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Review

Five Reasons why Inbreeding May Have Considerable Effect on Post-Reproductive Human Health

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A B S T R A C T

As the genetic architecture of common complex diseases of late onset is emerging through intensive research, it is intriguing to assess the predicted effect of inbreeding on those diseases. In this paper, we propose five reasons why we believe inbreeding may have a considerable effect on post-reproductive human health. (i) The joint effect of inbreeding depression on all polygenic quantitative phenotypes that confer risk for late-onset diseases is predicted to be multiplicative rather than additive. (ii) The »genetic load« of rare »Mendelian« variants with large deleterious effects in post-reproductive adults is unknown, but could be much greater than expected as these variants were invisible to selection through human history. (iii) Deleterious effects resulting from autozygosity in hundreds of affected rare recessive variants of small effect under common disease/rare variant (CD/RV) hypothesis could result in epistatic effects that could jointly impair capacity to compensate against environmental risks. (iv) Heterozygote advantage in loci under balancing selection could be reduced by inbreeding. (v) Published empirical evidence in animals and humans consistently report large inbreeding effects on late-onset traits. Since inbreeding is common in many populations and the effects of inbreeding depression could substantially contribute to disease burden and reduced life expectancy we believe there is now a clear need for further genetic epidemiological research in humans to investigate this issue.

***Key words**: inbreeding, consanguinity, late-onset diseases, complex diseases, post-reproductive age, inbreeding depression, genetic load, balancing selection, heterosis*

Introduction

In many parts of the developing World and in many communities within the developed World large proportions of all marriages are still among close relatives.

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The reasons for this include geographic, tribal, cultural or religious isolation or socio-economic motivation such as preservation of property, particularly land rights[1,2]. The degree of inbreeding in offspring of such marriages can be measured by the genetic term »inbreeding coefficient« (F), which indicates the proportion of the autosomal genome which is expected to be homozygous through inheritance of identical genes from common ancestors (i.e. proportion of alleles identical by descent (IBD) or »autozygosity«). The F value is calculated from genealogical information and it amounts to about 6% in the offspring of first cousin parents and 25% in the offspring of incestuous unions of first-degree relatives[1,3]. The apparent risk in the individuals with a considerable proportion of their genes homozygous for identical allelic variants is the occurrence of »Mendelian« (monogenic) diseases caused by rare and recessive deleterious autosomal mutations of large effect[4–9].

Research on the effects of inbreeding on human health has historically focused on early-onset diseases, mainly recessively inherited monogenic (Mendelian) diseases, birth defects, decreased fertility and early mortality. This was due to the widespread recognition that consanguineous unions were more likely to result in genetic diseases of children, most of which had a distinctive phenotype that was readily identifiable. Therefore, the great majority of research on inbreeding effects had been focused on pre-reproductive health problems, and the risks have been thoroughly evaluated by numerous groups and individual authors[3–12].

However, the genetic architecture underlying late-onset diseases such as cardiovascular diseases, cancer, adult-onset diabetes and psychiatric disorders, which represent the major health burden globally, is still a matter of open debate[13–18]. A genetic model that is finding increasing support from both animal experiments and human studies is one in which the genetic variants underlying complex chronic diseases are more likely to be rare rather than common in the population. They are also likely to be numerous (highly polygenic architecture) and of a small individual effect[13,18]. If this view of the genetic architecture of common complex diseases is correct then it would be important to consider the predicted effect of inbreeding. In this paper, we put forward and discuss five reasons why we believe inbreeding may have a considerable effect on post-reproductive human health.

Reason #1: The deleterious effects of inbreeding depression on quantitative (endo)phenotypes that confer risk for late-onset diseases may be multiplicative

Inbreeding depression is a recognised phenomenon that is common to polygenic traits in all living organisms[19]. It is thought to result from increased homozygosity of recessive alleles that act in the same direction at loci that influence the phenotype of interest (»directional dominance«)[20]. In an inbred individual, inbreeding depression is predicted to affect many polygenic endophenotypes (quantitative [patho]-physiological intermediates involved in physiological or disease processes). Many of these are established risk factors for late-onset diseases, such as blood pressure, body mass index, cholesterol and glucose levels and bone mineral density. A substantial effect of inbreeding acting to increase human blood pressure has been shown directly in at least four studies[21–24], and implied indirectly in several more studies[25–28]. Effects on body mass index and cholesterol levels have also been implied[25,26,28]. Similarly, effects on various measures of intelligence have been consistently shown[29–31], and in this issue we report on an effect on cortical index, a

predictor of susceptibility to osteoporosis[32]. It is known that the risk of e.g. increased blood pressure, body mass index and cholesterol levels on cardiovascular diseases is not threshold-dependent, but is increasing across the entire range of values observed in the population[33]. Thus, one important consequence is that inbred individuals are expected to be at slightly increased risk relative to the outbred general population to develop a late- onset disease, regardless of the absolute measurement of their blood pressure, body mass index and cholesterol. Furthermore, even if the effect of inbreeding depression on each of those phenotypes individually was rather small, it is known that the concurrent presence of several risk factors for the same disease increases risks in a multiplicative rather than additive manner. Therefore, the joint effect of inbreeding depression on all the potential quantitative phenotypes that confer risk to late-onset disease during lifetime could be more substantial than widely appreciated[34,35].

Reason #2:
Effects of inbreeding on rare variants with large effect in post-reproductive adults (»invisible Mendelian diseases« of late onset)

Inbreeding is predicted to have larger effects on the population-attributable fraction of disease if the underlying variants are rare rather than common. This is because common recessive variants will occasionally become homozygous in the population by chance, without a need for inbreeding to bring them together. If the variants are very rare in the population, and inbreeding is almost the only realistic scenario under which they can become homozygous in an individual, then the fraction of disease cases in the population who are the offspring of related parents will be much larger. This was shown to be the case with population attributable fraction of early-onset monogenic (Mendelian) diseases in the presence of inbreeding: it has been shown that the prevalence of autosomal dominant Mendelian disorders is constant in all world populations, but the prevalence of autosomal recessive Mendelian disorders is increased by 3–4-fold in regions where inbreeding is prevalent.[2,7] Therefore, the great majority of Mendelian disease that is caused by rare recessive variants of large effect and early age of onset is due to inbreeding in those countries. However, these diseases manifest in pre-reproductive period, so they are »visible« to selection. Although these variants continuously arise through mutations, most of the affected cases never reproduce, so they are being effectively removed from the gene pool by selection. Thus their overall public health burden is reasonably low, and Bittles and Neel estimated that each human carries about 1.4 such recessive lethal mutations in the genome[12].

However, rare variants of large effect also act in Mendelian fashion to cause late-onset complex diseases. For nearly all late--onset diseases, clustering in families has been reported and, in some, rare high- penetrance variants have been found which are associated with an extremely increased lifetime risk of disease[14–16]. Examples of this include variants in BRCA1 and BRCA2 and breast cancer[36], hMLH1 and hMSH and colorectal cancer[37], and GCK (glucokinase) and maturity-onset diabetes of the young (MODY) diabetes[38]. In large outbred populations, it is estimated that up to 15% of disease cases such as cardiovascular, cancer, diabetes and psychiatric disorders cluster in families, while 85% or more are due to combined effects of polygenic susceptibility and cumulative environmental exposures[39]. However, in countries where inbreeding is common, the prevalence of all recessively inherited monogenic forms of complex diseases could

be expected to increase by at least as much as seen jointly for all recessive early-onset Mendelian diseases, i.e. 3–4-fold. In theory, this could greatly increase both the overall disease prevalence and the proportion the late-onset disease burden caused by rare recessive variants.

It is also known that these rare variants can affect quantitative phenotypes, such as blood pressure or cholesterol (familial hypertension, familial hypercholesterolaemias)[25,40], which represent »invisible Mendelian diseases« as their phenotypes are not clinically apparent. These quantitative phenotypes are associated with increased morbidity and mortality from diseases of public health importance such as stroke and coronary heart disease. It is conceivable that there are many more such »invisible« Mendelian diseases affecting metabolic pathways at different levels and predisposing individuals to complex diseases in the post-reproductive period. The joint effect of inbreeding on all these variants could be expected to be of a magnitude of at least that seen for early-onset Mendelian diseases. Indeed there are reasons to believe that the number of rare and recessive Mendelian variants with large effect on late-onset complex diseases much larger than the estimated number with early effects. These rare variants have accumulated in the genome through mutations that are either neutral in early life, or even beneficial, but show deleterious effects in post-reproductive period (»antagonistic pleiotropy«)[34,35]. There is no known mechanism that would be expected to remove these mutations from the genome or act against their accumulation, as they are invisible to selection. Thus there are cogent reasons why the effects of inbreeding on late-onset Mendelian diseases should be carefully considered in the same way as has been done for early-onset diseases[12].

Reason #3:
Autozygosity in many rare recessive variants of small effect could result in epistatic effects that could jointly impair capacity to compensate against environmental risks.

Modest levels of inbreeding observed in human populations are expected to have much larger effects on the population distributions of polygenic traits than on oligogenic traits and diseases. This is because an excess in autozygosity of 6.25% of the genes in human genome (i.e. about 2,000 genes), which would be expected in a child from a first-cousin marriage, will lead to autozygosity of rare recessive mutations of small effect in those 2,000 genes. In a polygenic trait, it is expected that some of the genes that determine its expression would be affected even with only 6.25% of the genome autozygous. We have argued that the genetic component of late-onset diseases may be due principally to large numbers of rare variants in numerous genes – the common disease/rare variant (CD/RV) hypothesis.[13] Recent estimates[41] imply that each person carries, on average, 500–1200 slightly deleterious mutations, most of which are rare and present in heterozygous form. In an offspring of first-cousin marriage, 30–75 of these variants would be expected to become homozygous, with uncertain effects[42]. If the mutations are numerous and of small deleterious effect, their autozygosity throughout the genome might not lead to apparent syndromes of early onset, but may mildly impair the function of affected genes. As a result, the compensatory potential to oppose the harmful environmental stimuli would be non-specifically impaired. This impairment of homeostasis or repair capacity could lead to an earlier age at diagnosis of a late-onset complex disease. This is consistent with the model of these diseases arising over long periods of time, and becoming clini-

cally apparent when the compensatory potential is exhausted[19,35].

This theoretical mechanism is difficult to study in humans, but has been clearly demonstrated in animals, where a greater sensitivity of homeostatic mechanisms to inbreeding in later life has been suggested[19,35]. In an experiment with inbred and non-inbred mice strains, the two strains did not show large differences in survival when the animals were kept in the laboratories. However, when both groups were released into their natural habitat, the inbred mice strains had a dramatically reduced chance of survival in comparison to non-inbred group[43]. The effects of inbreeding are therefore thought to be much greater in natural populations (exposed to a less uniform and more challenging environment) than in those studied in laboratories.

Reason #4:
Heterozygote advantage in loci under balancing selection is expected to reduce by inbreeding

At some genomic loci, there may not be variants present in a population that are clearly deleterious, but the heterozygous genotype may be more favourable than either homozygous genotype. This effect is widely known as the »heterozygote advantage«, »hybrid vigour« or simply »heterosis«. The effects of heterosis usually act in an opposite way from those of inbreeding depression and they have been demonstrated in humans[44,45], and widely in animals and plants[46,47]. The type of selection that tends to maintain more than one allele in the population at intermediate frequencies, thus maximising the frequency of heterozygous genotypes in a population, is known as »balancing selection«[13]. It is clear that balancing selection probably has important role in shaping gene diversity in the genes that are important for defence against unknown and unpredictable environmental risks, such as infectious diseases[44]. Populations that are more genetically diverse are at less risk from diverse environmental threats (since it is more likely that someone would carry a rare protective variant)[48]. It is therefore likely that inbreeding leading to autozygosity in several hundred genes will affect some of these genomic loci under balancing selection, thus reducing the beneficial effects of heterosis in those individuals. This mechanism could be more important than generally thought, since recent evidence suggests that loci under balancing selection may be surprisingly common in the genome[49–52].

Reason #5:
Empirical evidence of inbreeding effects in humans and other organisms

The most extensive research into the effects of inbreeding in general, and particularly on genetic variation related to senescence has been carried out in *Drosophila spp*. A review of 25 years of this research has concluded that deleterious alleles generated by mutation and kept at low frequency by selection contribute between 33% and 67% of the genetic variation in a typical trait. This supports a polygenic model of genetic architecture of most phenotypes and suggests that the common disease / rare variant mechanism contributes to a substantial share of complex disease aetiology[20,53]. A recently published experiment in *Drosophila spp*[34] showed that genetic variation and inbreeding effects increase dramatically with age, supporting these hypotheses. Numerous recent studies of other animals, some of them performed in populations of large mammals, have also consistently reported that inbreeding negatively affected key components of fitness, resulting in increased morbidity and decreased life span[54–57]. A meta-analysis[58] and a critical

review and re-examination of these studies[51] have both concluded that, although unexpected and in some aspects against current understanding, their findings could not be easily dismissed on grounds of publication bias or apparent flaws in methodology.

Finally, our own intensive review of human literature since 1965 has managed to identify very few case-control studies of late-onset diseases in which inbreeding status was not determined by self-reporting, and disease status determination was based on a clear diagnostic criteria which did not change during the period of study. These studies investigated the effects of inbreeding on coronary heart disease[59,60], cancer[61,62], psychiatric disorders[63] and Alzheimer's disease[64]. There was only one longitudinal epidemiological study investigating the effects of inbreeding on 10 complex late-onset diseases[65]. All seven studies reported considerable relative risks associated with inbreeding, typically between 2.0–5.0, which persisted after adjustment for known or suspected confounding factors. Although the available evidence is surprisingly sparse, it appears to support the hypothesis that inbreeding could have a considerable effect on human health and disease occurrence in post-reproductive age adults.

Conclusion

We have argued that there is a coherent theoretical basis for a role for inbreeding in diseases of public health importance in humans. Available data from animal and plant studies strongly support the disease mechanisms put forward in this paper and suggest that these phenomena may be common across species. Available data on the effects of inbreeding in humans has focused on assessing the risk of early mortality due to rare recessive deleterious mutations. In an extensive review of inbreeding in the PubMed database from 1965 to date (nearly 10,000 references), we were able to find very few publications on inbreeding effects on late onset traits or diseases in humans. It is possible that this may be explained to some extent by the fact that in areas of the world where inbreeding is prevalent, late-onset diseases have not until recently represented the main public health problem (e.g. Mediterranean countries, parts of India and sub-Saharan Africa). In western societies, however, inbreeding is not prevalent enough to be studied in a large-scale epidemiological investigation. Nevertheless, we call for more genetic epidemiological research in humans to address this potential problem, and invite related papers from all regions of the world where this issue can be studied. We believe this to be an important epidemiological risk to evaluate, as with improving life expectancy in large human populations where inbreeding is prevalent these effects could substantially contribute to disease burden and life expectancy.

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PET RAZLOGA ZBOG KOJIH BI SRODIVANJE MOGLO ZNAČAJNO UTJECATI NA LJUDSKO ZDRAVLJE NAKON ZAVRŠETKA GENERATIVNOG RAZDOBLJA

S A Ž E T A K

Kako intenzivnim istraživanjima počinjemo nazirati genetsku arhitekturu kompleksnih bolesti starije dobi, zanimljivo je razmotriti kako bi srođivanje trebalo utjecati na pojavnost tih bolesti. U ovom članku, predlažemo pet razloga zašto bi srođivanje moglo imati znatan utjecaj na ljudsko zdravlje nakon završetka generativnog razdoblja. (i) Ukupan učinak »depresije srođivanjem« na sve poligenski određene kontinuirane ljudske fenotipove koji se povezuju s rizikom za bolesti starije dobi trebao bi biti multiplikativan, a ne aditivan. (ii) »Genetski teret« rijetkih (tzv. Mendelskih) alela s jakim negativnim učinkom na zdravlje u post-generacijskom razdoblju nije poznat, no mogao bi biti znatno veći od očekivanog jer su te varijante bile nevidljive utjecajima selekcije tijekom ljudske povijesti. (iii) Nepoželjni učinci kao rezultat autozigotnosti u stotinama zahvaćenih rijetkih recesivnih genetskih varijanti malog učinka u okviru hipoteze »česta bolest/rijetka varijanta«, gdje bi rezultirajući epistatski učinci mogli zajednički umanjiti sposobnost kompenziranja protiv okolišnih čimbenika rizika. (iv) Srođivanje bi moglo utjecati na gubitak povoljnih učinaka heterozigotnosti na lokusima koji su pod utjecajem balansirajuće selekcije. (v) Sistematski pregled rijetkih empirijskih dokaza u literaturi u eksperimentalnih životinja i ljudi konzistentno upućuje na snažne učinke srođivanja na svojstva karakteristična za stariju dob. Pozivamo na dodatna genetičko-epidemiološka istraživanja u ljudskim populacijama kako bi se ovaj problem istražio, jer rastom očekivanog trajanja života u velikim područjima svijeta gdje je srođivanje učestalo, navedeni bi učinci mogli značajno pridonijeti ukupnom pobolu i umiranju od bolesti starije dobi.