, Spain	0.378	0.622	0.500
Puerto Rican	0.362	0.624	0.493
Colombian	0.365	0.620	0.493
Punjabi, Pakistan	0.357	0.625	0.491
US Blacks	0.299	0.681	0.490
Mexican in L.A.	0.364	0.612	0.488
Indian Telegu, UK	0.350	0.626	0.488
Sri Lankan, UK	0.350	0.625	0.487
Afr.Car.Barbados	0.285	0.689	0.487
Mende, Sierra Leone	0.270	0.704	0.487
Gujarati Indian, Tx	0.351	0.621	0.486
Gambian	0.277	0.695	0.486
Bengali Bangladesh	0.349	0.622	0.485
Esan, Nigeria	0.271	0.700	0.485
Yoruba, Nigeria	0.269	0.700	0.484
Peruvian, Lima	0.357	0.610	0.484
Luhya, Kenya	0.274	0.692	0.483
Chinese, South	0.344	0.619	0.482
Vietnam	0.341	0.620	0.480
Chinese, Beijing	0.345	0.614	0.479
Chinese Dai	0.337	0.620	0.479
Japan	0.344	0.611	0.477

The top and bottom scores are obtained by European and East Asian populations, respectively. The correlation with average population height is $r=0.819$.

Discussion

Polygenic scores, created by averaging frequencies from 26 populations of all SNPs having attained genome-wide significance ($N=693$; $p<5 \times 10^{-8}$) in the largest and most recent human height GWAS, was positively correlated with the average height of 11 populations ($r=0.79$). Another polygenic score, obtained from 66 height increasing alleles pruned for linkage disequilibrium, was positively correlated with the average height of 11 populations ($r=0.83$).

The method of correlated vectors revealed that alleles with lower p values had a higher correlation with phenotypic height and polygenic score, suggesting that they tend to be enriched with signal of natural selection. A factor analysis of the top five GWAS hits produced a factor (whose loadings are all in the expected direction) which is significantly and strongly correlated both to population average height and to the polygenic scores. This showed an improvement over the correlation of the five single alleles with population height (Table 3, last row) which averaged 0.66, which in turn improved over the average correlation of the 66 alleles, which was near zero.

The rankings of polygenic and factor scores match with the folk perception on the stature of various racial groups: Africans>Europeans>South/Central Asians>Hispanics>East Asians (Table 2). However, the ranking of Africans was lower in the polygenic score computed using all the GWAS hits, whereas the others were little altered with respect to each other.

South East Asians had the lowest scores, a result which matches with their anthropometric description.

Within Europe, northern Europeans (Finns and White Americans) had a higher genotypic stature than their southern counterparts (Italians and Spaniards), confirming the results from a previous study on GWAS loci which compared northern vs southern Europeans (Turchin *et al.*, 2012).

A correction for background derived allele frequency (DAF) was performed using the SNPs for which this information was available ($N=691$). Derived alleles were less common among African populations, confirming findings from previous studies (Henn *et al.*, 2015). Since there were slightly more derived alleles among the GWAS hits (e.g. the alleles with a positive effect on stature), this biased downward the polygenic scores of African populations. When a DAF-corrected score was created, the African populations moved up from the bottom scores, which were in turn “occupied” by the East Asian populations (e.g. Japanese, Chinese and Vietnamese), confirming the traditional anthropometric description. There was also a marginal improvement in the correlation with average population height ($r=0.82$ vs 0.79 for the corrected and uncorrected scores, respectively).

A limitation was the unavailability of sound statistics on the average height of many populations. Moreover, although human height is largely heritable, it is also heavily influenced by nutrition and living conditions. The importance of environment is suggested by the dramatic secular trend which took place in the 20th century in developed countries (e.g. Arcaleni, 2006; Webb *et al.*, 2008); an association with dietary intakes (i.e. milk consumption) and socioeconomic status has also been observed (Mamidi *et al.*, 2011; Webb *et al.*, 2008). Most of the missing data were for developing countries which likely have not reached their full growth potential or ethnic groups living in Western societies (Indian Telegu or Gujarati) for which anthropometric statistics are not easily available. If the

allele frequency factor represents a genuine signal of natural selection, then the difference between it and current phenotypic height could be used as an indicator of the quality of diet and living conditions in general.

Conclusion

Factor analysis of allele frequencies is a promising method for detecting signals of recent selection on polygenic traits.

Data availability

F1000Research: Dataset 1. All Hits., [10.5256/f1000research.6002.d109935](https://doi.org/10.5256/f1000research.6002.d109935) (Piffer, 2015a).

F1000Research: Dataset 2. Hits 1+2+3, [10.5256/f1000research.6002.d41833](https://doi.org/10.5256/f1000research.6002.d41833) (Piffer, 2014c).

F1000Research: Dataset 3. Method of correlated vectors (MCV) for the top 66 SNPs., [10.5256/f1000research.6002.d109933](https://doi.org/10.5256/f1000research.6002.d109933) (Piffer, 2015b).

F1000Research: Dataset 4. Method of correlated vectors (MCV) for all SNPs., [10.5256/f1000research.6002.d109934](https://doi.org/10.5256/f1000research.6002.d109934) (Piffer, 2015c).

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Version 3

Reviewer Report 07 April 2016

<https://doi.org/10.5256/f1000research.8478.r12984>

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Andrew D Kern

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This paper is light on new results, so I'll focus my review purely on the conclusions mentioned by the author.

The author makes a single statement in the Conclusion section, that "Factor analysis of allele frequencies is a promising method for detecting signals of recent selection on polygenic traits." I don't see how that can be gleaned from this paper at all. The author has provided no justification for the method that he is using here, or in his other papers that he has cited in this manuscript which also use factor analysis. I was amazed by this but realize that the journal "Mankind Quarterly" isn't exactly known for its rigorous review of technical methods in genetics.

For this present manuscript to have any utility to the community I would suggest that the author back up and demonstrate that his ad hoc method has adequate power for use in empirical studies. In particular the author should compare the power of his method to the approach of Berg and Coop (2014)¹, which is been both mathematically justified and well characterized by simulation data.

References

1. Berg JJ, Coop G: A population genetic signal of polygenic adaptation. *PLoS Genet.* 2014; **10** (8): e1004412 [PubMed Abstract](#) | [Publisher Full Text](#)

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Version 1

Reviewer Report 30 October 2015

<https://doi.org/10.5256/f1000research.6422.r9015>

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Ben Busby

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The only major thing that, in my opinion, stands between this manuscript is the availability of the R scripts used to produce the data tables (especially given the difference between corr and rcorr). I looked for any linking to or availability of these scripts in Piffer 2013 or 2014a-d, and could not find it. Without these scripts, I do not think this work can be considered reproducible.

Two additional (minor) revisions are as follows.

First, the phenotypic data in table one seems to rely solely on Wikipedia. It seems likely that the author could find additional height information beyond Wikipedia.

Second, the last four paragraphs of the article could be combined into one.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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