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Genetic epidemiology of single gene defects in Chile

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Abstract

We have studied the correlation between the ethnic structure and the prevalence of single gene defects in Chile. At present the Chilean population is approximately 64% white and 35% Amerindian with traces of other admixture. Fewer than 4% of the Chilean population are foreign born. Investigations indicate that all severe diseases and many others without impaired reproduction have mutation rates within the range of the white population. Classical ethnic diseases are very rare. Autosomal recessive disorders have a wide range of variability: cystic fibrosis has a low incidence and PKU has a similar incidence to English rates. Only 30% of the inborn errors of metabolism have been described in Chilean medical publications. In addition, no Chilean haemoglobin or haptoglobin variants have been described.

Some rare inherited diseases in Chilean human isolates have been described, including achromatopsia, chondrocalcinosis, and Creutzfeldt-Jakob disease. The prevalence of intrahepatic cholestasis of pregnancy and supernumerary nipples is the highest in the world and they are associated with aboriginal origin. Single gene defects in Chile are probably shaped by factors related to its ethnic population structure. These local rare single gene defects may be good markers of population admixture for genetic epidemiological studies.

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The population frequency of single gene defects depends mainly on their mode of inheritance, mutation rate, and reproductive fitness. Other factors are defined by population features such as migration, inbreeding, assortative mating, and population size.

The population gene frequency of dominant and X linked disorders depends on impaired reproduction. With impaired reproduction, the incidence and prevalence are mainly determined by the mutation rate. The sources of selection against these mutations are disease specific and are presumably similar in all populations. Without impaired reproduction, the incidence may be unequal in different populations depending on factors such as population size, demographic history, breeding structure, and ethnic origin. However, in autosomic recessive disorders, the various influences that have shaped the current frequencies are largely unknown, as is their incidence. Epidemiological surveys show that these diseases have a variable incidence in the ethnic population.[1]

The ethnic sources of Chilean populations are basically an admixture between Amerindian and European peoples. Five centuries ago the Spanish conquest and the infectious diseases they introduced decimated the Amerindian population. Consequently, the Spanish population increased and the percentage of European admixture, which was initially small, increased. The Chilean population is grossly two-thirds white and one-third Amerindian admixture. During the last century immigrants never exceeded 4% of the population.[2] Black and Asiatic admixture is extremely low. Therefore, these differences must be seen in the diseases associated with ethnic groups rates.

The most common polymorphic genes have been surveyed in the Chilean population and different genetic diseases have been described, but their epidemiological characteristics are largely unknown in relationship to their population structure.

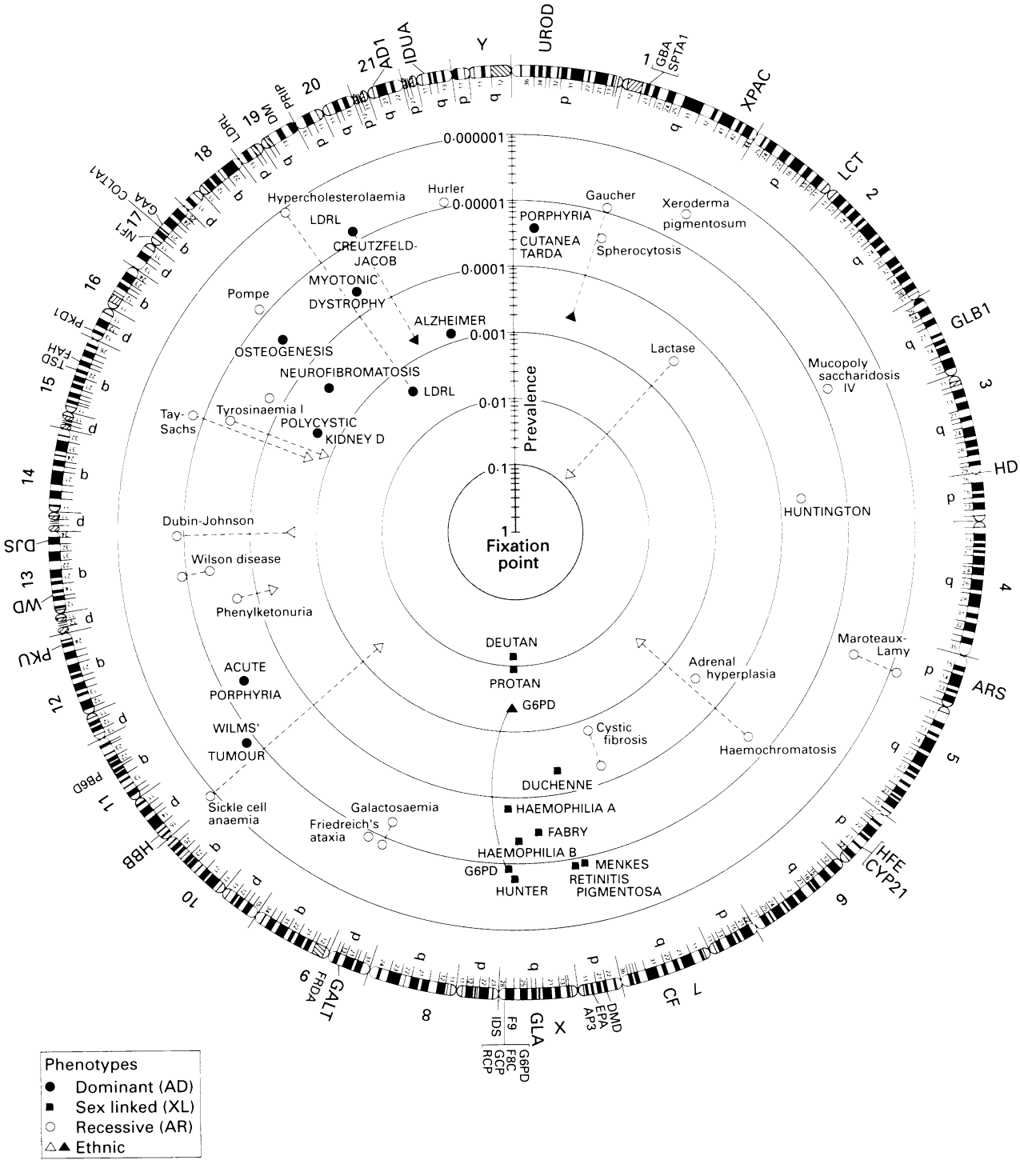
The purpose of this paper is to report the rates of single gene disease in Chile and to compare them with international data to review the influence of ethnic factors on the prevalence of single gene defects in Chile.

Materials and methods

The prevalence of single gene defects included in *Mendelian inheritance in man*[3] was grossly estimated for Chile. This was done by reviewing Chilean data obtained from published medical reports and hospital discharge records, estimating the rates in the twelve million population of Chile.

The results are shown in the tables and a circular diagram of the human genome. In this diagram (figure), prevalence is shown in a logarithmic scale, the frequency being one per million on the perimeter of the circle and one to one in the centre. This central point represents the fixation point of a single mutant gene. International prevalence rates are included for comparison.[4,5]

In the Amerindian populations of Chile before the arrival of the Spaniards, the O alleles of the ABO blood group and positive Rhesus factor of the Rh system had fixed frequencies. Thus, the genetic admixture of the Chilean population, estimated by European admixture with alleles A, B, and Rh negative factor, in different Chilean population groups is shown in tables 1 and 2 by their ethnic structure.[6–9]



The prevalence of single gene defects in the human genome. Prevalence is shown on a logarithmic scale, the frequency being one per million on the perimeter and one to one in the centre (fixation point). Different figures linked by dashed line indicate different values for general, ethnic, or Chilean populations.

Table 1 European admixture in the Chilean population

Type of population	No	European admixture (%)	Reference
Indian isolates			
Aymara	26	4	6
Pehuenche	148	5	6
Alacaluf	44	9	6
Atacameo	80	12	6
Mapuche	450	23	6
Urban blood banks			
Santiago North	63 309	61	7
Valparaiso	1000	77	8
Concepcion	9252	75	6
Santiago East	11 668	81	9

Table 2 European admixture in the Chilean population by socioeconomic level in urban centres

	European admixture	
Socioeconomic level	Santiago[b] (%)	Valparaiso[c] (%)
High	91	73
Middle	70	68
Low	41	48

Results

Table 1 shows that the percentage of European admixture is low in Amerindian isolates (mean 10·6%) and high in the general Chilean population (mean 73·5%). In addition, this admixture showed a wide range of variation with socioeconomic levels in urban centres (table 2).[6 8]

The circle in the figure is a summary of the prevalence of current single gene defects diagnosed in Chile. This figure is based on data from tables 3A, B, C, and included our review and estimations for Chile compared with international prevalences.[4 5]

Some classical ethnic disease rates found in international publications are compared with published cases diagnosed in Chile in table 4.[5 10]

Table 5 includes some rare inherited diseases discovered in Chilean isolates. They are achromatopsia,[11] chondrocalcinosis,[12] and Creutz-

Table 3A Prevalence of single gene defects: autosomal dominant

Locus	Symbol	Single gene defects	MIM	Estimated prevalence: General	Ethnic	Chile
1p34	UROD	Porphyria cutanea tarda	176100	1/50 000		1/50 000
1q21	SPTA1	Spherocytosis, recessive	182860		1/5000	1/50 000
2p25	AN1	Aniridia-1	106200	<1/100 000		Very rare
4p16.3	HD	Huntington's disease	143100	1/25 000		1/25 000
11p15.5	HBB	Sickle cell anaemia	141900	<1/1 000 000	1/625	<1/1 000 000
11p15.5	WT2	Wilms' tumour, type 2	194071	<1/100 000		<1/100 000
11q23-qter	PBGD	Porphyria, acute intermittent	176000	1/66 000		1/100 000
16p13.31-p13.12	PKD1	Polycystic kidney disease	173900	1/2500		1/2280
17q11.2	NF1	Neurofibromatosis	162200	1/5000		Common
17q21.31-q22.05	COL1A1	Osteogenesis imperfecta	120150	1/50 000		1/100 000
19p13.2-p13.1	LDLR	Hypercholesterolaemia, familial	143890	1/1 000 000	1/500	1/1 000 000
19q13	DM	Myotonic dystrophy	160900	1/25 000		1/75 000
20pter-p12	PRIP	Creutzfeldt-Jakob disease	123400	<1/100 000		1/100 000
21q11.2-q21	AD1	Alzheimer's disease	104300	1/1000		1/1000

Table 3B Prevalence of single gene defects: autosomal recessive

Locus	Symbol	Single gene defects	MIM	Estimated prevalence: General	Ethnic	Chile
1q21	GBA	Gaucher disease	230800	1/100 000	1/2000	<1/100 000
1q42-qter	XPAC	?Xeroderma pigmentosum	278700	1/250 000		Very rare
2	LCT	?Lactase deficiency, congenital	223000		1/10	1/5000
3p21-p14.2	GLB1	Mucopolysaccharidosis IVB	230500	<1/100 000		Very rare
5p11-q13	ARSB	Maroteaux-Lamy syndrome	253200	<1/1 000 000		None
6p21.3	CYP21	Adrenal hyperplasia, congenital	201910	1/8000		1/15 000
6p21.3	HFE	Haemochromatosis	235200		1/400	1/50 000
6p21.3	IDDM	?Diabetes mellitus, insulin dependent	222100	1/600		1/1000
7q31.3-q32	CF	Cystic fibrosis	219700	1/2000		1/3500
9p13	GALT	Galactosaemia	230400	1/62 000		1/40 000
9q13-q21.1	FRDA	Friedreich's ataxia	229300	<1/100 000		Very rare
12q24.1	PKU1	Phenylketonuria	261600	1/10 000		1/14 625
13q14-q21	WD	Wilson disease	277900	1/50 000		<1/100 000
13q34	DJS	?Dubin-Johnson syndrome	237500		1/3000	<1/100 000
15q22-225.1	TSD	Tay-Sachs disease: GM2	272800		1/3000	<1/100 000
15q23-q25	FAH	Tyrosinaemia, type I	276700	1/100 000		1/150 000
17	NPD	Niemann-Pick disease	257200		1/10 000	Very rare
17q23	GAA	Pompe disease	232300	1/100 000		1/150 000
22q11	IDUA	Mucopolysaccharidosis I	252800	1/100 000		Rare

Table 3C Prevalence of single gene defects: sex linked

Locus	Symbol	Single gene defects	MIM	Estimated prevalence: General	Ethnic	Chile
Xpter-p22.32	CPXR	Chondrodysplasia punctata	302950	<1/1 000 000		Very rare
Xp22.2-p22.1	CLS	Coffin-Lowry syndrome	303600	<1/1 000 000		Very rare
Xp22	HYP	Hypophosphataemia, X linked	307800	<1/100 000		Very rare
Xp21.2	DMD	Duchenne muscular dystrophy	310200	1/3300		1/5000
Xp21	RP3	Retinitis pigmentosa-3	312610	1/2000–1/7000		Rare
Xq12-q13	MNK	Menkes disease	309400	<1/1 000 000	1/34 500	Very rare
Xq22	GLA	Fabry disease	301500	1/40 000		Very rare
Xq22-q24	ATS	Alport syndrome	301050	<1/1 000 000		Very rare
Xq26-q27.2	HPRT	Lesch-Nyhan syndrome	308000	1/100 000	1/10 000	Very rare
Xq27.1-q27.2	F9	Haemophilia B	306900	1/50 000		1/50 000
Xq27.3	IDS	Hunter syndrome	309900	1/100 000		<1/150 000
Xq28	GCP	Deutan colour blindness	303800	1/70		1/100
Xq28	G6PD1	Glucose-6-phosphate deficiency	305900	<1/1 000 000	1/10	<1/100 000
Xq28	F8C	Haemophilia A	306700	1/10 000		1/11 000
Xq28	RCP	Protan colour blindness	303900	1/100		1/150

Table 4 Classical ethnic diseases in Chile

MIM	Disease	Ethnic population	Ethnic prevalence[5]	No of cases in Chile[10]
305900	G6P deficiency	Black, USA	1/50	10
273500	Thalassaemia	Black, USA	1/100	12
141900	Sickle cell anaemia	Black, USA	1/625	2
230800	Gaucher disease	Jews, Israel	1/2000	8
249100	Mediterranean fever	Jews, Africa	1/2700	1
237500	Dubin-Johnson disease	Jews, Iran	1/3000	1
272800	Tay-Sachs disease	Jews, USA	1/3000	12
257200	Niemann-Pick disease	Jews, USA	1/10 000	1

Table 5 Rare single gene defects in human isolates in Chile

MIM	Disease	Geographical region	No of cases in Chile	Reference
216900	Achromatopsia	Cachapoal	10	11
118600	Chondrocalcinosis	Chiloe	28	12
123400	Creutzfeldt-Jakob disease	Central Chile	69	13

Table 6 Rare single gene defects in Chile: distribution and prevalence by ethnic group

Ethnic group	Supernumerary nipple (‰)	Cholestasis of pregnancy (%)	Mydriatic response (%)
Chilean	0·07 (18)	2·5 (14)	5·8 (15)
Aymara	113·00 (16)	0·0 (14)	8·8 (15)
Atacameno	126·00 (16)	—	—
Araucanian	168·00 (17)	5·5 (14)	—

feldt-Jakob disease.[13] Other single gene defects, such as intrahepatic cholestasis of pregnancy,[14] mydriatic response,[15] and supernumerary nipples,[16-18] found in Amerindian people are shown with their prevalence rates in different populations (table 6).

Discussion

Epidemiological research in Chile is facilitated because vital statistics of the public and private hospitals and health services are centralised in the National Health Services System (SSNS) of the Ministry of Health and the National Statistics Institute (INE). Birth and death certificates are complete for 91% of the general population.[19] Rare diseases are studied in national centres of reference. National centres and clinical genetics units distributed in five major cities communicate their findings to the medical community. All the ethnic population isolates have been surveyed. Consequently the majority of rare hereditary disorders are ascertained in the whole country.

In addition, more than 90% of births and deaths receive medical attention. Only about 25% of the discharges are from private hospitals, and are also reported and controlled by the SSNS and INE.[19 20] Also, rare diseases are quickly reviewed at medical meetings and published. The ethnic population groups are not excluded from this health system.[19] Therefore, information on diseases and completeness of ascertainment are similar in all regions of Chile.

The white admixture in Chile is related to the ethnic structure of its people and the differences between the northern and eastern areas of Santiago city are explained by a socioeconomic cline associated with assortative mating.[21] This sociogenetic cline is also present in other cities in Chile.

Data on around 50 single gene defects confirm that Chilean prevalence rates of dominant and sex linked disorders with impaired reproduction are similar to those published for foreign white populations.[22-25] The prevalence of those diseases with no impaired reproduction also show values very similar to international ones.[26] Mutation rates for Huntington's disease calculated in the Chilean population are also comparable to those published elsewhere.[23]

Autosomal recessive disorders showed lower percentages than classical figures for white populations and have a wide range of variation. Only 30% of the inborn errors of metabolism have been diagnosed in the Chilean population.[10] In addition, no local haemoglobin or haptoglobin variants have been described in the general Chilean population or in the population of Amerindian origin.[10 27]

The rates of classical ethnic diseases in Chile have probably been shaped mainly by the low immigration rate indicated by census data.[2]

There is a high prevalence in Chilean populations of rare inherited diseases such as chondrocalcinosis, Creutzfeldt-Jakob disease, and achromatopsia.[11-13] These high frequencies are explained by inbreeding and drift in small isolated populations. Also single gene defects in the Amerindian people, such as intrahepatic cholestasis of pregnancy,[14] mydriatic response,[15] and supernumerary nipples,[16 17] have the highest prevalence in the world. These diseases show that a correlation exists between prevalence rates and percentage of white admixture. It is suggested that rare local single gene defects may be good markers to use for genetic epidemiological studies in mixed populations.

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