Association between runs of homozygosity and depression depends on religion

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Background

Long runs of homozygosity (ROHs; where identical haplotypes were inherited from each parent) are likely to be autozygous (stretches of the two homologous chromosomes within the same individual that are identical by descent). The Netherlands have long known a strict segregation in society based on religious affiliation, with religious groups having their own political parties, schools and universities, inducing isolation, decreasing mating options, and potentially increasing parental relatedness. Religion and mental health show complex associations, with both stress-buffering as well as depression-evoking effects of religious involvement (Braam et al 2004). Here, we investigated the association between autozygosity and religion, and whether such an association can confound associations between autozygosity and major depressive disorder (MDD).

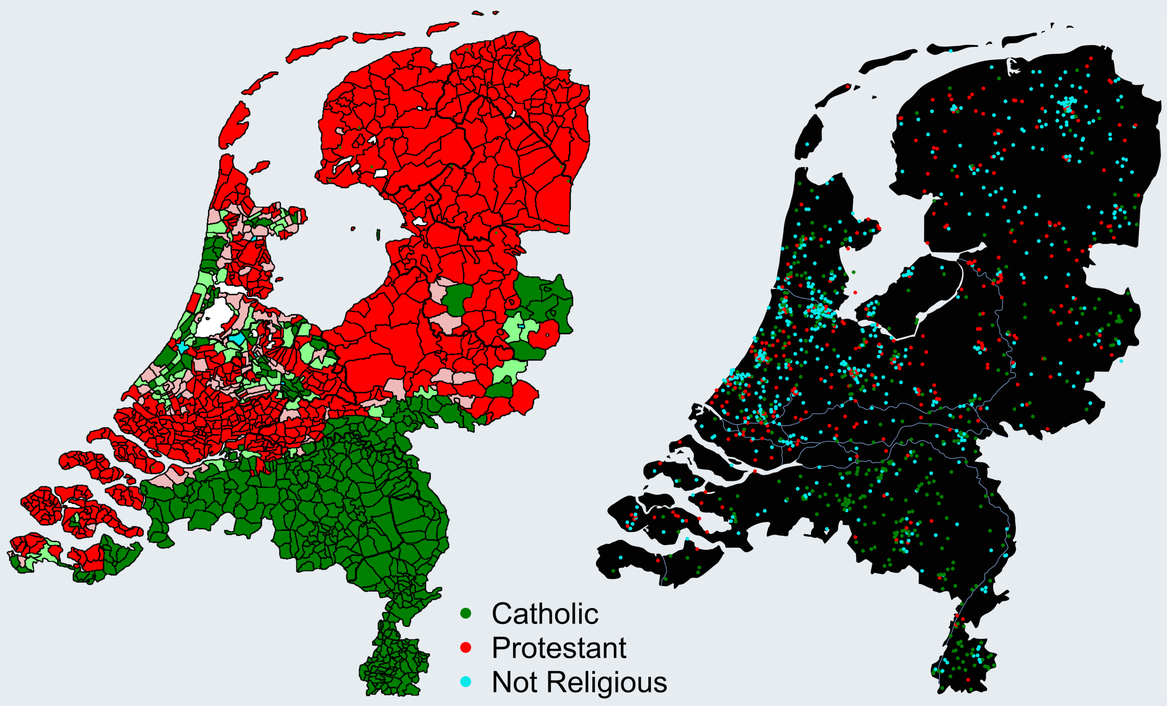
Methods

ROH was defined as ≥65 consecutive homozygous SNPs in an LD-pruned SNP-set (~130k SNPs). *Froh* (proportion of the autosome in ROH) was defined as: total length of all ROHs/2.77×10^9 (= total SNP-mappable autosomal distance). Outliers with respect to *Froh* were removed in order to exclude closer inbreeding ($Z > 1.96$, the 2.5% tail). Only unrelated subjects with Dutch ancestry were included.

Religion vs. autozygosity: The R^2 change was computed between multiple regressions on *Froh* with and without religious affiliation as an independent variable. Both regressions included: the three PCs reflecting ancestry (correlated significantly with geography: PC1=North-South PC, PC2=East-West PC, PC3=middle-band PC), and one variable reflecting whether the subject lives in a city with >100k inhabitants (coded as 0 & 1). To correct for the non-normal distribution of *Froh*, *Froh* was permuted 100,000 ×.

MDD vs. autozygosity: The R^2 change was computed between multiple regressions on *Froh* with and without MDD as independent variable (including the same covariates described in the previous paragraph, and also permuted 100,000 ×). This analysis was done once with, and once without religion as a covariate.

Figure: Distribution of Catholic, Protestant and not religious groups in the Netherlands in 1849 (left) and in the current dataset (right, where each dot represents a subject plotted on the current living address). The North-South distribution of Catholics and Protestants seen in previous generations is still maintained today, but with an overall increase (especially in the larger cities) of non-religious groups.



Religious group	N	*Mean Froh*
Catholic	799	.00131
Protestant	599	.00148
Not Religious	1727	.00116

Table 1: Significance test for the incremental change in R^2 when religion is added as an independent variable to a regression model with *Froh* as the dependent variable (permuted 100k times).

	Included in model	F (df)	R^2 change	Empirical *p*
Main test	Both religious groups and not religious group (as two dummy variables)	13.40 (2, 3118)	.008	**1×10^{-5}**
Post-hoc tests	Not religious vs. Catholic	20.89 (1, 2520)	.008	**$<1 \times 10^{-6}$**
	Not religious vs. Protestant	10.96 (1, 2320)	.004	**.001**
	Catholic vs. Protestant	.005 (1, 1392)	<.001	.942

Significance threshold for post-hoc = .05/3 = 0.0167. Bold = significant.

Results

In subjects from NTR and NESDA MDD was negatively associated with religion (*religious = less MDD*).

Religion vs. autozygosity: Significantly more variance in *Froh* was explained when including religion in a multiple regression analysis. Post-hoc analyses showed that this was due to the significant difference between the non-religious group and the two religious groups (Table 1).

MDD vs. autozygosity: When including MDD as an independent variable in the multiple regression, significantly more variance is explained than without MDD as a covariate ($p = .041$). When repeating this analysis with religion as a covariate as well, the effect disappears ($p = .165$).

Conclusions

Religious assortment is likely to have resulted in elevated levels of background parental relatedness, and this is detectable through ROHs. When investigating the effects of inbreeding on mental health, it is important to consider factors that might confound such associations.

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