European Journal of Medical Genetics 59 (2016) 104–110

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Review

Genetics and psychotic disorders: A fresh look at consanguinity

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ARTICLE INFO

Article history:
Received 17 November 2015
Accepted 20 December 2015
Available online 22 December 2015

Keywords:
Consanguinuity
Psychosis
GWAS
Schizophrenia
Bipolar disorder

ABSTRACT

Consanguineous unions refer to marriages between related individuals who share a common ancestor. These unions are still commonplace in certain regions of the world such as the southern coast of the Mediterranean, throughout the Middle East and South-East Asia. According to available data, couples of second cousins or closer and their offspring currently represent 10.4% of the world's population, thus resulting in increased frequencies of autosomal recessive disorders. Furthermore, consanguinity may be implicated in the increased frequency of multifactorial pathologies such as mental disorders.

The few existing epidemiological studies in consanguineous and/or geographically isolated populations confirm that there is a significant association between consanguinity and mental disorders and a higher risk of schizophrenia or bipolar disorders among offspring from consanguineous couples.

There exists a strong and complex genetic component in the predisposition to psychotic disorders that has been confirmed in numerous studies. However, the genetic basis of these disorders remains poorly understood. GWAS studies (Genome Wide Association Studies) over the past 10 years have identified a few weak associations, thus refuting the "common diseases–common variants" hypothesis. A model implicating numerous rare variants has been supported by the recent discovery of CNVs (Copy Number Variants) and their statistically significant association with psychiatric disorders such as schizophrenia, bipolar disorders and autism.

The study of consanguineous families may contribute to identifying rare variants in homogenous populations who have conserved certain alleles. Major developments in molecular biology techniques would facilitate these studies as well as contributing to identifying major genes.

These results emphasize the need for genetic counseling in high-risk communities and the importance of implementing preventive actions and raising awareness concerning the risk of consanguineous unions.

Contents

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http://dx.doi.org/10.1016/j.ejmg.2015.12.010
1769-7212/

1. Introduction

Psychotic disorders represent rare diseases with a major social handicap. In most countries, the life prevalence of schizophrenia is around 1% (Jablensky, 1986) and bipolar disorders between 1 and 4% (Cerimele et al., 2014). A hypothesized underlying genetic basis for these disorders was first formulated about a century ago, beginning with Kraepelin and his students. Twin and adoption studies, as well as family studies involving relatives of mentally ill patients, confirmed the existence of a genetic component in mental disorders and provided risk estimations of vulnerability to psychotic disorders (Harrison and Weinberger, 2005). Over the last 10 years, molecular techniques examining the entire genome (GWAS or pan–genomic association studies) have found some genetic associations with major mental disorders such as schizophrenia, autism and bipolar disorders. However, most of these associations are weak, thus refuting the "common disease–common variants" hypothesis to favor a "common disease–rare variants" hypothesis. Genetic epidemiological studies within specific populations (consanguineous and/or geographically isolated groups) have shown increased infant morbidity and mortality, high frequencies of monogenic recessive disorders and increased numbers of common multifactorial disorders such as psychotic disorders (Bittles and Black, 2010; Tadmouri et al., 2009). These studies are in favor of a significant association between consanguinity and mental disorders. Thus, there exists an increased risk of mental disorders among the offspring of consanguineous couples (Bittles and Black, 2010).

The recent discovery of rare genetic variants, namely copy number variants (CNV), and their implications in psychotic disorders represents an argument in favor of the "common disease–rare variants" hypothesis (Bittles and Black, 2010). The study of consanguineous families may enable us to test associations between rare variants and certain phenotypes and eventually to establish genotype-phenotype associations. Such an approach requires prior knowledge of the demographic, ethnic and genetic composition of the studied populations to avoid stratification errors.

The objective of this paper is to provide an updated review of consanguinity studies in the world, the cultural and religious aspects of consanguinity and its implications in genetic-based disorders and specifically in psychotic disorders.

2. What is consanguinity?

Consanguinity is the relation between two people who share a common ancestor (Tadmouri et al., 2009). It is usually defined as the result of sexual reproduction between two related individuals. In other words, consanguineous unions are contracted between people who are biologically related. This concept has been formalized in genetics and has been largely used in population genetics where consanguinity also refers to groups of individuals with at least one common ancestor, living in isolated areas, in small communities or within tribes practicing endogamous unions. Modell et col. estimated that roughly 20% of the world's population lives in communities that prefer consanguineous unions (Modell and Darr, 2002).

It is generally thought that the human race evolved from a very small original *Homo sapiens* population (Liu et al., 2006; Zhivotovsky et al., 2003), inevitably leading to significant endogamy with multiple unions between relatives. This phenomenon has persisted following slow demographic growth of small scattered human groups due to infections, starvation or war (Bittles, 2003; Harpending et al., 1998; Ottenheimer, 1990; Tenesa et al., 2007). Later, consanguinity became a hallmark of rural societies especially in Sub-Saharan Africa and the Middle East. Ottenheimer notes that until the middle of the 19th century, in Europe and North America, unions between first- cousins were socially accepted, even favored in upper-class society (Bittles, 2003; Ottenheimer, 1990). Bittles highlights that today they are a source of prejudice and negative opinions(4).

3. Sociocultural and religious factors and geographical repartition

Current social representations of consanguinity mostly derive from religious recommendations. In the Old Testament, unions between first-cousins are discouraged (Dyer, 2005), whereas until the beginning of the 20th century, the Catholic Church allowed unions between cousins under certain circumstances (Cavalli-Sforza et al., 2013). Sephardic Jewish as well Buddhist communities continue to practice unions between first-cousins and Hinduism allows uncle–niece marriages. In Islam, unions between first-cousins are permitted whereas uncle–niece unions are considered to be incestuous unions and thus forbidden.

Based on available data from the "consang" web site (Consanguinity/Endogamy Resource) (Bittles) and Bittles's analyses (Bittles et al., 2000), it seems that couples couples with a second-cousin relation or closer represent 10.4% of the actual world population. Despite decreased overall prevalence of consanguineous unions in most countries, the actual consanguinity rate in certain regions is greater than in previous generations, perhaps reflecting an ageing adult population that in turn increases the number of unions between relatives (Bittles, 2008).

The highest rates of consanguinity in the world are found on the southern and eastern shores of the Mediterranean, throughout the Middle East, Mesopotamia, the Gulf Region, the Indian subcontinent and in South-East Asia(15). A large number of Muslim countries are found in this region, but contrary to popular beliefs, Islam does not encourage consanguinity. The preference for this type of marriage stems from a pre-Islamic tradition in favor of community ties and maintaining inherited property within families (Hussain and Bittles, 1999). However, some Islamic laws governing inheritance strengthen traditional tendencies toward consanguineous unions (Hamamy et al., 2007). Tadmouri et al. note that these unions are perceived as more stable with fewer divorces, improving family ties, reducing domestic violence and reinforcing social relations within the community (Tadmouri et al., 2009). They also estimate that in many of these regions, roughly 25% of all marriages concern first- cousins; these rates are also the consequence of endogamous practices (marrying only within the community). According to Al-Gazali, in the Arab world, consanguineous unions of first-cousins are even more common, up to 60% (Al-Gazali et al.,