Oculocutaneous Albinism and Consanguineous Marriage among Spanish Gitanos or Calé – A Study of 83 Cases

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ABSTRACT

This paper studies 83 cases of oculocutaneous albinism (OCA) in family networks of Gitanos in southeastern Spain, and analyzes their sustained inbreeding patterns and complex genealogical relationships. It is based in the family and genealogy reconstitution of the Gitano population of 22 contiguous localities using ethnographic and historical demography methods. The study found a prevalence of OCA among Gitanos in the area of about 1: 1,200. Most of the cases belong to three extended kin networks in which consanguineous marriages have been common for generations. In these networks there are other cases of visual and auditive congenital anomalies, and other birth defects such as brachydactily, polydactily, neurological defects, Potter Sequence, etc. In 61 OCA cases it was possible to trace inbreeding links with a depth of three to nine generations. For these cases the estimated alpha (average of the inbreeding coefficient, F) is 0.0222. Relationships between the parents of people affected are of three types: close, as between first or second cousins; distant, as between third or fourth cousins, and non-existent, as in mixed marriages. In most cases, however, persons with albinism are linked by multiple consanguineous links. Albinism seems to be a visible example of a high prevalence of birth defects in this minority, associated with founder effects, sustained inbreeding and high fertility rates. These conditions derive from Gitano's marriage preferences and pronatalist strategies. In turn, these strategies have to be related to the exclusion, persecution and segregation that Spanish Gypsies have suffered for centuries.

***Key words**: albinism oculocutaneous, epidemiology, ethnic minorities, Roma/Gypsy people, Spain, inbreeding, medical anthropology, family reconstitution*

Introduction

In an anthropological and demographical research of Gitanos or Spanish Romani in 22 contiguous localities of Granada, Spain[1,2] we found numerous cases of oculocutaneous albinism, usually in clusters of kin-related people. Expanding the search to neighboring areas, we identified 83 cases born from 1932 to 2010, mostly in Southeastern Spain. Almost 80% of these individuals were born after 1970, and ten have died.

Although this is a considerable number of cases, they probably a represent a fraction of the total cases in the region, and appear to be related to a large incidence of ocular and hearing birth defects in the local Gitano population. This is just a visible instance of a much wider problem: the high incidence of congenital defects in this minority[3,4] that may be related to consanguineous patterns of marriage and high fertility. In turn, the marriage system of this people may be a response to their secular segregation and discrimination by the dominant majority.

In this paper we will describe the cases found and the complex consanguineous relations among their families. More precisely, the paper will analyze the intricate genealogical connections of the people affected, never studied in such detail.

This is just an exploratory paper, and we offer our data, experience and help to any genetic or medical research project that could improve our knowledge of genetic disease and foster the health and well being of the Gitano population.

Albinism

Albinism refers to a heterogeneous group of inherited disorders of melanin biosynthesis characterized by a par-

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tial or full absence of pigmentation. Albinism is generally classified in two broad categories: oculocutaneous albinism (OCA), when the pigment deficiency involves the skin, hair, and eyes, and ocular albinism (OA), when the deficiency involves only the visual system. Lack of pigmentation in hair and skin results in an alteration in color but not in a radical change in the development or function of these tissues. The absence of melanin pigmentation in the eyes, however, generally results in abnormal development and deficient functioning[5–7].

Albinism is a complex genetic condition with a relatively broad clinical spectrum. Hence it may present a diagnostic challenge. While oculocutaneous albinism is easily identified, especially in populations with darker skin, ocular albinism is likely to be overlooked or misdiagnosed[5–7].

Oculocutaneous albinism is usually an autosomal recessive disorder and its prevalence does not differ by sex. Ocular albinism is commonly an X-linked genetic condition, and as such, appears almost exclusively in males[5–7]. We are concerned here with oculocutaneous albinism, OCA, although there might also be non-identified cases of ocular albinism in the population studied.

Clinical manifestations

The degree of skin and hair pigmentation varies with the type of albinism, but is generally reduced. Despite its variable clinical manifestations, however, all forms of albinism show some ocular traits such as congenital nystagmus, iris hypopigmentation and traslucency, foveal hypoplasia, and misrouting of the optic nerves. These anomalies result in different degrees of delayed visual development and impairment, including reduced visual acuity (usually in the range 20/60 to 20/ 400), refractive errors, vision color impairment, photophobia, strabismus, and reduced stereo acuity[5,6].

As melanin protects the skin from the sun, persons with OCA are at increased risk of sunburn and skin cancer, and visual impairment may make them more vulnerable to accidents. But the physical and intellectual development and functioning of persons with albinism is generally normal, their general health is usually not affected, and their lifespan is not necessarily limited[5].

In many countries, however, people affected by albinism are rejected and stigmatized. Concerning this condition, social mistreatment may be more dangerous than physical impairment, as the current killings of albinos in eastern Africa dramatically show. Ignorance of the causes and consequences of albinism is widespread and contributes to prejudice and discrimination[8].

Main types of Oculocutaenous Albinism (OCA)

The current classification of albinism is based on genetic etiology. The four major types of oculocutaneous albinism (OCA1, OCA2, OCA3 and OCA4) reported to date are caused by mutations in genes that regulate the development and function of the melanocytes. There is some variation in the level of tyrosinase activity and thus in the depigmentation found in the various types and subtypes, although there is considerable clinical overlap between some of them. Most individuals affected are compound heterozygotes. Therefore, molecular diagnosis is required to establish the gene defect and the OCA subtype[5,7].

Epidemiology

Oculocutaneous albinism affects people of all ethnic and national backgrounds. Its prevalence has been estimated at approximately 1:17,000. Thus about 1 in 70 people carry a gene for OCA. But the prevalence of the diverse types varies considerably worldwide. OCA1 has a prevalence of approximately 1 per 40,000 in most populations, but is very rare among African-Americans[5].

OCA2 is the most prevalent form of albinism in humans, and the most common in Africa. Overall estimates of its prevalence range from 1/5,000 – 1/15,000, but cases of higher prevalence of up to 1 in 1000 have been reported for some populations in Southern Africa[9]. The overall prevalence of OCA2 is estimated to be 1:36,000 in the USA, but is about 1:10,000 among African Americans[5]. OCA2 also has a moderate to relatively high prevalence values (1 in 28 to 1 in 6,500) in various Amerindian populations in the southwestern United States, southern Mexico, eastern Panama, and southern Brazil[10].

OCA3 or Rufous oculocutaneous albinism has been reported to affect 1 in 8,500 individuals in Africa, whereas it is very rare in Caucasians and Asiatic populations[5].

OCA4 is the less frequent type to date, appearing in approximately 5–8% of German patients with albinism but in 18% of Japanese patients[5].

Albinism in Spain

In Spain there is no data about the prevalence of albinism, and usually international rates are applied. Relevant publications include the clinical or genetic analysis of isolated cases[11,12], but the only population evidence we found comes from the work of Martínez Frías and her team in the Spanish Collaborative Study of Congenital Malformations, where they collected data on more than 800.000 infants born from 1976 to 1990, and found a much higher incidence of OCA among children born of Gypsy parents[3].

The Spanish Romani: Gitanos or Calé

Gitanos or *Calé* are one of the main cultural minorities of Spain. They are distantly related to other Romani populations who live in most European and American countries, and are known as *Roma*, *Sinti*, *Kale*, etc. In Spain, the great majority of Roma/Gypsies come from the first wave of migrations into Western Europe in the fifteenth century. Their customs and their way of life are thus product of a secular coexistence and hybridizing with local Spanish populations.

Gitanos (the term they most often use to refer to themselves) long ago adopted the majority's language and religion, and lacked until recently a sense of father-

land or common history, although they maintain a distinct and usually proud identity. Often it is not easy to distinguish them from their neighbors, and there are no references to ethnic identity in registers or official documents. Hence, there is a lack of reliable demographic and epidemiological data on this minority. The most informed estimations put the number of Spanish Gypsies in the range of 450,000 to 600,000, or 1 to 1.5% of the total Spanish population[13,14].

Spanish Gitanos or *Calé* are sedentary. Today, they live in all regions of Spain and in all type of localities. After 1978, in democratic Spain, they have improved their status considerably and have gained access to free health care, public education, pensions, public housing and other social services. In consequence, the Gitano population is increasingly heterogeneous in terms of income, education and cultural political and religious orientation. However, they remain overrepresented in the most vulnerable and disadvantaged sectors of Spanish society. Anti-Gypsy prejudice is widespread, and discrimination, even if not usually overt, appears to be commonplace.

The demographic structure of the Gypsy population differs significantly from that of the Spanish population at large. Gitano populations include more children and young people, but a smaller proportion of elderly people. This is due to their different demographic history. They started the demographic transition some decades later than the dominant majority. According to our data, infant mortality declined rapidly in the 1950s and 1960s, and fertility dropped rapidly from 1980 onwards. From 1985 to 1999 TFR (Total Fertility Rate) may have dropped from around 5.5 to around 2.5 children per woman. Many socio-demographic changes are still taking place in this minority, such as a considerable increase in mixed marriages, mostly among its most integrated and educated groups[15].

Collectively, however, Gitanos appear to have the health problems associated with other Roma minorities, such as lower life expectancy, and greater vulnerability to accidents, infectious diseases, and degenerative illnesses such as diabetes, hypertension and cardiovascular disorders[16,17]. When controlled comparisons can be applied, Gitanos, particularly women, report worse health and a higher rate of chronic diseases and depression. Although health care is free and universal in Spain, some barriers to equal access still remain, and Gitanos tend to make less use of preventive programs, and more use of emergency facilities[18]. But there is a lack of sound and recent epidemiological and clinical studies of the health problems of the Gypsy minority, and also of culturally informed programs tailored to their needs.

Congenital and genetic anomalies, however, have received special attention in the scientific literature[16,17]. Most describe or analyze a small set of cases, and also the resulting very high relative prevalence resulting in such a small population[4].

Birth defects

A few studies have documented the high prevalence of congenital defects among Gitanos or Spanish Gypsies. In the most important series from a population perspective, Martínez Frías and her collaborators used data from the Spanish Collaborative Study of Congenital Malformations (ECEMC), a hospital-based surveillance system, and case-control study that surveyed 830,883 infants born in 51 hospitals all over Spain from 1976 to 1990. Of these, 16,736 were malformed and 16,576 were selected as controls. Ethnic affiliation was specified in 14,083 cases. These authors found a higher prevalence of multiple congenital anomaly syndromes in children born to Gitano parents. Moreover, recessive syndromes were about seven times more frequent among Gitanos. Thus, Gitano infants, who made up 1.6 % of all live births accounted for 10% of all the recessive syndromes detected. They attributed this to their higher rate of inbreeding[3].

Albinism was remarkable for its higher incidence in this minority: it was 154 times more frequent among Gitano infants. However, the number of cases they found was small: only 4 cases of albinism (type was not specified) among Gitano newborns, and 2 cases among non-Gypsies. From that, they estimated an incidence of 3.09 per 10,000 for Gypsy newborns compared to 0.02 per 10,000 in non-Gypsies. The associated carrier frequency was estimated as 1 in 29 for Gypsies and 1 in 320 for non-Gypsies[3]. This is a very low incidence for the Spanish population at large (about 1 in 415,000 cases) and may be a sign of underreporting.

Materials and Methods

Since 1997 our team has developed a long-term study of the genealogical and demographic history of *Calé* or Gitanos in Andalusia. In this region their presence is

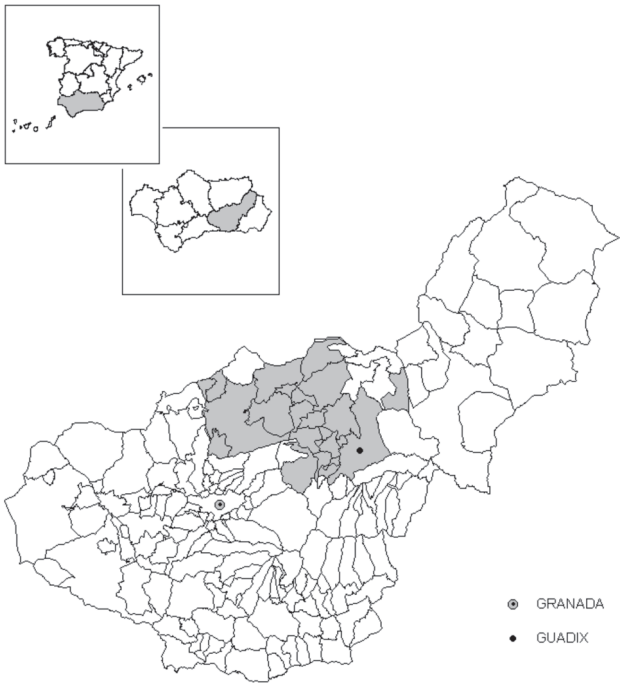

Fig. 4. Area of study: 22 localities of the province of Granada, Spain.

documented since the XV century, and, contrary to dominant assumptions, their ancestors can be identified in local Parish and Civil records[1,2].

The area of intensive study includes 22 contiguous localities of the province of Granada, both urban and rural (See Figure 4). Of the approximately 50,000 people who live in this area today about 7,000 (14%) are Gitanos. In some towns and villages, the proportion of Gitanos reaches 30 per cent. This is the highest rate found in most regions of Spain. And results in a great presence of Gypsies in primary schools, health care and social services[14,15].

Our team collected precise data of the local Gypsy population covering a period of over 150 years, from 1850 to 2008 and including references to about 19,000 people dead or alive. This data has been anonymously integrated in a genealogical grid and used for demographic and kinship analysis. Our team is also researching parochial records that allow our genealogical reconstitution to go back to generations born before 1850.

This research uses a combination of ethnographic, ethno-historical and demographic and historical methods. Essential to our approach is the use of a local perspective to gather local knowledge, mostly with the help of Gitano informants. Thus we have been able to collect data on present and past local Gitano populations based on self-identification. Moreover, the records themselves often corroborated Calé identity independently when genealogies reached the first decades of the twentieth century, when often Gypsies were identified as »jitano« or »jitana« and, more often, »castellano nuevo«, as well as associated with typical Gitano occupations such as that of horse dealer or horse-shearer, and to Gitano neighborhoods.

In this area our team found several clusters of birth defects in the concerned families, such as brachydactily, deafness, cleft palate, strabismus, Potter Sequence, and other no well-diagnosed conditions in several family networks. Oculocutaneous albinism was perhaps the most visible and easiest to diagnose of these conditions.

Our team started to collect systematic data on persons with albinism in 2001. In our area of study we found 42 cases, but extending family links to neighboring provinces we eventually identified 83 cases. Then we traced the genealogical history of this people using family and genealogy reconstitution methods.

In 43 cases we were able to interview the individuals affected. We also contacted some of their family doctors with the informed consent of patients to get data from their records, if available. We also interviewed family members and neighbors to complement our information on social and cultural responses, as well as to collect information on those persons with albinism who had died. There does not seem to have been a systematic diagnostic or follow-up process concerning this cases and the evolution of their condition. Thus, the clinical data available is poor.

In 61 cases, we were able to develop a genealogical reconstitution that expanded from 3 to 9 generations using parochial and civil registers with the help of local people, mostly Gitanos themselves. All information was codified and processed anonymously.

Results

This research documents 83 cases of oculocutaneous albinism among people who identify themselves as Gitanos. Of these, 41 were females (49%). The oldest was born in 1932, the youngest in 2010; near 80% were born after 1970 (see table 1). Average age was 26.7; median age was 27. Ten of these persons have died; the rest live today in four regions of Spain, mostly in Eastern Andalusia.

Three cases also showed other congenital anomalies, such as clubfoot (congenital *talipes equinovarus*), immunological problems, and deafness. In another case, an albino child died days after birth. Furthermore, some close kin such as parents, children, siblings or first cousins showed other congenital defects, including ocular, hearing and dermatological problems.

In these families there is memory of ancestors who died in the beginning of the twentieth century who were also »albinos«, but we could not confirm this and it is unlikely that any medical records remain for these people.

TABLE 1
SEX AND DECADE OF BIRTH OF THE 83 SPANISH GITANO PERSONS WITH OCULOCUTAENOUS ALBINISM

Decade of birth	Women	Men	Total	%	% Acum	Dead	% Dead
1930 to 1939	2	1	3	3.6	3.6	3	100.0
1940 to 1949	5	1	6	7.2	10.8	5	83.3
1950 to 1959	1	2	3	3.6	14.5	1	33.3
1960 to 1969	4	1	5	6.0	20.5		
1970 to 1979	11	10	21	25.3	45.8		
1980 to 1989	9	14	23	27.7	73.5		
1990 to 1999	7	8	15	18.1	91.6	1	6.7
2000 to 2010	2	5	7	8.4	100.0		
Total	41	42	83	100		10	12.0

Type of Oculocutaneous Albinism (OCA)

Of the 43 cases we could examine directly all but five showed most of the symptoms of OCA-1A, such as snow--white hair, pink-white skin with no pigmented naevi, blue irises, a red reflex from what seems an unmelanised fundus, severe nystagmus (mostly horizontal), photophobia, strabismus, and greatly reduced visual acuity at young age (20/200 or worse). All adults were legally blind.

Two of the cases observed showed pigmentation in hair and skin compatible with other subtypes of OCA, such as OCA1B or o OCA2. Finally, in three individuals affected, the skin in their faces and hands had developed color with age, due perhaps to the effect of intense sun exposure.

All persons have experienced episodes of intense sunburn, mostly in summer. Two cases had been diagnosed as suffering from actinic keratosis, and two others from squamous cell cancer. There was a case of *xeroderma pigmentosum* in the non-albino mother of one albino child. Interview data shows that persons with albinism suffered more domestic and road accidents than their *moreno* (darker and »normal«) siblings. This is probably due to their reduced visual acuity.

Three of the individuals examined had developmental problems and other congenital conditions. The rest (41 of 43) seem to show a physical and mental development normal for their age, and they often appear to be taller and stronger than their non-albino siblings.

Prevalence of OCA among Gitanos

Half of the living albinos in this sample (37 cases out of 73, 51%) live in the province of Granada. Another 40% live in four contiguous provinces: Malaga, Jaen, Almeria and Murcia. The rest migrated with their families to other Spanish regions such as Valencia, Catalonia and the Balearic Islands. Almost all cases in the sample can trace links to ancestors who were born and lived in the area were we developed our genealogical reconstitution.

In the province of Granada (population in 2009: 907,500) we have recently estimated the Gypsy population to be in the range of 39,000 to 42,000. An independent survey found about 7,000 Gitano households in this province, and estimated a Gypsy population of about 34,000[13]. Therefore, the minimum prevalence of oculocutaneous albinism in the Gitano population of this area would be in the range of 1 in 1,100 to 1 in 1,400; this suggests that about 1 in 20 people of Gitano descent carry a gene for OCA in this province.

Social characteristics

All these albinos belong to working-class families whose members usually combine different menial jobs. Most live in humble but adequate houses, although six of these families live in a decayed shantytown, waiting to be relocated.

Most of the albinos born before 1960 were functionally illiterate; they barely attended school. Those born after 1980 have followed 8 or 10 years of compulsory primary and lower secondary education, and their level of education improved. In three cases they completed formal training and higher education programs, including one university graduate.

Most of the older OCA cases in this sample married and had children. But younger OCA cases (especially those born in the 1970s and later) seem to have increasing difficulty in marrying, although all manifest a desire to do so. There is probably a gradual but important change in the perception of the disease among Gypsies that we plan to address in other publications.

Access to health care

As Spanish citizens, Gitanos have free access to public health care and social care services. All families of albinos visit their local health centers and have access to specialized medicine, including ophthalmologists. Few, however, follow preventive programs, including those tailored for their ocular or skin problems. For instance, few carry eyeglasses or sunglasses, even when prescribed. These attitudes seem to be changing in respect to children born in the last decade, as both parents and other family members are becoming more aware of the need for regular check-ups and protection measures.

On the other hand, most albinos have access to the services of ONCE (Organización Nacional de Ciegos Españoles) a well funded NGO that provides specialized attention, education and help to over 70,000 visually handicapped persons in Spain (See: www.once.es). In our sample, four children are attending ONCE schools, and one man completed a University Degree with support from this organization.

Social status, discrimination

We have not detected special discrimination of albinos, beyond that which they suffer as Gitanos. Subjects themselves do not complain about mistreatment or discrimination, although they reported some rejection and misunderstanding by their peers in school years. Although in two cases we were told about parents who rejected their albino children, in all cases we were able to observe directly we found that parents showed intense love and care for their albino children, who also find great support in their family network. We have observed that persons with albinism are usually well treated and respected by their relatives, although some stigma is attached to the condition and to its inheritance by the minority at large.

Persons affected and their family members do not seem to have a clear idea of the origin of this condition apart from vague considerations about inheritance. Thus, there is a great need for education about the causes, consequences and preventive measures for albinism and other birth defects.

Fertility

In the families affected high fertility was the norm until the 1990s. Our team could establish the number of

TABLE 2
AVERAGE NUMBER OF BORN-ALIVE CHILDREN PER WOMAN IN THE OCULOCUTANEOUS ALBINISM (OCA) SAMPLE. MOTHERS OF 68 OCA CASES

Period of birth of the mother	N: Children (Average)	N: Mothers	N: Albinos
1910–1939	7.6	5	13
1940–1955	6.6	9	21
1956–1975	4.9	19	30
1976–2010	2.3	4	4
Total 68 albinos	5.4	37	68
Percent of 83 albinos		82.2	81.9

TABLE 3
MAIN KNOWN KINSHIP RELATIONSHIP BETWEEN THE PARENTS OF THE 83 INDIVIDUALS AFFECTED BY OCULOCUTANEOUS ALBINISM

Main kind of relationship	N	%	% Acum.
First cousin	11	18.0	18.0
First cousin once removed	5	8.2	26.2
Second cousin	24	39.3	65.6
Half second Cousin	1	1.6	67.2
Third cousin	12	19.7	86.9
Third cousin once removed	1	1.6	88.5
Fourth cousin	2	3.3	91.8
No relationship (mixed marriages)	5	8.2	100.0
Total	61	100.0	
Not established	22		

siblings of the persons affected in 68 out of 83 cases (82%), and the reproductive history of the 37 of the mothers concerned. The total known fertility rate of these group of women was 5.4, very high for Spanish citizens in the period considered. In mothers born prior to the second half of 1950s we find a very high fertility (see table 2). These women did not have access to family planning or contraceptive methods.

Couples with several albino children usually had a large number offspring. In all cases but one, couples with three or more albino children had 8 or more living children. The couple with the largest number of OCA children was also the one that had the most living children: 6 albinos out of 13 live births (see cluster C, Figure 3).

Inbreeding and consanguinity

The genealogical reconstitutions made by combining ethnographic interviews and parish and civil records, allow our team to establish the main consanguineous relationship among parents of albinos in 61 cases (74 %). In another 12 cases available data shows that the kin relationship was distant (third cousins or less), and they did not consider themselves related. In the other 10 cases the relationship among the parents of OCA cases could not be established.

For the known 61 cases, the average value of the inbreeding coefficient F is 0.0221*.

Legal relationships as declared in civil or parish registers correlate highly with what people consider »blood« relationships and, thus, probably, with genetic relationships. We have contrasted the data in our genealogical reconstitution (N: 19,093) with data from ethnographic fieldwork and interviews (concerning over 600 people), and found that in about 98% of cases both sources cohere.

Considering the main consanguineous link, we find three main patterns of inbreeding in our sample:

1. **Close inbreeding**: In two thirds of cases (65.6%), the parents of affected individuals were related as second cousins or closer, that is, they were first cousins, first cousins once-removed or second cousins.

2. **Distant consanguinity**: in 26.2 %, the main consanguineous relationship was distant: further apart than second cousins. That is, parents were third cousins, fourth cousins, or third cousins once-removed. These links were of little significance for the informants themselves.

In both groups, albinos' parents were also related by multiple consanguinity.

3. **Not related** by consanguineous links: In a third group, 5 individuals (8% of cases), were children of mixed marriages in which one of the spouses was non-Gypsy and we established that their parents are not related.

In the other group of 22 cases, the precise relationship between parents could not be established, although in 12 of these cases it was determined that the closer link would be that of third cousins.

Multiple consanguinity

In most cases, couples are related by many consanguineous links, as inbreeding has been repeated trough generations. The family and genealogical reconstitution allows a detailed study of this phenomenon. For instance, the mother of an albino child born in 2001, Ana, born in 1976, and the father, Juan, born in 1975, knew they were first cousins once removed (Juan is a first cousin of Ana's mother), but they were unaware of other six independent kin relationships that we could establish in their genealogical reconstitution (see Figure 1). They were also third cousins twice, fourth cousins, fifth cousins and twice fourth cousins twice removed. According to this, the inbreeding coefficient of this couple, F, was 0.041. The six

* The coefficient of inbreeding, symbolized by the letter F, is the probability that a person received two identical genes by descent. Children from a first-cousin marriage have a coefficient of inbreeding F 0.0625.

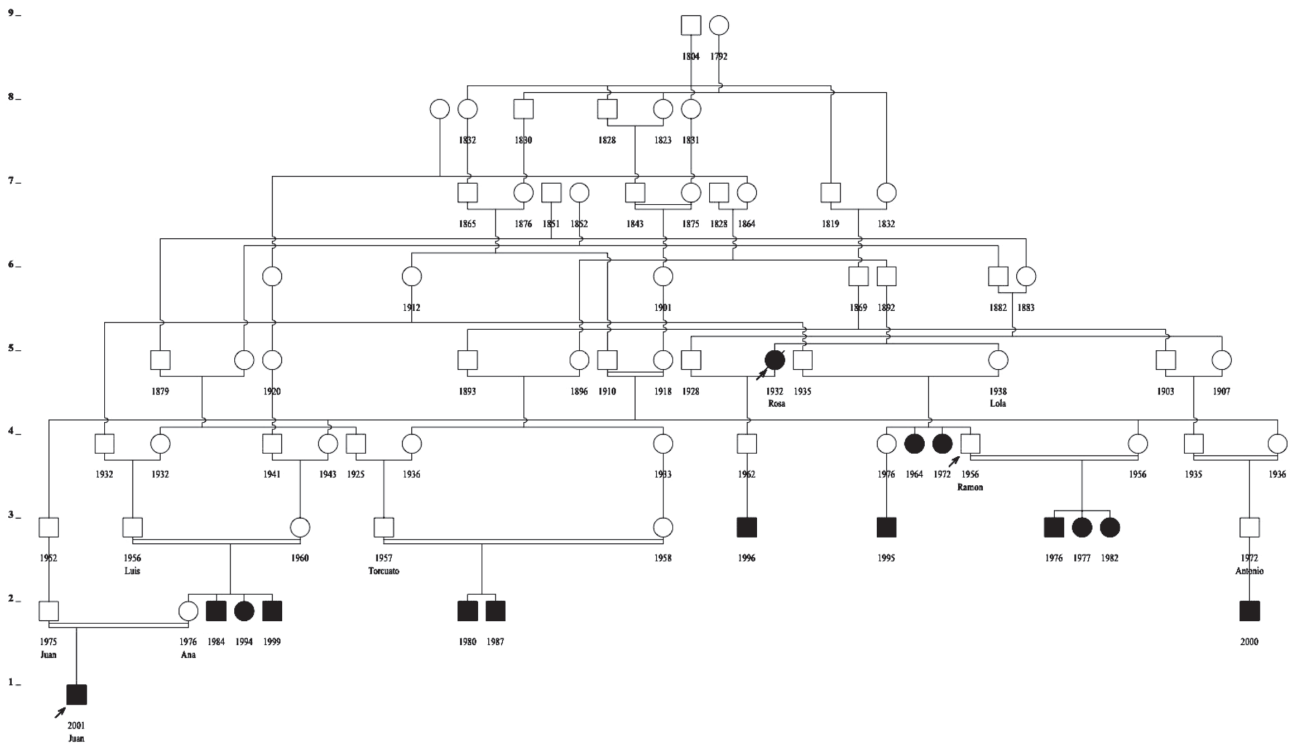

Fig. 1. Cluster A. Genealogical links between 15 cases of oculocutaneous albinism found in an old town of Granada Province, Spain.

distant inbreeding relationships contribute 31% of the total of this coefficient, a relevant proportion.

These different kin relationships are common in a group that has been intermarrying for over 10 generations. Some of them are known by older members of the family, but the more distant are considered irrelevant, and seen as a confirmation of the fact that »here all Gitanos are family, we all share some blood, even a drop«.

Three major kin networks

As an illustration of the complexity of consanguineous relationships in the family of the persons affected, three diagrams with some of the genealogical relationships that obtain in three of these clusters of OCA will now be analyzed.

Cluster A: Fifteen cases of OCA in an old town in Granada Province

These 15 persons affected by OCA belong to four generations of a kin network, whose members live in a town of about 20,000 people, 50 km away from Granada. In this town, Gitanos' presence has been documented continuously since late sixteenth century. Our genealogy reconstitution establishes direct links between living Gitanos and their ancestors born between 1690 and 1732, that is, up to 15 generations. In the diagram of this cluster (see Figure 1) we include data concerning consanguineous links in the last 9 generations.

The first OCA in this network (marked by an arrow), Rosa* *La Piliblanca*, »the white haired«, was born in 1932 of a mixed marriage: her mother was non-Gypsy. Rosa had three living children, none of them albino. Her only son, however, had an albino son in 1996.

Rosa's younger sister, Lola (born in 1938), married a Gypsy man and they had six children. Two of Lola's daughters, born in 1964 and 1972, were OCA. Besides, their oldest son, Ramón, born in 1956 (also marked by an arrow), married one of his first cousins once removed, and they had 8 children, three of them albinos, born in 1976, 1977 and 1982. Another of Lola's daughters, Luisa, born in 1976, also married a first cousin once removed, and had an albino son in 1995.

Besides, a second cousin, Antonio, born in 1972, and who was also the nephew of Ramon's wife, married a Gypsy woman from a village 35 km away, and they had an albino son in 2000. This couple do not consider themselves related »by blood« (*parientes de sangre*), although our genealogy reconstitution found they are fourth cousins.

One of Antonio's brothers, married to a third cousin, has had four daughters, all born with cleft lip and palate, and three of them (born in 1982, 1983 and 1988) were also congenitally deaf. Strabismus has also been endemic in some branches of this family.

* All personal names are pseudonyms. We used them to facilitate the understanding of the graphs and the complex consanguineous relationships.

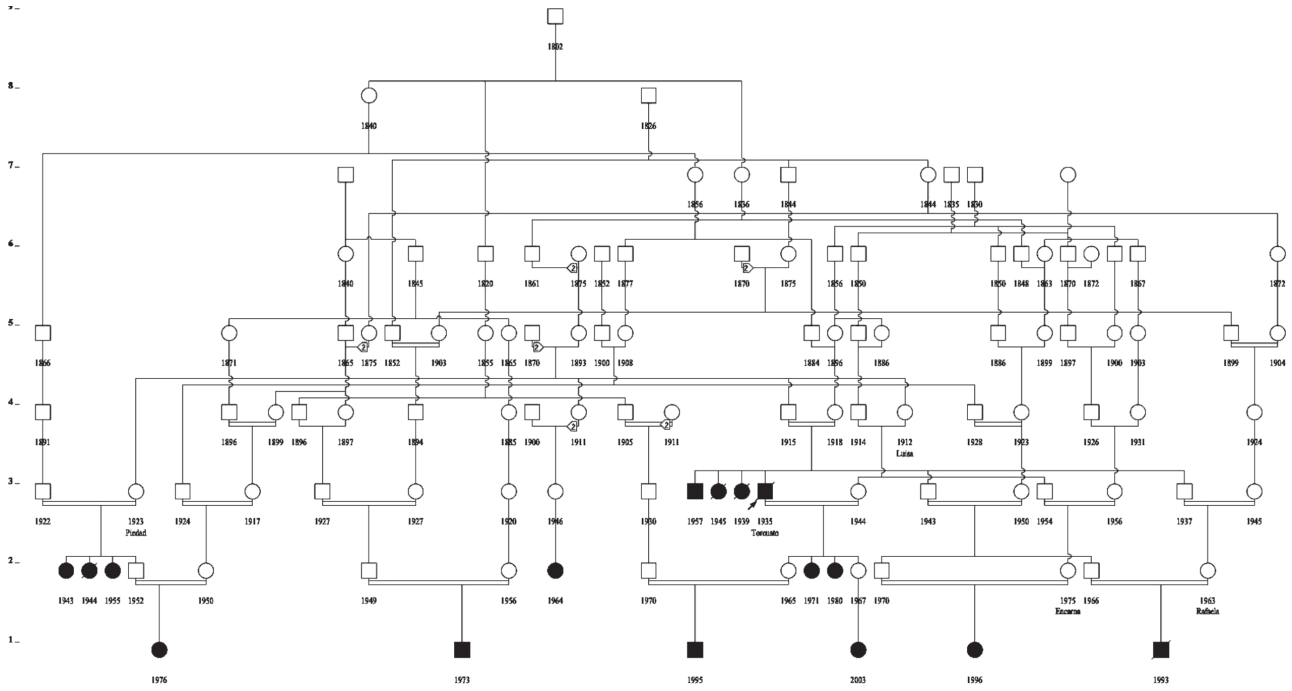

Fig. 2. Cluster B. Genealogical links among 16 cases of oculocutaneous albinism found in a kin network in rural Granada, Spain.

Another second cousin of Ramón, Torcuato, born in 1957, whose father was blind, married a first cousin (born in 1958) and they had two albino sons, born in 1980 and 1987.

And a first cousin of Ramón on his father's side, Luis, born in 1956 (on the extreme left of Figure 1), married a second cousin born 1960 and they had 10 children, three of them albinos (born in 1984, 1990, and 1999). The oldest daughter of this couple, Ana, born in 1976, a »morena« (dark, »normal« woman), married Juan, a first cousin once removed, and they had an albino son in 2001 (also marked by an arrow). We examined the ancestry of this couple before as an example of multiple consanguineous links.

Each person in this extended family has a different set of relationships with the individuals affected by OCA. For instance, Ramón (1956) has had an aunt, two sisters, three children, a nephew and four cousins once removed who suffered from albinism. In total, he has 11 albinos among his close relatives, and another 4 in his more distant family. As it can be seen in Figure 1, the consanguineous connections are multiple, go back to several generations, and are very difficult to know in depth even by the people involved.

Distant »blood« connections with albinos from other areas could be traced as well. So, in a contiguous town of about 3.500 people we found two OCA siblings born in 1976 and 1980, who were related to people in this network. For instance, Ramon is twice third cousin once removed of these two albinos. People in both families ignored these connections: they see themselves perhaps as *parientes muy retiraos* (»too distant kin«), and thus, of no social or »natural« importance to each other.

Cluster B: Sixteen cases of oculocutaneous albinism in a rural area of Granada

People in this kin network have lived in a four villages north of Granada for over 250 years. We were able to study 9 generations in this cluster. The oldest albino here, Torcuato, born in 1935 (marked by an arrow), lead a relatively normal life, although he was almost blind since his childhood. He married, had 5 children and died in 2005 at 70. He told us that his grandfather, who was born in 1870 and died when he was three years old, was also albino. We could not confirm this.

Torcuato's parents, born in 1915 and 1918, were third cousins. They had 9 living children between 1935 and 1957, four of them albinos. The two albino daughters, born in 1939 and 1945 died in their infancy in the »years of hunger«, the 1940s. The youngest brother, an albino born in 1957, is alive and lives in Barcelona.

Torcuato married a first cousin (also his second cousin) born in 1944. They had six living children, two of them OCA, born in 1971 and 1980. Another daughter, born in 1965, married a second cousin and they had an albino son in 1995*. Their fourth daughter also had an albino child in 2003. Her husband was a Gitano from a non-related family.

* The grandmother of the husband, born in 1911, appears twice in figure 2, as she married twice, and had albino grandchildren from both marriages.

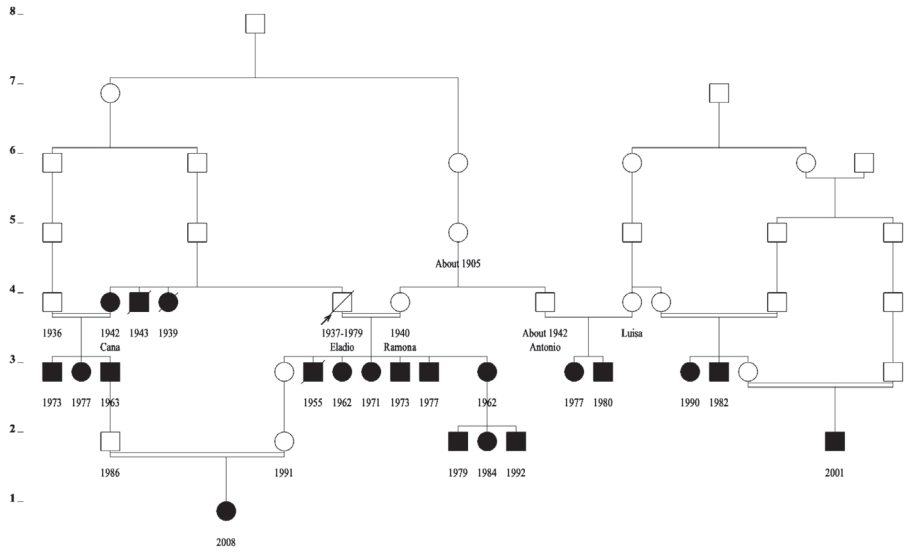

Fig. 3. Cluster C. Main genealogical links among the 21 cases of oculocutaneous albinism found in a family network in Southeastern Spain.

Several of Torcuato's siblings had children who married each other. In one case, Rafaela, a niece of Torcuato born in 1966, married a parallel paternal cousin (the son of her father's brother) and in 1993 they had an albino son who died shortly after birth. Some years later they had another two children who were diagnosed with Potter's Sequence and died shortly after birth. Rafaela and his husband are also related from their mothers' side. We identified four different independent links between them.

A sister of Torcuato's father, Piedad, born in 1923, married a third cousin, born in 1922, and they had 9 living children, three of whom were albinos: three women born in 1943, 1944 and 1955. A son, born deaf in 1952, also had an albino daughter in 1976. His wife – who was his half-second cousin – developed a neuropathy from which she died in 2005 when she was 53.

Another aunt of Torcuato from his father side, Luisa, born in 1912, had a granddaughter, Encarna, born in 1975, who was diagnosed with *xeroderma pigmentosum* in her youth. Encarna married her second cousin, born in 1970, who is also a nephew from Torcuato, and they had an albino daughter in 1996.

Recurrent inbreeding has been the norm in this network for generations. For instance, we could trace six independent consanguineous relationships between Encarna (1975) and her husband: they are second cousins, third cousins, twice fourth cousins, half fourth cousins, and fourth cousins once removed.

From the perspective of Torcuato, he was albino himself, and had three siblings, two children, two grandchildren, three cousins, two cousins once removed, two grandnieces and a distant »nephew« (son of his half first cousin once removed) who were albino, a common experience in his family that they find difficult to explain and often to cope with.

Cluster C: 23 cases of oculocutaneous albinism in a family network in Southeastern Spain

Affected people in this cluster live in the outskirts of the city of Malaga and in an agricultural town in Murcia about 325 km away. In Figure 3 we present a simplified view of the kin relationships that exist among these cases. Information has been gathered using only interview data from the individuals affected, some near kin, and health and educational professionals that care for them. Thus we could not trace as many genealogical connections as in the previous clusters.

We will review this network from the viewpoint of Eladio (pseudonym) a Gitano who was born in 1937 and died in 1979. Eladio had three albino siblings, born in 1939, 1942 and 1943. Two of them died as infants in the 1940s, a terrible decade for disadvantaged Spaniards. His surviving OCA sister, Cana, born in 1942, married a second cousin, and they had four children. Three of them were OCA, born in 1963, 1973, and 1977.

Eladio married Ramona, a distant relative (apparently a third cousin) born in 1940 in one of the villages in Granada included in our demographic study. Antonio and Ramona had 13 living children (out of 14 pregnancies), six of whom were OCA. One of them, a daughter born in 1962 (together with a twin, also albino) in turn also had three albino children, born in 1979, 1984 and 1992.

Recently, a grandchild of Eladio married a grandchild of his sister Cana and they had an albino daughter in 2008. Another albino child was born in this family in May 2010, but we did not include it in the diagram.

On the other hand, one of Ramona's brothers, Antonio, born about 1942, married Luisa, a distant relative from L. a town in Murcia 325 km away from Malaga and moved there with her. They had six children, two of them

albinos, born in 1977 and 1980. Furthermore, a sister of Luisa, married a second cousin from the same town and also had two albino children, born in 1982 and 1990. A daughter of this couple married a second cousin and they had an albino son in 2001. A nephew married a non-Gypsy woman in 2001 and had another albino child in 2002 (this case does not appear in figure 3).

In sum, Eladio's kindred include three siblings, six children, three grandchildren, two grandnephews, one grandniece one great-grandchild, and six nephews and nieces from his wife's side who are affected by albinism. In total we found 23 OCA individuals born during a 70-year period in two towns of Southeastern Spain.

In this kin network we find other birth defects and congenital dysfunctions. For instance, one of Eladio's albino sons had two daughters affected by a rare undiagnosed syndrome; another son had three children affected by polydactyly with one supernumerary finger and toe in each hand and foot. On his wife's side, there are clusters of several children born deaf at least in two conjugal families…

Discussion and Conclusion

The first thing of note in our results is the large number of persons affected by this rare condition in a relatively small population. We have not found any similar description of OCA cases in any Romani group or in any other European population. For instance, in the period considered by Martínez Frías and her collaborators (1976 to 1990) in the Spanish Collaborative Study of Congenital Malformations, they reported a total of four cases of OCA among newborn Gypsies in the whole of Spain (3). In the same period, our research found 29 cases in the area under study alone. In 12 of these cases we confirmed that they were born in the three hospitals in the region that reported data to the national record system. Thus, our data points to a larger incidence of this condition that has been considered before.

All information available, however, indicates that albinism is only a manifestation of a larger problem in the Gitano minority: the high incidence of birth defects, probably related to marriage practices enacted through generations. These included endogamy, early age at marriage and long reproductive spans favored by a pervailing pronatalist ideology (1, 2).

Reiterated inbreeding increases the level of homozygosis and the chances that recessive deleterious mutations are expressed. Chance genetic processes such as founder effects, bottleneck effects, and genetic drift may have also occurred in the partial reproductive isolates formed by Gitano families. Other complex interactions or sequential processes have probably played a role, leading to an increase of the frequency of deleterious mutations in some families.

In consequence, the genealogical reconstitution of these populations may be of importance both for cultural and genetic research. In fact, populations that have maintained such a degree of cultural isolation offer fertile ground for investigating the molecular mechanisms involved in human diseases. This is particularly relevant for rare diseases in which »founded alleles can be rapidly driven to a high frequency due to restriction of gene flow in the population«[19].

In sum, cultural preferences may have important genetic manifestations that should be considered in medical practice and research. Moreover, marriage patterns as those of Roma/Gypsies may be part of an oppositional culture that was developed historically as a reaction to exclusion and deprivation, and was also likely affected by the effects of social deprivation in morbidity and mortality patterns. In turn, resistant and oppositional attitudes may have increased rejection and segregation in complex recursive ways.

In Spain Gitano couples are now reducing their fertility and mixed marriages are increasing quickly. This would probably alleviate some of the problems associated with inbreeding. But consanguineous marriages are still very common, and often favored in the same family networks where mixed marriages abound.

Our genealogical reconstitution also indicates that birth defects have a complex relationship with consanguinity. In some of the cases reported couples with affected children were distantly related or not at all. This makes genetic counseling more difficult. Even so, health education and genetic counseling are specially needed in the most disadvantaged and vulnerable minorities. In this respect the challenge is to avoid the stigmatization of minorities affected differentially by noted genetic problems. In the case of Roma/Sinti/Calé, stigmatization is an increased risk in groups who are already ostracized. It could be argued that the diffusion of information on this topic decreases the chances of breaking marriage isolates, and therefore it is counterproductive. Who would like to marry those who are portrayed as »having bad genes«? So the dissemination of this information has to be measured carefully against its misuse, and presented responsibly. We think, however, that the situation should not be silenced. In fact, invisibility and lack of interest may be another sign of exclusion and neglect. It often means that nobody cares, and children affected by genetic defects continue to be born in Gypsy families without a single action being considered.

In our case, the medical establishment has overlooked a very visible pattern of hereditary anomalies. Local specialists have shown little interest in a very notorious condition affecting so many people. In fact, we could not get help from geneticists to do molecular diagnoses, even if we offered to collect samples and informed consent authorizations from the people affected.

Therefore, the dilemmas of medical and cultural intervention have to be confronted both by medical professionals and the people affected. Genetic problems in excluded minorities have to be seen, first, in the perspective of larger problems, such as segregation, poverty and marginality. In several African countries today the social treatment of persons with albinism is much more harm-

ful than the genetic condition itself. Moreover, the cultural rejection of minorities is often at the root of their self-segregation strategies.

In depth study of congenital problems in Romani populations seems an important area of research both for genetic analysis, health education and social integration. Our detailed description of intricate kin relationships could contribute to the understanding of complex decisions and processes that obtain in this community. It can also help in the genetic research of rare conditions, and also in the development of culturally adequate forms of health education and genetic counseling. Genealogical research could improve the analysis of inbreeding and genetic diseases. Genealogical knowledge, however, belongs first and foremost to these people themselves, and we have to find ways for professionals and local communities to work together, and to give voice and decision-making capability to Romani minorities themselves.

In sum, our research may be useful to geneticist and health specialists and to the minority itself. We hope that this will be the case, and offer all our data to any serious research group that will make a responsible use of it.

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OKULOKUTANI ALBINIZAM I ISTOKRVNI BRAK MEĐU GITANOSIMA U ŠPANJOLSKOJ. STUDIJA 83 SLUČAJA

SAŽETAK

Članak se bavi sa 83 slučajeva okulokutanog albinizma (OCA) u mrežama obitelji Gitanosa u jugoistočnoj Španjolskoj. Analiziraju se obrasci njihovog srođivanja te složeni genealoški odnosi. Studija se temelji na rekonstrukciji rodoslovlja Gitano stanovništva 22 susjedna lokaliteta rabeći metode etnografske i povijesne demografije. Studija je pokazala prevalencija OCA među Gitanosima od oko 1: 1.200. Većina slučajeva pripadaju trima proširenima rodbinskim mrežama u kojoj su brakovi u bliskom srodstvu bili učestali generacijama. U tim mrežama, postoje i drugi slučajevi vizualnih i auditivnih prirođenih anomalija te drugih urođenih mana poput brachidaktilije, polidaktilije te neuroloških oštećenja. U 61 OCA slučajeva bilo je moguće ući u trag srođivanju s dubinom od tri do devet generacija. U tim je slučajevima procijenjena alfa (prosjek koeficijenta srođivanja, F) od 0,0222. Odnosi između roditelja oboljelih su trojaki: bliski, kao između prvih ili drugih rođaka; daleki, kao između trećih ili četvrtih rođaka, te nepostojeći, kao u mješovitim brakovima. U većini slučajeva, međutim, osobe s albinizmom povezane su višestrukim vezama u bliskom srodstvu. Albinizam se čini kao dobar primjer visoke prevalencije urođenih mana u ovoj manjini, povezanoj s efektom osnivača,

kontinuiranog srođivanja te visoke stope plodnosti. Ovi uvjeti proizlaze iz bračnih odabira Gitanosa te njihove pronatalne strategije. S druge strane, ove strategije povezane su sa isključenosti, progonom i segregacijom koju španjolski romi trpe već stoljećima.