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High altitude and microtia in Ecuadorian patients

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Abstract. *Objective:* To examine the relationship between high altitude and microtia in Ecuador.
Methods: We evaluated the epidemiological issues of 1298 cases of microtia reported in Ecuador from 2001 to 2007. It used data arising from the Vital Statistics National Reports: Annual Survey of *Admissions and Discharges* in this 7 year period. The register is national and population based, run and funded by the government.
Results: It reported a total of 1298 cases of microtia out of 34654 cases of congenital malformations described in the registries. The overall prevalence was 2.38/10000 admissions/discharges calculated out of 5462263 admissions. An overall percentage (of 90.22%) were admitted before 19 years of age with the most prevalent group between 5 to 9 years of age (31.90%). There was progressive increase of cases every year; from 132 cases in 2001 to 304 in 2007. Total male cases in this study were 723 (55.70%) and female cases were 575 (44.30%). Tungurahua reported the highest prevalence of 18.31/10000 births, followed by Chimborazo, Azuay, Pichincha and Cotopaxi; all of them located over 2500 meters above sea level. It found that highest prevalence was 10.21 over 2700 meters above sea level followed by 8.28 over 2800 meters above sea level; with both having a cumulative prevalence of 8.81.
Conclusion: There is a higher prevalence of microtia in patients living above 2500 meters above sea level. This study was not able to establish a clear relationship between microtia and different ethnic groups.

Keywords: Ecuador, Microtia, high altitude, genetics, birth defects surveillance, database, prevalence

List of abbreviations

ECLAMC	Latin-American Collaborative Study of Congenital Malformations
BPR	birth prevalence rate
APR	admission prevalence rate
m.a.s.l.	meters above sea level

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1. Introduction

1.1. Clinical issues

There is a wide range of external ear abnormalities, related to the size, shape, position of the ear or even presence of pre-auricular pits or tags [1]. Microtia is a developmental malformation of the external ear, characterized by a small, abnormally shaped auricle with variable severity ranging from minimal structural abnormalities to complete absence of the outer ear [2]. There is a high correlation between the level of malformation and the frequency of external and middle ear abnormalities also [3]. The majority of patients have a combination of microtia with atresia or stenosis of the auditory canal [4]. It can occur unilaterally or bilaterally. The unilateral form is much more common, occurring in 79–93% of cases [5]. In unilateral form right ear is more frequently affected [6]. There are different classifications of microtia; the most used is the Marx's classification that presents four degrees of abnormality [7].

Several risk factors, related to this malformation, have been described, such as: prenatal exposure to drugs [8], ethnic origin, high altitude [9], maternal diabetes [10], low maternal education [11], advanced paternal age [12], advanced maternal age [13], first parity, first trimester disease of mother, excessive drinking and smoking of father, primiparous and non-primiparous parity [14], male sex [15], multiple births, high parity and low birth weight [16].

The worldwide prevalence of microtia ranges from 0.83 to 17.4/10000 in different populations, (see Table 1). In 1986, the Latin-American Collaborative Study of Congenital Malformations (ECLAMC) [17] described an increased frequency of microtia in the city of Quito, suggesting high altitude as a potential risk factor of this defect due most likely to hypobaric hypoxia.

1.2. Demographics

Ecuador is located in western South America. It has a population of almost 14 million inhabitants (August 2009 estimated) [18]. It is a multi-ethnic country with a stronger Amerindian Native culture, especially Amerindian Kichwa [19]. Ecuadorian ethnic groups have three distinguishing characteristics: a) a substantial proportion of the inhabitants live in the larger cities, b) a considerable proportion of residents live at high altitudes and, c) they show a complex ethnic admixture [20]. The ethnic differences are relevant in the Epidemiology of the genetic disorders, possibly related to genetic mutations. The contributions of Native Amerindian genes to pathologies remain poorly characterized. Several studies have described the admixture process underlying in the existing populations with relation to the Y-chromosome [21]. Other authors show a higher prevalence of Microtia in Native Amerindians [22,23].

Ecuador has four main regions: Highlands (Sierra), Coast, Amazonia and Insular region (Galápagos). Most highlands cities are above 2000 m.a.s.l. (Fig. 1). Half (54%) of Ecuadorians live in urban zones, especially in the four bigger cities including Quito, Guayaquil, Cuenca and Santo Domingo.

1.3. Altitude factors

An ECLAMC study compared the birth prevalence of specific types of congenital anomalies at both low and high altitudes in South America. They found higher values in the high altitude than in the lowlands for six types of defects: cleft lip, microtia, preauricular tag, branchial arch anomaly complex, constriction band complex and anal atresia [24]. Other studies of South American populations showed that altitude is associated with low birth weight and intrauterine growth retardation [25]. Birth weight at cities located above 2000 m.a.s.l. showed a decrease of approximately 200 g. When high and low socioeconomic levels are compared, birth weight also showed differences for levels of altitude analyzed (lowland, $< 2{,}000$ m; middle land, 2600 m; and highland, 3600 m). Interaction between both factors showed no effect. High altitude seems to act independent of socioeconomic status in explaining birth weight reduction [25].

The aim of this study is to analyze the relationship between microtia, high altitude and ethnicity in Ecuador and, it attempts to elucidate the likely cause of this malformation.

2. Subjects and methods

This is an observational descriptive study of the prevalence and epidemiological issues of 1,298 cases of microtia reported in Ecuador since 2001 until 2007.

2.1. Source of information

The data used in this study were extracted from the National Register of Hospital Admissions/Discharges from the *Instituto Nacional de Estadísticas y Censos* (INEC) [18], and from data of the Ministry of Public Health (MSP) [26]. The register is national, population based and funded and controlled by the government. The information contained in the registry is provided by the centers and hospitals belonging to the Ministry of Public Health. This covers the whole country and includes public maternity clinics, childrens hospitals and general hospitals. This register has been extensively used in former epidemiological studies even when Ecuador does not have an official Medical Birth

Table 1
Comparison of the prevalence of microtia around the world

Rank	Prevalence*	Country	No. cases	Births	Authors	Year	Ref.
1	17.4	Ecuador, ECLAMC	80	46041	Castilla & Orioli	1986	[12]
2	12.0	USA, Navajo Indians	19	15890	Nelson & Berry	1984	[28]
3	10.8	Ecuador	72	66843	Montalvo et al	2005	[29]
4	5.20	Chile, ECLAMC	214	412168	Nazer et al	2006	[30]
5	4.34	Finland, FRCM	335	771425	Suutarla et al	2007	[6]
6	3.79	USA, Hawaii	120	316058	Forrester & Merz	2005	[31]
7	3.20	Latin-America, ECLAMC	175	553068	Castilla & Orioli	1986	[12]
8	2.35	Sweden	954	1950148	Harris et al	1996	[32]
9	2.16	USA, California	636	2537099	Shaw et al	2004	[33]
10	2.00	USA, California	NA	1921698	Harris et al	1996	[32]
11	1.46	Italy	172	1173794	Mastroiacovo et al	1995	[34]
12	1.40	China	453	3246408	Zhu et al	2000	[35]
13	1.15	France, Central-East	152	1319757	Harris et al	1996	[32]

*Prevalence rate by 10000 births. FRCM = Finnish Register for Congenital Malformations, ECLAMC = Latin-American Collaborative Study of Congenital Malformations.

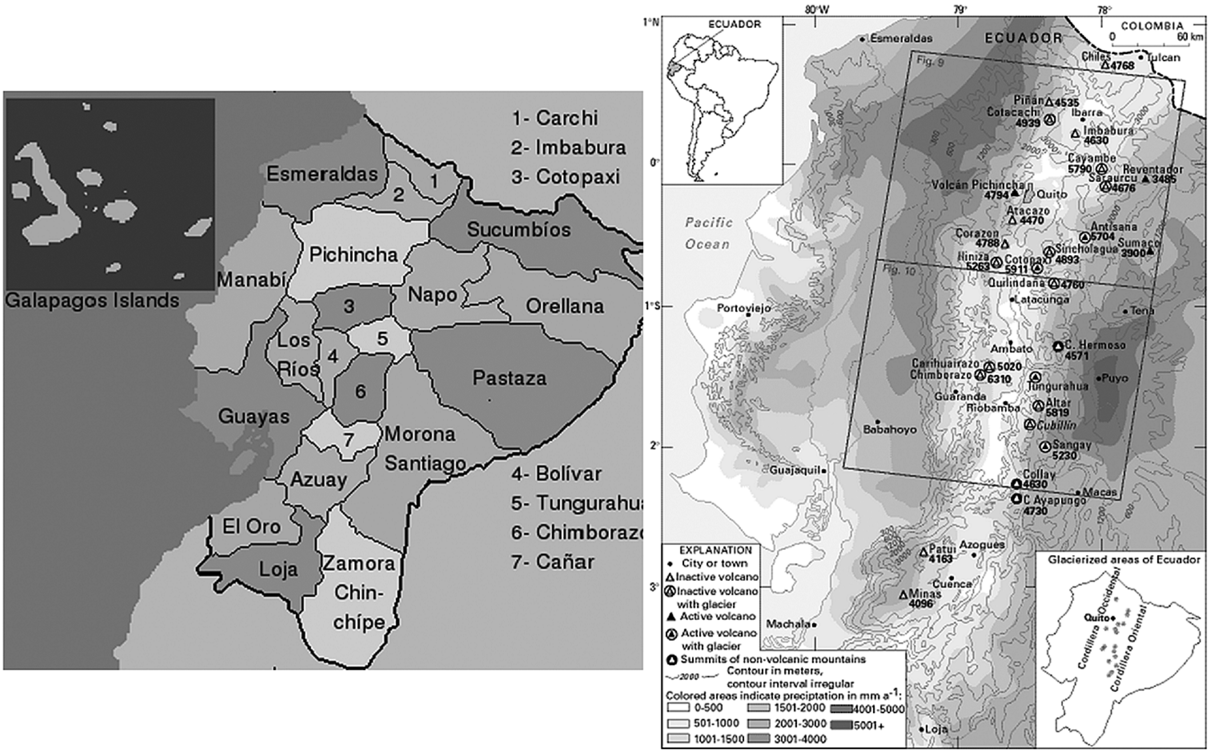

Fig. 1. Maps of Ecuador. RIGHT: Distribution by provinces, LEFT: Ecuador's Andean region at a scale of 1:2,000,000 showing glacierized areas characterized by volcano type, topography, and precipitation distribution. The map is based on the Atlas Geográfico de la República del Ecuador (Instituto Geográfico Militar, 1978), (2) official maps of the Instituto Geográfico Militar, and (3) fieldwork by the author (Ekkehard Jordan) in 1977, 1980, and 1981.

Registry nor a register of Congenital Malformations or Diseases. The register collects the data of admissions, gender, age and province of admission, however, it excludes second admissions or more (when a single patient was admitted multiple times). Our data include patients of all ages. As an additional measure, duplicate records were excluded from the database and were reviewed to assure that a patient was registered only once.

2.2. Study variables

Congenital anomaly was defined as a physical anat-

Table 2
Prevalence of microtia/anotia in Ecuador over time

Year	N =	Discharges/ year	APR / 10000
2001	132	681711	1.93
2002	144	707825	2.03
2003	148	723057	2.04
2004	162	763643	2.12
2005	198	802943	2.46
2006	210	863037	2.43
2007	304	920047	3.30
Total	1298	5462263	2.38

DPR = Discharges Prevalence Rate.

omical anomaly detected at birth and was listed in Chapter XVII of the International Classification of Diseases, 1997 (ICD-10) [27].

2.3. Statistical analysis

The admission/discharge prevalence rate (DPR) by 10000 admissions/discharges was calculated within the 5462700 registered admissions/discharges and the overall prevalence rate by 10000 inhabitants was presented. The analysis did not include the last two provinces recently created because their information has been added to the former province. It contrasts data with prior publications. A PubMed literature search was carried out to identify publications describing the prevalence and characteristics of microtia in different populations [28–35] (Table 1).

3. Results

It reported 1298 cases of microtia within 7 years period in Ecuador. Table 1 shows the comparison between the Birth Prevalence Rates (BPR) of microtia throughout the world. Since our study is based on Discharge Prevalence Rates (DPR), we did not include it in this comparison. It compared 11 populations of 8 different countries. Table 2 shows the overall discharge prevalence rate (DPR), which was 2.38/10,000 admissions/discharges, calculated with 5462263 admissions.

Table 3 shows the changes in prevalence over time by year and age. A 90.22% of overall patients were admitted before 19 years of age. Most prevalent group analyzed was the group between 5 to 9 years of age that accounted for 31.90%. There was a progressive increase of cases every year, from 132 cases in 2001 to 304 in 2007. Total male cases in our study were 723 (55.70%) and female cases were 575 (44.30%). Male cases were most prevalent. Our study ranked this defect in 15th position in the general prevalence of congenital malformations in Ecuador [36].

Table 4 shows the change in microtia prevalence by province. Tungurahua reported highest prevalence with 18.31/10000 births, followed by Chimborazo, Azuay, Pichincha and Cotopaxi; all of them located over 2500 m.a.s.l. Those provinces have the highest quoted of Native Amerindian Kichwa population of the whole country.

Table 5 shows the prevalence relative to altitude. It found that highest prevalence is 10.21 over 2700 m.a.s.l. followed by 8.28 over 2800 m.a.s.l., and the cumulative prevalence of both were 8.81.

4. Discussion

This study has some limitations in connection with findings. First, it does not specify the severity of this particular birth defect; it analyzed the crude information without analyzing in depth study of each clinical condition. This limited the usefulness of the data for health-care planning. Second, this research could not separate children with isolated defects from those with more than one major defect or those with a recognized syndrome because the used registries do not emphasize those details, and the training and expertise in genetics of the health care providers, especially in primary care, is still quite limited. Third, the sources of prenatal diagnoses used varies amongst the hospitals and the provinces in Ecuador. In some cases, the limitations are greater and the clinical experience still remains as the main criteria of diagnosis. The findings in this report represent a conservative estimate of the number of cases each year across the nation. This material is only an estimate of microtia which would be higher if it included sources of ascertainment of prenatal and postnatal levels. Fourth, these national records maintain minimum estimates of the impact of microtia, because even those surveillance systems with active case-finding do not reach 100% ascertainment. Unfortunately, Ecuador does not have a national official Medical Birth Registry or Register of Congenital Malformations.

The data we used for this study does not differentiate between whether the increased incidence of microtia is related to increased hospital admission for cosmetic procedures of the ear or whether there is a truly increased prevalence rate in high altitude locations.

The population prevalence of microtia has been studied in many large population-based registers. There is a marked variation in the prevalence range from 1.15

Table 3
Distribution of the cases by year and age

	< 1 mo	> 1 mo – 4yr	5–9	10–14	15–19	20–24	25–34	35–44	44–55	> 55	Total
2001	10	9	48	33	17	7	4	2	1	1	132
2002	8	20	45	41	16	3	7	2	2	0	144
2003	14	12	64	37	11	3	3	3	1	0	148
2004	26	5	41	53	20	8	5	1	0	3	162
2005	47	6	47	52	27	9	2	3	2	3	198
2006	40	19	56	57	23	7	5	0	1	2	210
2007	6	31	113	97	20	16	11	7	2	1	304
N =	151	102	414	370	134	53	37	18	9	10	1298
%	11.63	7.86	31.90	28.51	10.32	4.08	2.85	1.39	0.69	0.77	100

Table 4
Distribution of cases by province

Altitude*	Province	2001	2002	2003	2004	2005	2006	2007	Total	%
2,550	Azuay	9	18	6	10	4	3	13	63	4.85
2,668	Bolívar	–	–	–	–	–	5	–	5	0.38
2,770	Cañar	–	4	6	2	1	–	2	15	1.15
2,952	Carchi	–	–	2	–	1	1	4	8	0.61
2,785	Cotopaxi	4	15	6	–	1	14	3	43	3.31
2,750	Chimborazo	8	9	22	23	26	19	2	109	8.39
1,200	El Oro	–	–	1	–	5	1	1	8	0.61
10	Guayas	61	48	60	59	97	102	177	604	46.53
2,270	Imbabura	3	1	6	1	2	4	5	22	1.69
2,463	Loja	11	1	1	8	9	5	2	37	2.85
55	Los Ríos	–	–	–	–	–	1	2	3	0.23
400	Manabí	1	1	2	4	1	7	5	21	1.61
500	Napo	–	–	–	–	–	–	3	3	0.23
2,850	Pichincha	19	31	24	39	32	31	54	230	17.71
2,803	Tungurahua	16	16	12	16	19	16	31	126	9.70
1,560	Zamora Ch.	–	–	–	–	–	1	–	1	0.07
	Total	132	144	148	162	198	210	304	1298	100

*m.a.s.l. = meters above sea level. Patients recorded in Guayas are presumed to come not only from this province, but from the surrounding provinces of Chimborazo, Cañar and Bolívar. Guayas province has regional centers that offer specialized services of reconstructive surgery thus it explains the higher prevalence in this province.

Table 5
Cases by altitude, province and prevalence

Altitude*	Local altitude*	Province	Rank	%	N =	Local Births	Prevalence	Cumulative prevalence by altitude
Above 2800	2850	Pichincha	4	17.71	230	360980	6.37	8.28
	2803	Tungurahua	1	9.70	126	68811	18.31	(N = 356)
Above 2700	2785	Cotopaxi	5	3.31	43	65192	6.59	10.21
	2770	Cañar	8	1.15	15	25620	5.85	(N = 167)
	2750	Chimborazo	2	8.39	109	72625	15.00	
Above 2500	2550	Azuay	3	4.85	63	87133	7.23	7.23
Above 2400	2463	Loja	6	2.85	37	64914	5.69	5.69
Above 2200	2270	Imbabura	7	1.69	22	65005	3.38	3.38
				100	645	810280	7.96	7.96

*m.a.s.l. = meters above sea level; Prevalence rate by 10000 admissions: 645/1298 cases = 49.69% of overall.

to 17.4 (Table 1) The highest prevalence rate is seen in the populations from Ecuador and Navajo Indians from the USA. Ethnicity plays an important role to be identified in the future. In former studies, it established that the admixture proportions in male Mestizos were 0.730 ± 0.243 Native Amerindian, 0.193 ± 0.280 European, and 0.078 ± 0.077 African. This would mean that Ecuadorians have almost 75% of a component Na-

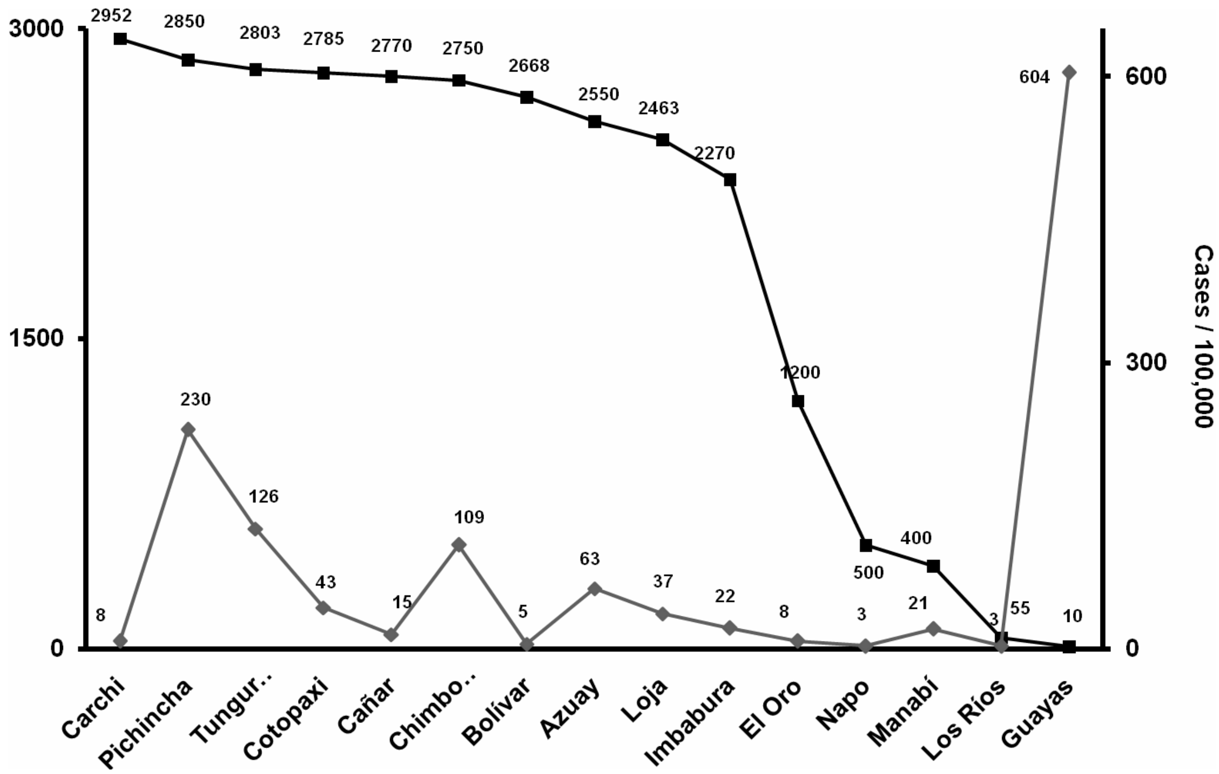

Fig. 2. Distribution of the number of cases by province and by altitude of the capital of the province, in a 7 year period of analysis. Patients recorded in Guayas are presumed to come not only from this province, but from the surrounding provinces of Chimborazom, Cañar and Bolivar. Guayas province has regional centers that offer specialized services of reconstructive surgery thus it explains the higher prevalence in this province.

tive Amerindian and it also would explain the relation between the traits in Navajos and Ecuadorians, even when there is not a direct geographic relation between both. It is actually possible that neighboring countries with a strong component of native ancestries would show the same results as well. It is important to remember that problems exist in gathering information for population-based studies and congenital malformations in our country.

In relation to the microtia/anotia in Ecuador, we analyzed two different studies. The first one, Castilla and Orioli [17] showed birth prevalence rate of 17.4/10000 births. It also showed higher prevalence if it compares to remaining countries of South-America, greater severity, higher frequency of prenatal exposure to unspecified drugs, higher birth order and greater paternal age. The second study was done using the ECLAMC network in Ecuador [29] Microtia was ranked in 4th position with a birth prevalence rate of 10.69/10,000 births. This is the most prevalent genetic malformation in comparison to the neighboring countries.

Microtia is difficult to define and there are variations in the diagnostic criteria. Ecuador does not have a public official Medical Birth Registry nor a range of Congenital Malformations or Disease-specific registries. Tables 2 to 4 show the absolute number of some variables analyzed in the country among admitted patients, as published by the Vital Statistics National Report. These figures should be taken as minimal estimates with uncertain diagnostic accuracy. Socioeconomic status, income, gender variations, and variations in occupation, could confound the association between high altitude and microtia reported in this paper. The discharge prevalence rate increases from 2001 until 2007, mainly due to an heightened awareness of the diagnosis and increased access to healthcare in the country.

In relation to age, over 90% of the cases are seen in hospitals before the age of 19. The main reason is because most patients only visit a medical office when they have a serious medical problem. Rural populations use to receive delayed hospital care. It could not establish if the chief complaint of the medical visit was the microtia or other medical condition such as deafness, ear infections or other secondary clinical complication. Total male cases in our study were 723 (55.70%) and female cases were 575 (44.30%), with higher prevalence in males.

More than 140 million people live and work at altitudes above 2500 m. The three largest high altitude populations are the Andeans, the Himalayans and the lesser studied inhabitants of the East African high altitude plateau. These populations have different phenotypes and different strategies for coping with their inhospitable hypoxic environment. However, their genotypes and the molecular signatures that contribute to good or poor adaptation of these people remains poorly understood.

Provinces of higher altitude show higher number of cases. The provinces Azuay, Cañar, Chimborazo, Cotopaxi, Pichincha, Imbabura, Loja and Tungurahua, all of them above the 2200 m.a.s.l, and located in the highlands, have the highest population of Amerindian Kichwas; especially Tungurahua, Chimborazo and Cotopaxi. The highest city is Quito, 2850 m.a.s.l. Tungurahua has highest prevalence of 18.31 and Chimborazo has 15.00. It is worth mentioning that the five provinces with higher prevalence are located over 2500 m.a.s.l.

This confirms our suppositions about ethnicity, geographical location and altitude. These provinces have the biggest population of Native Amerindian (Kichwas) in the whole country. They live in the rural areas in the "*páramo*" (high plateau) above 3,000 to 4,700 m.a.s.l. *Páramo* is a neotropical ecosystem. It is located in the high elevations, between the upper forest line, about 3800 m altitude, and the permanent snow line, about 5000 m.a.s.l. The ecosystem consists of accidented, mostly glacier formed valleys and plains with a large variety of lakes, peat bogs and wet grasslands intermingled with shrublands and forest patches. The rates fall in other provinces; even in Cotopaxi that is likely under-represented due to closer location to the capital, Quito. A similar phenomenon can be seen in Cañar close to Azuay, the third city in the country (Figs 1 and 2).

On the other hand, the provinces of Esmeraldas (00 m.a.s.l), Morona Santiago (1070 m.a.s.l), Pastaza (950 m.a.s.l), Galápagos (00 m.a.s.l), Sucumbíos (300 m.a.s.l) and Orellana (500 m.a.s.l.) do not report any cases. High altitude living produces physiological changes in the adaptation process due to chronic hypobaric-hypoxemic conditions. Although much is known about these physiologic adaptations, no clear separation has been made regarding what is native or genetic adaptation and what is acquired. It is apparent that both nature and nurture influence the acquisition of a high altitude phenotype and genotype in humans and while there is some evidence for genetic adaptation in Andean highlanders, it is evident that these characteristics are expressed in concert with substantial environment-dependent developmental adjustments.

This study concludes that there is a higher prevalence of microtia in patients living above 2500 meters. It was not able to establish whether ethnicity has a direct role in the development of microtia, even when the Ecuadorian population has a strong genetic component mostly Amerindian.

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The authors do not have any financial interest to disclose.

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