Medical Hypotheses 104 (2017) 128–132

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

High altitude and pre-eclampsia: Adaptation or protection

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ARTICLE INFO

Article history:
Received 1 January 2017
Accepted 6 May 2017

ABSTRACT

Adaptive genes of high altitude can also be protective in diseases like preeclampsia, hypertension, and diabetes mellitus, Alzheimer, Parkinson Disease and Cancer, which may result from deregulation of hypoxia pathway. The example of pre-eclampsia and normal pregnancy were studied to see if the hypoxia-induced disorders can be dragged towards adaptation. Here, we analyse the genetic variants that are known to be associated with adaptation to high altitude hypoxia. Our results demonstrated that the genetic variants of *EPAS1*, *ADAM9*, and *EGLN1* increased approximately three-fold in the cases of preeclampsia compared to normal pregnancy. This may suggest the ability of the hypoxic cells of preeclampsia to respond to the high selective pressure of hypoxia with a higher degree of genetic variability, which can lead to adaptation. Signs of "acclimatisation" were seen both in cases and controls but with higher frequencies in controls. This can be a new approach that follows patients' genetic selection and susceptibility of individuals for adaptability, which could be enhanced by drug development.

Introduction

Environmental pressure like hypoxia increases the chance of genetic variation, which is the basis for natural selection. Within the one species, individuals with a high degree of genetic variability are more likely to survive in a changing environment than those with limited variability [1]. Human adaptation to hypoxia is an instance of evolutionary modification in certain human populations, including those of Tibet in Asia, the Andes of the Americas, and Ethiopia in Africa, who have acquired the ability to survive at extremely high altitudes. This adaptation means long-term physiological responses to high-altitude environments, associated with heritable behavioural and genetic changes. While the rest of the human population would suffer serious health consequences, the indigenous inhabitants of these regions thrive well in the highest parts of the world [2]. In a recent study, Tomar et al., showed that sea level Sojourners, on the ascent to high altitude, can undergo acclimatisation through integrated physiological processes for defending the body against oxygen deprivation while the high altitude natives are adapted to the prevailing hypoxic condition through natural selection. They observed statistically similar genotypic and allelic frequencies in the "acclimatized" sea level Sojourners and the "adapted" high altitude natives in the variants of the gene *EDN1* (endothelin 1), *ADRB2* (beta-2 adrenergic receptor, surface), *ADRB3* (beta-3 adrenergic receptor), *eNOS* (nitric oxide synthase, endothelial), *SCNN1B* (sodium channel, non voltage gated 1 beta subunit), *TH* (tyrosine hydroxylase) and *VEGF* (vascular endothelial growth factor) [3].

Pre-eclampsia is the leading worldwide cause of maternal and fetal morbidity and mortality. It affects 2–8% of pregnancies worldwide. In spite of extensive research in the pathophysiology of this disease, the aetiology is still poorly understood. It may be due to the insufficient adaptation of spiral arterioles or due to the shallow trophoblastic invasion, resulting in reduced uteroplacental blood flow leading to placental hypoxia [4,5].

This led to the question, can a hypoxia-induced disorder like Preeclampsia overcome the scarce microenvironment of oxygen deprivation by "acclimatisation", as a rapid form of adaptation.

Methods

Samples

A total of 36 RNA-seq samples from the maternal-fetus interface, the amniotic fluid, were retrieved from NCBI. The cases are from 19 pre-eclamptic preterm birth women, while the controls are from 17 full-term birth samples. Raw sequence data from two different studies are available publically at the Gene Expression Omnibus (GEO) database (www.ncbi.nlm.nih.gov/geo/) under accession number GSE79783 and GSE68180.

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http://dx.doi.org/10.1016/j.mehy.2017.05.007
0306-9877/

Data analysis

Variant calling pipeline was performed for the raw RNA-seq reads. FASTQ files were downloaded from the database and were aligned to the human genome build GRCh37/hg19 using STAR-based aligner 'Hisat2' to identify both known and novel SNPs and indels. Samples were further processed by marking duplicates and sorting, trimming, realigning indels and recalibrating sequences, according to the recommended workflow from the Broad Institute. All the samples have passed quality control assessment using FASTQC. Filtered variants were evaluated by variant annotation using snpEff, and were further annotated using Ensemble Variant Effect Predictor. All the variants in the variant calling file (VCF) were considered and were compared between cases and controls.

Results and discussions

High altitude adaptive genes variability in patients samples

More than 40 genes that are known to be associated with hypoxia were tested for their genetic variability in the cases and controls, Table 1. In the samples, *EPAS1* gene shows the highest number of variants, followed by *ADAM9*, *EGLN1*, with a higher frequency in cases than in controls. Interestingly, the number of gene variants of *EPAS1*, *ADAM9* and *EGLN1*, which are well known to be associated with adaptation to high altitude, were almost three times higher in cases compared to control, Figs. 1 and 2. This is suggested to be an evidence for the higher selective pressure on the deprived cells of preeclampsia that leads to high degree of genetic variability, which reflects their potency to survive the hypoxic microenvironment.

Patients samples and signs of acclimatisation

The variant calling results show that four of the adaptive variants are found in the samples; *ADRB2* (beta-2 adrenergic receptor, surface) rs1042713:A > G, *ADRB2* rs1042714:G > C, *TH* rs6356: G > A, and *VEGFA* (vascular endothelial growth factor) rs3025039:C > T (see Table 2). *ADRB2* affects vasodilation and improves oxygen delivery during acclimatization at high altitude through adrenergic contribution, and *TH* gene is associated with adaptive ventilator mechanism essential for respiratory homeostasis during hypoxia, while *VEGF* is a known angiogenesis-related gene and a potent permeability factor regulated by hypoxia, and has an important role in the pathogenesis of high-altitude adaptation and sickness [3].

To know the hypoxic state of the samples, we suggest that samples with higher number of mutations in the genes of *EPAS1*, *ADAM9*, and *EGLN1* are more hypoxic samples, and we called the variants "hypoxic variants", then samples were plotted in a linear graph to see the distribution of adaptive variants in the sample (Fig. 3). *VEGFA* adaptive variants are seen in the less hypoxic samples, which might suggest the essential role of the angiogenesis factor in relieving the hypoxic pressure. The only control sample with a relatively higher number of variants in compare to the other control samples has three adaptive variants, two *ADRB2* and *TH* variants. This can suggest that normal pregnancy might overcome the normal hypoxic pressure through acclimatisation or adaptation.

Although the cases of preeclampsia are more hypoxic and have the highest number of hypoxic variants, but yet have a lower number of adaptive variants (42.1%) in compare to controls (52.9%) (see Table 2), this might suggest the role of adaptive variants in relieving hypoxic pressure. Indeed, this result has to be verified with more number of samples and by studying other types of adaptive variants. Interestingly, there is a kind of reciprocal relation between the number of acclimatised variants and the number of hypoxic variants. In the controls, a higher number of acclimatised variants relieves the high pressure and thus result in a lower number of hypoxic variants, and in the cases, the high number of hypoxic variants is an indication for the persistence signal of high selective pressure.

Table 1
Number of cases and control that show genetic variation for some of the high altitude adaptive genes.

Genes	Cases of PE (N = 19)%	Controls of term pregnancy (N = 17)%
EPAS1 (HIF2α)	78.94	76.47
ADAM9	89.47	88.24
EGLN1	84.21	70.59
VEGF –B	26.32	11.76
TH	63.16	41.18
PPARG	21.05	0
MDH1B	42.11	17.65
LRRC7	31.58	17.65
SRF	42.11	23.53
ADAM17	63.16	41.18
ECE1	63.16	41.18

Allele and genotype frequency of adaptive variants in patients samples

Allele and genotype frequency of adaptive and wild variants were compared between cases and controls. The mean Allele frequency (A) for adaptive variants were calculated. The results show a higher frequency in controls (A = 0.103) in compare to cases (A = 0.065) with *P value* = 0.003. The mean homozygous genotype frequency (GF) for adaptive variants were even much higher in controls (GF = 0.074) than in cases (GF = 0.027) with *P value* = 0.0001. Unlike controls, cases have higher heterozygosity (GF = 0.079) than adaptive allele homozygosity, and this reflects the higher genetic variability of cases. In controls, the decline in heterozygous genotype (GF = 0.059), accompanied by an increase in homozygosity is probably due to the increase in the frequency of one of the alleles i.e. adaptive allele, which leads eventually to the particular allele fixation. This suggests that controls have higher ability to retain beneficial variants, which ultimately drives the natural selection of variants towards fitness.

Patients samples and possible scenarios of adaptation

The samples represent five groups of pregnancy; highly hypoxic sample with no signs of adaptation, moderately hypoxic samples with and without signs of adaptation, and less hypoxic samples with and without signs of adaptation. In Fig. 3, the black arrows tell two different scenarios; the first is a story of acclimatisation: starts with high hypoxic pressure and then the selective relief through gaining one or more adaptive variants until it reaches the acclimatisation state with a lower number of variants. The second scenario has a static picture of sever, moderate or mild forms of hypoxia. The follow-up of preeclamptic patients with their genetic profile, like in the first scenario, not only help in understanding the mechanisms of acclimatisation and adaptation of disease but also can be a new start in transferring those mechanisms to other hypoxia-related disorders.

Molecular basis for genetic variability

Stress-induces mutagenesis is a highly regulated process that is considered to be the basis of adaptive evolution. Interestingly, the genetic instability in human cell and cancer is believed to be