J Community Genet (2013) 4:273–284
DOI 10.1007/s12687-012-0128-7

COUNTRY REPORT

Consanguinity, endogamy, and genetic disorders in Tunisia

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Received: 14 May 2012 / Accepted: 18 November 2012 / Published online: 4 December 2012

Introduction

Consanguinity refers to marriages between individuals who share at least one common ancestor. In clinical genetics, a consanguineous marriage is defined as a union between two individuals who are related as second cousins or closer, with the inbreeding coefficient (*F*) equal or higher than 0.0156 (Bittles 2001). However, reports on consanguinity rates may sometimes include marriages between third cousins or more distantly related individuals (Hamamy 2011). It is estimated that more than 690 million people in the world are consanguineous (Bittles and Black 2010). Middle East, Northern Africa, and South Asia are regions that have historically and culturally had a high rate of consanguineous unions (Al-Awadi et al. 1985; Al-Gazali et al. 1997; Jaber et al. 1997; Bittles et al. 2002; Bener and Alali 2006). Recent studies have shown that 20 % to 50 % of marriages in Arab countries are between relatives (Tadmouri et al. 2009; Bittles 2011; Hamamy et al. 2011). The rate was 68 % in Egypt (Mokhtar and Abdel-Fattah 2001), 51–58 % in Jordan

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(Khoury and Massad 1992; Sueyoshi and Ohtsuka 2003; Hamamy et al. 2005), 52 % in Qatar (Bener and Alali 2006; Bener and Hussain 2006), 50 % in the United Arab Emirates (Bener et al. 1996), 54 % in Kuwait (Al-Awadi et al. 1985; Hijazi and Haider 2001), 58 % in Saudi Arabia (El-Hazmi et al. 1995), 40 % to 47 % in Yemen (Jurdi and Saxena 2003; Gunaid et al. 2004), and 50 % in Oman (Rajab et al. 2000). Consanguineous unions are also frequent in many Non-Arab Middle Eastern countries such as Turkey with 21.2 % (Başaran et al. 1988) and Iran with 38.6 % (Saadat et al. 2004). The tendency in these societies of marrying relatives is a deeply rooted cultural trait (Hamamy 2011) related to ethnical, cultural, and socioeconomic factors (Khlat and Khoury 1991). Among Arab societies, it is believed that a consanguineous marriage preserves family structure and provides social, economic, and cultural benefits (Khlat et al. 1986; Bittles 2008). These consanguineous marriages generally involve first or second cousins or relatives within the large family or the same tribe (Al-Khabory and Patton 2008). Theoretically, the offspring of related parents are more often homozygous by descent than those of non-consanguineous parents. In this context, recent studies based on high density SNPs genotype data (Carothers et al. 2006; McQuillan et al. 2008; Kirin et al. 2010; Nothnagel et al. 2010) reported a gradual increase in average genome-wide homozygosity with increasing levels of consanguinity and endogamy, which is defined as marriage within one's own tribe or group as required by custom or law (Lathrop and Pison 1982). Consequently, such consanguineous matings have a relatively higher risk of producing offspring with genetic damage, caused by the expression of rare recessive genes inherited from common ancestors, than that of the general population (Khlat and Khoury 1991; Teebi 1994).

A positive correlation between inbreeding and numerous health outcomes has been reported in several studies. Indeed, unions between relatives are generally associated with an increased risk of abortions, stillbirths (Al-Awadi et al. 1986; Hussain 1998, 1999; Hussain et al. 2001), perinatal mortality (Stoltenberg et al. 1999), and congenital malformations (Abdulrazzaq et al. 1997; Chéhab et al. 2006; Yunis et al. 2006).

Consanguineous marriages are also recognized as being associated with higher risk for autosomal recessive diseases than in the general population (Taillemite et al. 1985; Alwan and Modell 1997; Kumaramanickavel et al. 2002) by favoring the expression of recessive deleterious alleles. Many reports have highlighted a positive association between inbreeding and a number of recessive single gene disorders like achromatopsia (Tchen et al. 1977), Leber's congenital amaurosis, xeroderma pigmentosum (Mokhtar et al. 1998), and metabolic defects like aminoacidopathies and mucopolysaccharidoses (Jaouad et al. 2009). However, some authors believe that a long practice of inbreeding over several generations leads to the elimination of deleterious recessive mutations from the population gene pool (Khoury et al. 1987).

On the other hand and to the best of our knowledge, no significant association has been reported in the literature between inbreeding and autosomal dominant disorders (Zlotogora 1997b; Hamamy et al. 2007).

For complex diseases, the contribution of inbreeding to these conditions remains contentious and under investigated. Some authors suggest that inbreeding could exert a greater influence on the etiology of multifactorial diseases, when autosomal recessive alleles are causally implicated (Bittles and Black 2010). Indeed, the enhancing of disease susceptibility gene dose resulting from increased homozygosity may affect the risk of developing the disease (Bittles 2001). Other authors explain certain complex impairments by genetic disturbances and epistatic effects due to homozygosity at disease susceptibility loci which alter the capability to adapt to environmental risks (Acevedo-Whitehouse et al. 2003). However, other reports claim that it is unlikely that consanguinity contributes significantly to complex diseases once basic lifestyle factors have been controlled as highlighted by an editorial in Nature Genetics (No authors listed 2006).

A limited number of reports have focused on the inbreeding effect on multifactorial disorders (Jaber et al. 1997; Soliman et al. 1999; Bener et al. 2001; Rudan et al. 2003, 2006; Hamamy et al. 2005; Alzolibani 2009; Mansour et al. 2009). These studies have revealed an important role of inbreeding in the etiology of many specific diseases following a multifactorial pattern of inheritance like diabetes mellitus, hypertension, mental disorders, and cancer. The outcome of these studies suggests the implication of deleterious recessive variants in the etiology of such diseases (Campbell et al. 2009; Bittles and Black 2010).

In Tunisia, as in many Arab countries, there is a high preference for unions between relatives. Local customs, social and geographic isolation, along with the ethnic heterogeneity of the Tunisian population made up of a mosaic of communities [Amazigh (Berber), Roman, Arab, etc.] have all influenced mate selection and contributed to an increased level of endogamy and consanguinity (Ben Arab et al. 2004). According to the National Office for Family and Population Affairs data, consanguinity remained relatively high during 1991 to 2001 with rates of close and unknown consanguineous unions representing, respectively, 21 % and 19 % of all marriages in the country. A similar level of inbreeding has also been reported by other studies (Chalbi and Zakaria 1998; Ben Mrad and Chalbi 2006). While consanguineous matings continue to be commonly practiced in several areas of Tunisia, their health impact remains underestimated because of the limited number of epidemiological studies. A better understanding of the

impact of inbreeding on the occurrence of some specific diseases may raise public awareness of the potential negative effects of intra-family marriages.

One possible method to study these possible inbreeding effects is to compare the level of inbreeding among parents of individuals affected with different disorders and a healthy control sample.

The purpose of this current study is to assess the rate of consanguineous unions in the Tunisian general population, to evaluate the risk associated to inbreeding on a large class of Mendelian monogenic conditions after stratifying the disorders according to their pattern of inheritance, and to investigate if consanguineous unions contribute significantly to common complex diseases such as diabetes and cancer, which are major public health problems.

Patients and methods

As part of a study of various genetic disorders among the Tunisian population like genodermatosis, metabolic diseases, kidney diseases, eye diseases, and diabetes mellitus, we have collected in collaboration with health professionals all the files of a group of unrelated patients suffering from these diseases and were referred to major tertiary care national referral centers in Tunisia. All cases included in this study are patients who have had confirmation of their underlying disease by specific clinical features or specific laboratory investigations. A total of 1,289 unrelated confirmed cases (638 males and 651 females), aged 1 to 92 years with an overall mean age of 35.3±24.9 years, were considered for this present study.

Patients were classified in three etiological groups. Group 1 included patients with autosomal recessive disorders. Group 2 included patients with autosomal dominant disorders, and group 3 included multifactorial conditions. The autosomal recessive and dominant modes of inheritance were confirmed by a pedigree consistent with a specific mode of inheritance and genotyping (linkage analysis or mutation screening).

We retrospectively reviewed multiple variables like family history and the geographical origin of both patients' parents and gave particular attention to genealogical data in order to draw a consanguinity profile for each propositus and to calculate individual inbreeding coefficient (F) by Wright's "paths" method (Wright 1922).

To generate case–control datasets, we collected data from 1,067 unrelated volunteers (417 males and 650 females) who were free from any anomaly as controls from different Tunisian localities. In addition, selected controls are representative of all age groups with a mean age of 45.4±14.4 years. All controls were interviewed in order to collect information about consanguinity and its degree in the family. All patients (or their parents in the case of children) and controls gave their informed consent.

Consanguineous marriages were divided into four categories according to the degree of consanguinity: individuals yielding an F greater than or equal to 0.0625 (mainly first cousins and double first cousins), individuals yielding an F from 0.0156 to 0.0625 (mainly second cousins and first cousins once removed), distant related marriages (beyond second cousins, $F<0.0156$), and those in which there is no relation ($F=0$).

Statistical analysis was performed using STATA statistical package (version 11.0) for Windows. Chi-squared test and logistic regression were used to assess the association between consanguinity and the overall occurrence of each etiological category. p values less than 0.05 were considered statistically significant in calculations of consanguinity rates.

Results

Among the 1,289 patients and 1,067 controls primarily included in this study, only 1,121 patients (549 males and 572 females) and 963 controls (378 males and 585 females) were finally selected. The remaining subjects were excluded because of incomplete genealogical data. Among patients, the underlying pattern of inheritance was autosomal dominant in 8.2 % (92 cases) and recessive in 51.1 % (573 cases). The remaining 40.7 % corresponded to a multifactorial etiology (456 cases; Table 1). Table 2 presents consanguinity classes and etiological categories of the 1,121 patients and the 963 healthy controls included in this study. Consanguinity was observed in 642 cases (57.3 %). First cousin unions were the most common type of consanguineous marriages: 31.8 % of the overall patient sample and 55.5 % of all consanguineous unions. Consanguinity rates were 78.4 % among autosomal recessive condition group, 38.0 % among dominant group, 34.7 % among multifactorial group, and 29.8 % among control group. First cousin mating rates among each studied group were 31.8 %, 20.7 %, 16.2 %, and 16.7 %, respectively.

The difference in the distribution of the consanguineous versus nonconsanguineous matings was highly significant ($p<10^{-3}$) when comparing the control group with patients in group 1, but not significant with patients in groups 2 and 3 ($p>0.05$). A univariate logistic regression was applied to assess the association between consanguinity and recessive conditions. The odds ratio was strongly significant indicating that inbreeding is associated with an 8.53 times increased risk of developing these kind of disorders [OR= 8.53; 95 % CI=(6.70–10.86); $p<10^{-3}$]. In order to control the possible confounding effects of some demographic variables like sex, age, and geographical origin, a multivariate

Table 1 Specific disorders and etiological categories considered in the current study

Diseases		No. of patients (%)		
		Male	Female	Total
Autosomal recessive diseases (*N*=573)	Recessive genodermatosis	72 (67.29)	35 (32.71)	107
	Ichthyosis	25 (64.10)	14 (35.90)	39
	Dystrophic epidermolysis bullosa	40 (72.73)	15 (27.27)	55
	Meleda disease	5 (55.56)	4 (44.44)	9
	Richner–Hanhart syndrome	2 (50.00)	2 (50.00)	4
	Recessive metabolic diseases	47 (46.08)	55 (53.90)	102
	Primary hyperoxaluria	2 (25.00)	6 (75.00)	8
	Glycogenosis type I	11 (36.67)	19 (63.33)	30
	Glycogenosis type III	11 (52.38)	10 (47.62)	21
	Gaucher disease	15 (48.39)	16 (51.61)	31
	Wilson disease	8 (66.67)	4 (33.33)	12
	Recessive kidney diseases	17 (70.83)	7 (29.10)	24
	Distal renal tubular acidosis	13 (81.25)	3 (18.75)	16
	Bartter syndrome	4 (50.00)	4 (50.00)	8
	Recessive chromosomal breakage syndromes	91 (50.28)	90 (49.72)	181
	Xeroderma pigmentosum	57 (47.90)	62 (52.10)	119
	Bloom syndrome	3 (60.00)	2 (40.00)	5
	Fanconi anemia	31 (54.39)	26 (45.61)	57
	Recessive ocular diseases	71 (53.38)	62 (46.62)	133
	Syndromic retinitis pigmentosa	3 (60.00)	2 (40.00)	5
	Nonsyndromic retinitis pigmentosa	53 (56.38)	41 (43.62)	94
	Stargardt disease	5 (45.45)	6 (54.55)	11
	Cone-rod dystrophy	2 (66.67)	1 (33.33)	3
	Leber congenital amaurosis	1 (100.00)	0 (0.00)	1
	Congenital nystagmus	1 (50.00)	1 (50.00)	2
	Microphthalmia	1 (25.00)	4 (80.00)	5
	Corneal dystrophy	0 (0.00)	4 (100.00)	4
	Achromatopsia	5 (62.50)	3 (37.50)	8
	Hypogonadotropic hypogonadism	13 (72.22)	5 (27.78)	18
	Familial Mediterranean fever	6 (75.00)	2 (25.00)	8
Autosomal dominant diseases (*N*=92)	Dominant genodermatosis	17 (43.59)	22 (56.51)	39
	Darier disease	8 (42.11)	11 (57.89)	19
	Keratosis palmoplantaris papulosa	6 (54.55)	5 (45.45)	11
	Hailey–Hailey disease	3 (33.33)	6 (66.67)	9
	Dominant cardiopathies	16 (64.00)	9 (34.00)	25
	Wolff–Parkinson–White syndrome	8 (80.00)	2 (20.00)	10
	Atrial septal defect	1 (25.00)	3 (75.00)	4
	Brugada syndrome	2 (50.00)	2 (50.00)	4
	Catecholaminergic polymorphic ventricular tachycardia	0 (0.00)	1 (100.00)	1
	Arrhythmogenic right ventricular dysplasia	1 (100.00)	0 (0.00)	1
	Long QT syndrome	1 (100.00)	0 (0.00)	1
	Hypertrophic cardiomyopathy	2 (100.00)	0 (0.00)	2
	Dilated cardiomyopathy	1 (50.00)	1 (50.00)	2
	Dominant ocular diseases	13 (46.43)	15 (53.57)	28
	Blepharophimosis	1 (50.00)	1 (50.00)	2
	Kjer type optic atrophy	2 (100.00)	0 (0.00)	2
	Choroidal dystrophy central areolar	5 (38.46)	8 (61.54)	13
	Juvenile glaucoma	4 (40.00)	6 (60.00)	10
	Dyschromatopsia	1 (100.00)	0 (0.00)	1

Table 1 (continued)

Diseases		No. of patients (%)		
		Male	Female	Total
Complex diseases (N=456)	Multifactorial ocular diseases	50 (57.47)	37 (42.53)	87
	Diabetic retinopathy	15 (45.45)	18 (45.55)	33
	Age related macular degeneration	35 (64.81)	19 (35.19)	54
	Type I diabetes	42 (50.60)	41 (49.40)	83
	Type II diabetes	94 (32.87)	192 (67.13)	286
	Total	549 (48.97)	572 (51.03)	1,121

logistic regression model was performed considering all these parameters as covariates with consanguinity. The adjusted odds ratio reported from the multiple regression model was lower than that obtained from the univariate analysis. However, the level of significance was still relatively high with an almost six times increased risk (OR=5.90; 95 % CI=[4.22–8.25]; $p<10^{-3}$) to be affected by a recessive condition (Table 3). These results clearly demonstrate that consanguinity is indeed a major risk factor in the occurrence of autosomal recessive diseases.

For a better evaluation of the risk associated to consanguineous unions on autosomal recessive conditions, we carried out a logistic regression model defining the increased risk for each class of consanguinity compared to the outbred one as a reference group. Findings from this analysis (Table 4) revealed that the excess risk related to kinship unions increases significantly with the degree of consanguinity (adjusted odds ratios of 3.90, 4.69, and 7.68 for beyond second cousin unions, second cousin unions, and first cousin unions, respectively).

In addition, in order to test a possible interaction effect between family history of disease and consanguinity on disease occurrence, we assessed the increased risk due to inbreeding either in presence or in absence of first- or second-degree family history (i.e., history of the disorders among first- or second-degree relatives). Results in Table 5 show that the impact of consanguineous unions on this etiological category is more than 1.5-fold in individuals with first- or second-degree family history compared to individuals with no close affected relatives (adjusted odds ratio of 8.59 versus 5.43, respectively).

Finally, we assessed the extent of the geographical endogamy among autosomal recessive patient group. Indeed, regional endogamy corresponds also to a nonpanmictic reproductive pattern that guides the evolution of the genetic structure of the population (Cavalli-Sforza et al. 1966). We determined the rate of geographical endogamy from data on the locality of origin of both parents. We found that the overwhelming majority (91.87 %) of autosomal recessive cases have both parents from the same regional locality (Table 6).

Table 2 Consanguinity classes and etiological categories in patient and control samples

Etiology	No. of patients (%)						Total
	Consanguineous					Nonconsanguineous (F=0)	
	Double first cousins (F=0.125)	First cousins (F=0.0625)	First cousins once removed (F=0.0313)	Second cousins (F=0.0156)	Beyond second cousins (F<0.0156)		
Patients	642 (57.27) 12 (1.07)	356 (31.76)	60 (5.35)	51 (4.55)	163 (14.54)	479 (42.73)	1,121
Patients affected by autosomal recessive disorders (group 1)	449 (78.36) 10 (1.75)	263 (45.90)	53 (9.25)	43 (7.50)	80 (13.96)	124 (21.64)	573
Patients affected by autosomal dominant disorders (group 2)	35 (38.04) 1 (1.09)	19 (20.65)	4 (4.35)	0 (0.00)	11 (11.96)	57 (61.96)	92
Patients affected by complex disorders (group 3)	158 (34.65) 1 (0.22)	74 (16.23)	3 (0.66)	8 (1.75)	72 (15.79)	298 (65.35)	456
Controls	287 (29.80) 4 (0.42)	161 (16.72)	14 (1.45)	34 (3.52)	74 (7.68)	676 (70.20)	963

Table 3 Logistic regression analysis of the case–control study of different types of mode of inheritance and consanguinity

Etiologies	Consanguineous	Nonconsanguineous	OR	CI	*p* value	OR[a]	CI[a]	*p* value[a]
Autosomal recessive diseases (group 1)	449 (78.36)	124 (21.64)	8.53	[6.70–10.86]	$<10^{-3}$	5.90	[4.22–8.25]	$<10^{-3}$
Autosomal dominant diseases (group 2)	35 (38.04)	57 (61.96)	1.45	[0.93–2.25]	0.10	1.34	[0.82–2.18]	0.24
Multifactorial diseases (group 3)	158 (34.65)	298 (65.35)	1.25	[0.99–1.58]	0.07	1.15	[0.84–1.57]	0.38
Controls	287 (29.80)	676 (70.20)						

[a] Adjusted for age, sex, and geographic origin

Discussion

As in other MENA countries, consanguineous marriages are culturally favored in Tunisia. According to the 1975 general Tunisian population census and the 2008 National Office for Family and Population Affairs data, the rate of close consanguinity unions among general Tunisian population remained relatively high and constant during the last 30 years (18.2 % and 21 % in 1975 and 2008, respectively). A study on the demographic situation in Tunisia in 1985 reported a significant urban/rural difference (16.3 % vs. 25.36 %) in the percentage of consanguineous marriages (Ben M'Rad 1986). In the same context, an epidemiological study (Riou et al. 1989) conducted in 1989 on a cohort of 5,767 married couples from the Northern region of Tunisia has even shown a consanguinity rate of 31.62 % with first cousin unions being the most common class (20.23 % of all unions). A similar prevalence of global consanguinity and first cousin unions has also been reported in a more recent study carried out on a sample of 370 married women from the Greater Tunis area (32.71 % and 16.21 %, respectively; Ben Mrad and Chalbi 2004).

When referring to the control cohort used as a representative group of the overall consanguinity level in the Tunisian population, a very close level of inbreeding to that reported previously has been found (29.80 %) mainly between unions among first cousins (17.13 %; Table 2).

Our findings confirm that consanguineous unions are still highly common in Tunisia (about one in three unions) despite the impressive educational, demographic, and behavioral changes that have taken place during the last four decades. These changes involve several indicators such as urbanization (from 43.5 % in 1970 to 66.9 % in 2009), female education (from 62.52 % in 1984 to 95.79 % in 2008), raising of the marital age for women (from 20.8 years in 1966 to 29.8 years in 2004), and a decrease in the total fertility rate (from 6.42 in 1970 to 2.05 in 2009; data from National Office for Family and Population Affairs (ONFP) and National Institute of Statistics (INS; http://perspective.usherbrooke.ca/bilan/pays/TUN/fr.html; Romdhane et al. 2011). This mating pattern is similar to that observed in many Arab populations with a high level of inbreeding and first cousin marriages (Al-Awadi et al. 1985; Khoury and Massad 1992; Al-Gazali et al. 1997; Mokhtar et al. 1998; Bener and Alali 2006; Jaouad et al. 2009) despite several factors such as increased population movement and admixture that contributed to the decline of this kind of mating among other population groups like Western European populations (Bittles 2003). This high rate and the long practice of consanguineous marriages are expected to increase the observed levels of homozygosity and therefore the proportion of clinical conditions with suspected genetic etiology, especially those with recessive inheritance (Woods et al. 2006; Bittles and Black 2010). In this context, many previous reports have described an association between inbreeding and different autosomal recessive disorders (Taillemite et al. 1985; Reddy et al. 2006). It has also been stated that the less common the disease allele is in the gene pool, the higher the risk will be in the expression of an autosomal recessive disorder in the progeny of consanguineous unions (Rudan et al. 2003). On the other hand, the biological outcome of inbreeding may have been overestimated in several investigations because of a poor control of nongenetic variables such as maternal age, education level, occupation status, and area of residence (Bittles 2008).

In this study, we confirm the very strong impact of consanguinity on the expression of autosomal recessive

Table 4 Logistic regression analysis of the case–control study of autosomal recessive disorders and different classes of consanguinity

Degree of consanguinity	Patients	Controls	OR	CI	*p* value	OR[a]	CI[a]	*p* value[a]
First cousins ($F \geq 0.0625$)	273 (62.33)	165 (37.67)	9.02	[6.87–11.84]	$<10^{-3}$	7.68	[5.17–11.41]	$<10^{-3}$
Second cousins ($0.0156 \leq F < 0.0625$)	96 (66.67)	48 (33.33)	10.90	[7.34–16.20]	$<10^{-3}$	4.69	[2.64–8.35]	$<10^{-3}$
Beyond second cousins ($F < 0.0156$)	79 (51.97)	73 (48.03)	5.90	[4.07–8.55]	$<10^{-3}$	3.90	[2.37–6.42]	$<10^{-3}$
Nonconsanguineous ($F = 0$)	123 (15.39)	676 (84.61)	1	–	–	1	–	–

[a] Adjusted for age, sex, and geographic origin

Table 5 Logistic regression analysis of the case–control study of autosomal recessive disorders and consanguinity by familial history

Status	Consanguineous	Nonconsanguineous	OR	CI	*p* value	OR[a]	CI[a]	*p* value[a]
Patients with first or second degree family history	160 (81.22)	37 (18.78)	10.19	[6.94–14.94]	$<10^{-3}$	8.59	[5.27–14.00]	$<10^{-3}$
Patients without first or second degree family history	215 (77.62)	62 (22.38)	8.17	[5.96–11.19]	$<10^{-3}$	5.43	[3.56–8.26]	$<10^{-3}$
Controls	287 (29.80)	676 (70.20)						

[a] Adjusted for age, sex, and geographic origin

diseases. In fact, our findings reveal an increased risk of nearly six times for developing a recessive disorder. This result is consistent with a prior publication on genetic disorders in the Arab world which reported that consanguineous marriage increases the incidence of autosomal recessive disorders by five to ten times at the population level (Tadmouri et al. 2006). In Tunisia, few studies have focused on inbreeding and its genetic consequences. However, some reports have also described a correlation between consanguinity and some genetic conditions like polydactyly (Ben Arab and Chalbi 1984), deafness (Ben Arab and Chalbi 1984), degenerative spinocerebellar diseases (El Gazzah et al. 1985), and bipolar disorder (Mechri et al. 2007). Another study has even revealed a significant association between inter-family marriages and offspring mortality (Kerkeni et al. 2007). Similarly, a previous report on nonsyndromic deafness in Northern Tunisia showed that the risk of being deaf in the case of first cousin marriages is over ten times higher than in nonconsanguineous marriages (Ben Arab et al. 2004). Moreover, our findings seem to confirm those found in other nearby populations. Indeed, a similar recent study conducted in Morocco among 176 patients with autosomal recessive diseases showed that these disorders are strongly associated with consanguinity (Jaouad et al. 2009). Likewise, a previous study conducted on a cohort of 100 Egyptian patients suffering from various recessive autosomal conditions reported that the frequency of consanguinity among parents of patients was significantly higher ($p<0.01$) than that reported for the general Egyptian population (Mokhtar et al. 1998). A previous report on genetic disorders in Arab countries shows that the majority of genetic conditions reported over the last decades among Arab populations are recessively inherited (Tadmouri et al. 2006). This finding was recently confirmed by a study that aimed at assessing the burden of these inherited disorders on the Tunisian population. On the 346 reported genetic conditions, 62.9 % were autosomal recessive (Romdhane et al. 2011).

Table 6 Consanguinity and endogamy classes among autosomal recessive patients sample

	Number	%
Consanguinity classes		
Double first cousins	10	1.75
First cousins	263	45.90
Patrilateral parallel-cousins[a]	109	19.02
Matrilateral parallel-cousins[b]	80	13.96
Patrilateral cross-cousins[c]	35	6.11
Matrilateral cross-cousins[d]	39	6.81
First cousins once removed	53	9.25
Second cousins	43	7.50
Beyond second cousins	80	13.96
Nonconsanguineous	124	21.64
Total	573	100
Geographical endogamy classes		
Endogamous	418	91.87
Exogamous	37	8.13
Total	455	100

[a] Patrilateral parallel-cousins are father's brother's children

[b] Matrilateral parallel-cousins are mother's sister's children

[c] Patrilateral cross-cousins are father's sister's children

[d] Matrilateral cross-cousins are mother's brother's children

Indeed, both large family and patriarchal tribe models based on common ancestry and commonly characteristic of Arab societies tend to display specific distribution patterns for genetic diseases that are typical to Arab and many Middle Eastern populations. Interestingly, findings from our study (Table 6) confirm this patriarchal model where patrilateral parallel-cousin marriage is the preferred form of first cousin unions (Bittles 2008). Through these specific reproduction patterns, a cumulative history of consanguineous unions may lead to a specific enrichment of founder mutations, which are inherited from a common ancestor, a high prevalence of unique genetic disorders, and to a relative homogeneity of the mutation spectrums of these populations (Papponen et al. 1999). In fact, among the 68 genetic diseases due at least to one founder mutation, 59 (86.8 %) are caused by nucleotide changes at homozygous state that are common between these inbred communities (Romdhane et al., under review). In the Tunisian population, which shares historical features with other North African and Middle Eastern ones, the mutation distribution model seems to be similar. In addition, these specific models are also characterized by a high concentration of mutation carriers within the extended family and an increased homozygosity leading to a particularly high prevalence of this kind of conditions

(Rajkumar and Kashyap 2004). This could also lead to the expression of more than one morbid phenotype in the same family (Romdhane et al. 2011). As a consequence, the burden imposed by inbreeding in these populations is particularly serious given that recessive conditions are generally severe and account for a substantial proportion of mental and physical disabilities (Teebi and Farag 1996). Moreover, results from our study reveal a quite significant endogamous behavior among the parents of autosomal recessive patients with 91.87 % of all cases which the father and mother originate from the same geographical locality. These findings confirm once again the specificity of reproduction models in Arab populations characterized by a high geographical endogamy, limited inter-community marriages, and a reduced human dispersal levels (Bittles 2005). This population stratification due to intra-community unions have an important genetic outcome and may lead to a quick fixation of harmful recessive founder or de novo mutations in several sub-communities (Bittles and Black 2010). This phenomenon is reported in many Middle-Eastern countries where several deleterious alleles are specific to a single tribe or village (Zlotogora et al. 2007; Miller et al. 2007). In these sub-communities, many parents of affected children do not know they are related (Bittles 2008). Indeed, the high level of geographical endogamy reported in this study suggests the underestimation of consanguineous unions that have occurred in distant generations (data beyond second and even first cousin unions). It is noteworthy that during this study and based on our personal experience, when interviewing the families of patients and controls, we found out that consanguinity beyond second degree was usually unknown or non defined, i.e., individuals did not know if their grandparents were related, and if so, how. Indeed, many apparently nonconsanguineous unions may possibly share a common ancestor as a result of non-recorded consanguinity. This fact is particularly observed in several Middle Eastern and North African populations like Tunisia which include a multitude of small endogamous communities where, after several generations, the genetic kinship of related mutation carriers become unrecognizable (Tadmouri et al. 2006). This makes detection and prevention of the potential deleterious effects of inbreeding more difficult given that couples who do not know their relatedness are less aware of the importance of premarital counseling and prenatal diagnosis given the information on family history, suggesting a genetic basis of their predisposition to recessive disease state is missing. In the same context, the deleterious effects of distant consanguinity are more evident in Western countries where close biological unions are very rare and often prohibited. This is the case of Finland where the simultaneous effect of distant consanguinity with founder effect and genetic drift are involved in the etiology of 36 genetic disorders in the country (Norio 2003). All these statements may suggest that the effective increased risk of recessive disorders due to marriages between relatives could be even higher than that found in this study because of the underestimated effects of distant consanguinity. Furthermore, in many communities where the family pedigrees show complex multiple pathways of consanguinity, it is difficult to accurately estimate the actual level of homozygosity in an individual and the corresponding associated risk (Bittles 2002).

This study has also reported that the excess risk that an autosomal recessive disorder will be expressed in the progeny of a consanguineous union is more than 1.5 times among cases with a positive family history of the disease and is therefore proportional to the frequency of the disease allele in the family. In fact, the consanguinity may significantly amplify the already increased risk for familial autosomal recessive disorders. Our findings confirm that inbreeding in itself is not responsible for the appearance of unfavorable traits. However, deleterious autosomal recessive alleles are sometimes hidden within the family in the heterozygous state for many generations, and consanguineous unions between mutation carriers will lead them to come to the surface. This effect is more remarkable for rare diseases since there is little probability that the carrier finds a partner who bears the same mutation in the general population (Jaouad et al. 2009). A previous study on the effects of parental consanguinity on genetic disorders in the Iranian population has reported that consanguineous couples who already have an affected child are 13 times more likely to have another affected sibling (Mokhtari and Amrita 2003). Consequently, recognition and molecular diagnosis of the genetic abnormalities in the first affected individual in a family is of great importance as the recurrence risks are often high and the disorders are mostly incurable (Mokhtar et al. 1998).

This study also shows that the excess risk for developing recessive conditions related to inbreeding is proportional to the degree of consanguinity. This finding confirms that the probability of homozygosity decreases from a more closely inbred to a less inbred offspring (Bener et al. 2009) and indicates that inbreeding coefficient may be a reliable indicator of genome homogeneity.

For autosomal dominant conditions, we found that dominant disease occurrence was not significantly associated with consanguinity. This finding may be explained by the fact that it is widely known that kinship unions are generally not associated to this mode of inheritance. Indeed, in the case of dominantly inherited disorders, the morbid phenotype is expressed as a cause of one copy of the deleterious mutation; thus, two related parents do not have a greater probability of having an affected child than an unrelated couple. Moreover, in humans, homozygosity for dominant alleles is rare (Zlotogora 1997a) because of the effect of natural selection which tends to eliminate dominant mutations in the homozygous as well as in the heterozygous state especially that this homozygosity is often associated with a more severe phenotype of the disease

(Ouragini et al. 2009). Therefore, dominant disorders are often caused by de novo mutations.

The impact of consanguinity on multifactorial disorders in humans is largely unknown, and a matter of debate though experimental studies in animals have reported deleterious effects of inbreeding on numerous multifactorial traits (Charlesworth and Charlesworth 1987; Charlesworth and Hughes 1996; Wright et al. 2003). Some authors predict that inbreeding in humans might influence a wide class of complex disorders especially if the genetic component of the disease is mainly due to a large number of rare variants in numerous genes according to the common disease/rare variant hypothesis (Ahmad 1994; Rudan et al. 2003; Bittles and Black 2010). Indeed, as most identified genetic variants causing complex diseases in humans are partially recessive (Bittles and Neel 1994), it appears that inbreeding could increase the disease risk by increasing homozygosity at many genetic loci with small deleterious effects on homoeostatic pathways (Rudan et al. 2003). In this context, a recent study estimated that each individual bears an average of 500 to 1,200 slightly deleterious rare mutations in the heterozygous state, and many of these variants become homozygous in consanguineous individuals with resulting significant effects on polygenic traits that influence human health (Fay et al. 2001). The reported finding of uninterrupted runs of homozygosity (ROH) which are more common in patients with schizophrenia is consistent with this and suggests the implication of autozygosity and recessive alleles on the disease etiology (Lencz et al. 2007). Likewise, other studies on highly endogamous and consanguineous Israeli Arab communities have highlighted the implication of autozygosity on Alzheimer etiology (Farrer et al. 2003). Long-term studies conducted on autochthonous residents from Dalmatian islands in Croatia also showed a correlation between consanguinity and several common complex disorders such as hypertension, coronary heart disease, stroke, cancer, bipolar depression, asthma, gout, peptic ulcer, and osteoporosis (Rudan et al. 2003, 2004; McQuillan et al. 2008). On the other hand, many other reports state that adverse complex conditions have been uncritically ascribed to consanguinity without adequate allowance for other socioeconomic factors (Gropman and Adams 2007), and thus, it is unlikely that consanguinity contributes significantly to polygenic and multifactorial diseases once socioeconomic variables have been controlled for (No authors listed 2006). Indeed, because of both gene–gene interactions and environmental contribution to the disease phenotype, the attribution of the condition only to an increased homozygosity at some susceptibility loci seems to be an oversimplistic explanation (Bittles and Black 2010).

Accordingly, we did not find any significant correlation between inbreeding and multifactorial disorders in this study. These findings indicate that the susceptibility gene variants for these diseases may be relatively common in the population gene pool and/or that environmental factors may be important (co)factors for the occurrence of these disorders. On the other hand, these disorders may have a large genetic contribution, but the genetic variants accounting for much of the variability in such traits are additive (additive variance) rather than recessive (dominance variance). The assumption that these disorders may follow a non-Mendelian pattern of inheritance (mitochondrial inheritance, modifying genes, or parental imprinting, etc.) should also be considered (Teebi and Farag 1996).

In conclusion, this cross-sectional study, which includes to our knowledge the largest cohort ever studied in North Africa, shows a high impact of inbreeding and regional endogamy on the occurrence of some specific disorders especially those with an autosomal recessive inheritance. More importantly, it emphasizes the persistence of a relatively high level of parental consanguinity in the Tunisian population at a rate which has remained almost unchanged over the last four decades despite the profound societal changes that have occurred. This highlights the strong resilience of this deeply rooted social behavior and the need for reinforced and continuous information of general public and health professionals on its potential negative medical impact. Finally, consanguinity and endogamy have some clear socioeconomic advantages as conveyed orally through centuries via proverbs and "wise sayings" that condensate the experience of several generations. As an example, we could cite "who would give his wealth to others" (wealth includes children, so cousins were promised to each other since their young age). Advantages of consanguinity also include familial structure cohesion, as it is more difficult for a couple to divorce if they belong to the same family. As suggested by the recent Geneva international consanguinity workshop report (Hamamy et al. 2011), there is a need for detailed assessment of social and genetic benefits of consanguinity in future studies.

Acknowledgments We would like to thank the patients and their family members and to acknowledge all the members of the Laboratory LR11IPT05 and collaborators for their valuable contribution in this work. We would like also to express our sincere gratitude to Professor Noureddine Chalbi for his supervision and guidance. The authors are also grateful to Mrs. Kawther Ben Romdhane for proofreading this manuscript. This study was supported by the Tunisian Ministry of Higher Education and Scientific Research, the Tunisian Ministry of Health, the NEPAD/NABNet T2D project, and EMRO-COMSTECH RAB&GH grant.

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