Published in final edited form as:

Schizophr Res. 2010 July ; 120(1-3): 108–112. doi:10.1016/j.schres.2010.03.026.

Consanguinity and increased risk for schizophrenia in Egypt

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Abstract

Background—Consanguinity has been suggested as a risk factor for psychoses in some Middle Eastern countries, but adequate control data are unavailable. Our recent studies in Egypt have shown elevated parental consanguinity rates among patients with bipolar I disorder (BP1), compared with controls. We have now extended our analyses to Schizophrenia (SZ) in the same population.

Methods—A case-control study was conducted at Mansoura University Hospital, Mansoura, Egypt (SZ, $n = 75$; controls, $n = 126$, and their available parents). The prevalence of consanguinity was estimated from family history data ('self report'), followed by DNA analysis using short tandem repeat polymorphisms (STRPs, $n = 63$) ('DNA-based' rates).

Results—Self reported consanguinity was significantly elevated among the patients (SZ: 46.6%, controls: 19.8%, OR 3.53, 95% CI 1.88, 6.64; $p = 0.000058$, 1 d.f.). These differences were confirmed using DNA based estimates for coefficients of inbreeding (inbreeding coefficients as means $\pm$ standard error, cases: 0.058 ± 0.007 , controls: 0.022 ± 0.003).

Conclusions—Consanguinity rates are significantly elevated among Egyptian SZ patients in the Nile delta region. The associations are similar to those observed with BP1 in our earlier study. If replicated, the substantial risk associated with consanguinity raises public health concerns. They may also pave the way for gene mapping studies.

Keywords

Schizophrenia; consanguinity; DNA; genetic; association; inbreeding

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1. INTRODUCTION

Consanguineous marriages occur among diverse ethnic groups, numbering over a billion persons world-wide (Rudan, Smolej-Narancic et al. 2003). In the USA such groups include the Old Order Amish, some Mennonite communities in the mid-west and some Hutterite and Utah Mormon populations (Puffenberger 2003) (Patton 2005) (Ober, Hyslop et al. 1999) (Jorde 2001). In Middle Eastern populations, approximately 20 – 70% of marriages are between consanguineous individuals (Teebi and Farag 1997) (al-Gazali, Bener et al. 1997) (Hoodfar and Teebi 1996) (Rudan, Campbell et al. 2006) (Bittles 2008). The consanguinity rate in Dakahlia, one of the most heavily populated areas of the Nile Delta region of Egypt, was estimated at 24% overall (Settin and Algelani 1997). The most common consanguineous marriages in Egypt occur between first cousins (50%), followed by first cousins once removed (15%), second cousins (15%) and others (Hafez, El-Tahan et al. 1983). The consanguineous marriages are practiced for economic and social reasons. They are more common among lower socio-economic classes. Though consanguineous marriages occur among Muslims and Christians alike, the rates are lower among Christians, who also prefer second cousin marriages (Teebi and Farag 1997).

It has been suggested that consanguinity (inbreeding) may be associated with increased risk for a wide range of genetically complex disorders, such as diabetes mellitus, certain types of cancer, coronary artery disease and hypertension (Bener, Hussain et al. 2007) (Rudan, Rudan et al. 2003) (Charlesworth and Hughes 1996) (Rudan, Smolej-Narancic et al. 2003) (Rudan, Campbell et al. 2006). Several reports also suggest that consanguinity is more likely among parents of patients with SZ in Middle Eastern countries. A study in Saudi Arabia reported that offspring of first and second cousin marriages ($n = 36$) were more likely to have a positive family history of SZ than offspring of distantly related and non-consanguineous marriages ($n = 107$, $p = 0.006$) (Chaleby and Tuma 1987). An earlier study in Sudan did not find such differences, suggesting regional variation (Ahmed 1979). Investigators in Azerbaijan have reported increased frequency of parental consanguinity among patients with SZ, in comparison with control individuals (Skoblo 1975). Dobrusin and colleagues have studied consanguinity among parents of Bedouin Arab patients with SZ who were hospitalized from a defined catchment area in southern Israel. They found a small but significantly higher rate of parental consanguinity among patients compared with controls recruited for another study ($X^2 = 13.55$, df_3 , $P .01$) (Dobrusin, Weitzman et al. 2008). Thus, the SZ studies are consistent with the observed positive association between consanguinity and risk for other common disorders.

In earlier work we showed that parental consanguinity rates are increased risk for bipolar I disorder (BP1) in Egypt (Mansour, Klei et al. 2009). The increased risk was evident whether consanguinity was inferred from genealogical report or from analyses of highly polymorphic markers. We wondered if consanguinity could have a broader impact on risk for other psychiatric disorders. To address this question we conducted a study similar to that reported by Mansour et al (Mansour, Klei et al. 2009) but with cases being diagnosed with SZ.

2. MATERIALS AND METHODS

The study was conducted at Mansoura University Hospital (MUH), a Government funded facility that serves as the primary psychiatric care facility for a population of over 7 million from Mansoura and the surrounding villages. Mansoura, the capital city of Dakahlia governorate (province) is located 70 miles north of Cairo and 40 miles from the Mediterranean Sea. Dakahlia is not geographically or genetically isolated and marriages across village lines are common. Marriage between individuals in Dakahlia and individuals

outside the regions is permitted. This area in the Northern Nile Delta region does not include any specific tribal or clan populations. Such tribes reside in the desert areas. First cousins marriages is the most common form of consanguineous marriages in Egypt, and uncle niece marriages are rare.

2.1 Clinical

2.1.1 Cases—Consenting, unrelated outpatients attending the MUH Psychiatry outpatient clinics who received a clinical diagnosis of SZ (DSM IV criteria) were ascertained without knowledge of their family structure. Only individuals for whom both parents could provide family history data were included, in order to ensure reliable family history data in both parental lineages. The parents provided family histories, but did not complete diagnostic evaluations.

2.1.2 Controls—The controls were consenting adults who resided in the same geographic areas as the patients. The control individuals were recruited without knowledge of family structure and were balanced with regard to age and area of residence to the cases. The control sample included two groups: those analyzed in our previous study ($n = 90$ (Mansour, Klei et al. 2009) and another group not reported before ($N = 36$). They were recruited over the same period as the cases. Individuals with a history of psychosis or BP1 were excluded. Available parents were recruited.

2.1.3 Interview schedules—Participants were interviewed by trained psychiatrists using the Arabic version of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN), a structured diagnostic interview schedule (Wing, Sarotorius et al. 2001). Family history of parental consanguinity, as well as family history of BP1 and psychoses was obtained using the Arabic version of the Family Interview for Genetic Studies (FIGS) (Mansour, Klei et al. 2009). Inter-rater reliability was maintained throughout the study.

2.2 Laboratory

Short Tandem Repeat Polymorphisms (STRPs, $n = 63$) were assayed among cases and controls. The STRPs were selected from the Human Linkage Mapping Set v2.5 and assayed using an ABI 3130 machine as described (Applied Biosystems Inc., ABI) (Mansour, Klei et al. 2009). No sex chromosome markers were genotyped in the study. There was 100% concordance rate between our calls and reference genotypes for the CEPH sample 1347-02. The overall missing genotype rates are 2.56 – 5.84%.

2.2.1 Estimates for rates of consanguinity

2.2.1.1 DNA based rates: The inbreeding coefficient (f) for an individual is defined as the probability that two alleles at any locus are inherited from the same ancestor, i.e., the alleles are identical by descent (IBD) (Malécot 1948). Genotype based estimates from cases or controls necessarily utilize data based on identity by state (IBS), rather than IBD. The IBD process for marker genotypes along the genome can be modeled for individuals from a finite random mating population (Stam 1980) and the parameters for this process, including IBD can be estimated using a hidden Markov model (HMM) (Leutenegger, Prum et al. 2003). For a person with consanguineous ancestors, longer stretches of the genome are IBD compared with a person from outbred populations, so the IBD transition probabilities are expected to differ along the genome. The transition probabilities and the inbreeding coefficient can be estimated using a maximum likelihood method (Leutenegger, Prum et al. 2003). Essentially, this method estimates $\hat{f}$, the inbreeding coefficient, for individual i by using maximum likelihood on the marker genotypes. $\hat{f}$ ranges from 0, or no consanguinity, to 1, with off-spring of first cousin marriages corresponding to a $\hat{f} = 0.0625$.

2.2.1.2 Self reported rates: Parental consanguinity was estimated as a dichotomous variable, based on family history data, consistent with prior published studies (Hafez, El-Tahan et al. 1983) (Helgason, Palsson et al. 2008). A participant was considered to be consanguineous, if her parents shared a common ancestor no more remote than a great-great grandparent.

The study was approved by the Mansoura University Ethics Committee and the University of Pittsburgh Institutional Review Board (IRB). All participants provided written informed consent.

2.2.2 Statistical Analysis—The DNA based estimates of $\hat{f}$ for 75 cases and 126 control individuals were tested for a mean difference, assuming these data were distributed exponential with a common mean and variance of the difference estimated from the data (see Figure 1). This is a test for equality of the exponential parameter for the two distributions, based on maximum likelihood estimation. Other data were compared using SPSS version 16.0.

3. RESULTS

The sample was composed of 75 patients with SZ, 126 community based control individuals and their available parents (total 432 participants). All participants reported themselves as Muslims. There were no significant differences in age or gender between the cases and controls (Table 1).

3.1 DNA-based estimates of consanguinity

The rates of homozygosity for markers varied from 7.46 to 49.25% among cases and 4.07 to 37.1% among controls (see supplementary Table 1). The estimated genetic rates of consanguinity tend toward higher levels in cases relative to controls (Figure 1). Assuming rates of consanguinity are distributed exponential, which is consistent with the data (Figure 1), the mean estimated genetic consanguinity rates for the cases versus control individuals were tested (mean inbreeding coefficients $\pm$ standard error of the means, cases: 0.058 ± 0.007 , controls: 0.022 ± 0.003), resulting in a test statistic of 6.76, which is highly significant ($p = 6.6 \times 10^{-12}$).

3.2 Self reported rates of consanguinity

The SZ patients had significantly elevated rates of self reported consanguinity compared with the controls ($n = 35$ cases with consanguineous parents, 46.6% of all cases; $n = 25$ controls with consanguineous parents, 19.8% of all controls, Chi square = 16.15, $p = 0.000058$; odds ratio 3.53, 95% confidence intervals 1.88, 6.64; see Table 1). The prevalence of parental consanguinity did not vary by gender among the cases or controls (data not shown). The majority of the controls were included in our earlier study of BP1 (Mansour, Klei et al. 2009). To evaluate the possible impact of biased control selection, we separately compared the consanguinity rates among the cases with control individuals unique to this study ($n = 36$); significantly elevated rates were observed among the cases ($n = 35$ cases with consanguineous parents, 46.6% of all cases; $n = 7$ controls with consanguineous parents, 19% of all controls, Chi square = 7.66, 1 df, p value = 0.0056, odds ratio 3.62, 95% confidence intervals 1.41, 9.29).

3.3 Types of self-reported parental consanguineous relationships

We evaluated whether the nature of consanguinity differed quantitatively between cases and controls. Among 34 cases with parental consanguinity, there were 17 first cousin parental marriages and 17 with more remote relationships among the rest. Among 23 controls with

consanguineous parents, 10 had parents who were first cousins, the rest being related more remotely prior to marriage ($n = 13$). There is no significant difference between cases and controls in terms of first-cousin versus more distant marriages.

3.4 Consanguinity by area of residence

Individuals living in villages or small towns (population less than 10,000) were classified as rural dwellers (65% of cases and 73% of controls), while the remainder were considered urban residents. The rates self reported consanguinity were similar among cases (36.11% among rural and 38.10% among urban groups) and controls from both groups (17.14% among rural and 20% among the urban control groups).

4. DISCUSSION

We have detected a significant increase in the prevalence of consanguinity among Egyptian SZ cases, compared to individuals without a diagnosis of SZ. The difference was detectable using self reported estimates, as well as DNA based measures. Thus, biased recall is unlikely to explain the case-control differences. We also took care to recruit cases and controls without prior knowledge of their familial structures, so biased recruitment in this regard is also an unlikely explanation. Indeed, the rates of self-reported consanguinity among the controls are similar to prior community surveys (Hafez, El-Tahan et al. 1983) (Settin and Algelani 1997). Other possible confounding factors were also addressed. All cases were interviewed using structured interview scales and consensus diagnoses assigned following review of all available sources of information. In addition, the distribution of gender and area of residence were balanced for the cases and controls. The cases and controls were also balanced with regard to age to ensure that similar proportions of parents were available to provide family information in both groups. This entails that not all cases may have passed the risk period for SZ. Based on available lifetime morbidity data (Gottesman 1991), one or two control individuals may later be diagnosed with SZ. Even if these individuals are non-consanguineous, the misclassification is unlikely to alter the ORs substantially. The OR estimates are comparable to those obtained in an earlier study of BP1 (BP1; OR estimate from this study: 3.53; estimates for BP1: 2.66, 4.64) (Mansour, Klei et al. 2009). Thus, it is unlikely that non-consanguineous SZ cases tend to be misdiagnosed as BP1.

The association has several important implications. The substantial risk observed in our study ($OR \sim 3.5$) suggests that consanguinity is an important risk factor for SZ in Egypt. The association raises the possibility of recessively inherited genetic risk factors. Another explanation is general physiological decline due to inbreeding. We have reported on similar risk associated with BP1 in Egypt ($ORs \sim 2.66 - 4.64$) (Mansour, Klei et al. 2009). Thus, consanguinity may not only increase susceptibility to SZ, but also to other psychiatric disorders and to specific infections (Lyons, Amos et al. 2009; Lyons, Frodsham et al. 2009). It would be important to see if the risk extends to other disorders and traits. Analogous decline has been observed in plants and in wild animals, albeit at higher levels of inbreeding (Crnokrak and Roff 1999) (Charlesworth and Hughes 1996) (Charlesworth and Charlesworth 1999).

Consanguinity is likely to be more common among lower socio-economic groups, which may in turn lead to increased prevalence of environmental risk factors for SZ, such as obstetric complications (OCs) or exposure to putative infectious etiological agents. Though socioeconomic status was not evaluated systematically, the distribution of income is uniformly low among rural dwellers in Dakahlia, the majority of whom are subsistence farmers. Though we detected case-control differences in consanguinity even among rural dwellers, the impact of consanguinity needs to be addressed further.

Regardless of the mechanism underlying the association, the observed risks have potential public health consequences. Dating from the eugenics era, there continues to be a vigorous debate about prohibition of consanguineous marriages and their likely public health benefits (Bennett, Hudgins et al. 1999) (<http://www.nsgc.org/>). Indeed, it is prohibited by law in some US states (Paul and Spencer 2008). Though consanguinity is also discouraged by Islam, it is permitted in many Arab countries (Hussain 1999) (Akrami and Osati 2007). Economic or cultural factors may motivate consanguineous marriages in Middle Eastern countries (Klat and Khudr 1984) (Teebi and Farag 1997). The efficacy of preventive programs will thus likely depend on four key factors: their acceptance by the lay public; the frequency of the causative mutation/s; the likely risk due to prevalent environmental factors and the mean coefficient of inbreeding in the population (Paul and Spencer 2008). While genetic counseling has tangible benefits for rare Mendelian disorders with identified mutations, their benefits for common, multifactorial disorders merits further investigation.

In conclusion, we report on significant and substantive elevated rates of consanguinity among SZ cases in Egypt. We recommend carefully designed population based studies to enable more precise estimates of the risk associated with consanguinity. Preventive public health efforts should be deferred till such replicate studies are completed. Studies to investigate the mechanisms for the observed associations, as well as gene mapping studies should be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Distribution of DNA- based Inbreeding coefficient for cases and controls

The mean inbreeding coefficients among cases is significantly elevated in comparison with controls (mean $\pm$ standard error of the mean; cases: 0.058 ± 0.007 , controls: 0.022 ± 0.003 ; $p = 6.6 \times 10^{-12}$)

Table 1

Self reported consanguinity rates

Group	N	Age (in years)		Gender		Parental Consanguinity Present	OR (95% CI)
		Mean	standard deviation	Male	Female		
SZ	75	28	7	44	31	35 (46.6%) *	3.53 (1.88, 6.64)
Controls	126	27	7	71	55	25 (19.8%)	

SZ: Schizophrenia
OR: Odds ratio; CI: confidence interval
@ Control individuals not analyzed in our prior study of consanguinity and bipolar I disorder
Parental consanguinity significantly different from controls:

* $\chi^2 = 16.15$, $p = 0.000058$, 1 df

Table 2

Levels of self-reported parental consanguineous relationships

Consanguinity		Schizophrenia Cases (n = 75)	Controls (n = 126)
Self reported	No reported consanguinity	40 (53.3%)	101 (80.1%)
	Remote *	17 (22.6%)	15 (11.9%)
	First Cousin	18 (24%)	10 (7.9%)
DNA based (mean inbreeding coefficient ± standard error of the means)		0.058 ± 0.007	0.022 ± 0.003

* Consanguineous relationship less than first cousin marriage.