Clustering of neuropsychiatric disease in first-degree and second-degree relatives of patients with amyotrophic lateral sclerosis

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Title: Aggregation of Neuropsychiatric Disease in Amyotrophic Lateral Sclerosis Kindreds: Evidence of Clustering within Families**. Running head:** Clustering of neuropsychiatric disease in ALS.

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Key points

Question: This study examines the incidence of neuropsychiatric conditions within ALS kindreds.

Findings: This population-based, case–control family aggregation study confirms our previous epidemiologic observations of an association between ALS and schizophrenia in Irish kindreds. In addition, a significant family history of suicide, autism and alcohol overuse was reported in ALS kindreds compared to controls.

Meaning: There are significant differences in the incidence of several neuropsychiatric conditions in ALS kindreds compared to controls which is not accounted for by the *C9orf72* expansion.

Abstract

Importance ALS is a progressive neurodegenerative condition primarily involving the motor system. There is increasing epidemiological evidence of an association between ALS and a wider spectrum of neurodegenerative and neuropsychiatric disorders among family members, including schizophrenia / psychotic illness and suicidal behaviour.

Objective To examine the frequency and range of neuropsychiatric conditions that occur within individual ALS kindreds.

Design and Setting A population-based, case–control family aggregation study was designed. All patients included in the Irish ALS Register between January 2012 and January 2014 with definite, probable, or possible ALS by El Escorial criteria were invited to participate.

Participants All incident patients in the Irish ALS Register between January 2012 and January 2014 with definite, probable, or possible ALS by El Escorial criteria were invited to participate (n=202). 75 patients were unable or refused to participate and were excluded. 127 incident ALS patients genotyped for the *C9orf72* repeat expansion, and 132 age and gender matched controls were included in the study.

Main Outcome and Measures The prevalence of defined neuropsychiatric disease in first and second degree relatives of ALS patients and matched controls was determined.

Results Mean age at diagnosis was 64.2, 58% of patients were female. Reported data from 2116 relatives of patients with ALS included 924 first-degree relatives and 1128 second-degree relatives. Data from controls comprised 829 first- and 1310 second- degree relatives. 78 (61%) of ALS kindreds and 51 (39%) of control kindreds reported at least one first or second degree relatives with a history of schizophrenia, psychosis, suicide, depression, alcoholism or autism (RR1.5, 95% CI 1.08-2.17, P=0.017,). Cluster analysis suggested two subgroups based on the number of family members with a neuropsychiatric condition: Expected (0-2) and High (≥3). Within the high sub-group, ALS kindreds (71%) presented a significantly higher than controls ((71% ALS; X=4.29±1.41; p=.001). A strong family history of schizophrenia (RR 3.4, 95% CI1.27-9.3, P=0.015), suicide (RR 3.3, 95% CI 1.07-10.05, p=0.037), autism (RR 10.1, 95% CI 1.3-78.8, p=0.027) and alcohol overuse (RR 1.48, 95% CI 1.01-2.17, p=0.04) was reported in ALS kindreds. 17% of probands with a strong family history of neuropsychiatric conditions (>3 first or second degree relative) carried the *C9orf72* repeat expansion.

Conclusions and relevance Neuropsychiatric symptoms in addition to schizophrenia, including obsessive compulsive disorder, autism and alcoholism occur more frequently in

ALS kindreds than controls. The presence of the *C9orf72* expansion does not fully account for this, suggesting the presence of additional pleiotropic genes associated with both ALS and neuropsychiatric disease in the Irish population.

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative condition primarily involving the motor system. Recent deep phenotyping studies have provided compelling evidence of phenotypic heterogeneity, suggesting that ALS is a disease spectrum rather than a single entity. Though originally considered a pure motor system degeneration, the spectrum has expanded to include extra-motor involvement in sub-cohorts of ALS patients, including the presence of behavioural variant frontotemporal dementia (bvFTD) in up to 13% at the time of diagnosis[1], with known executive dysfunction, behavioural and social cognitive change in up to 70% of cases. The phenotypic heterogeneity in bvFTD and ALS can be attributed in part to pathogenic mechanisms associated with the presence of a hexanucleotide expansion in *C9orf72,* which accounts for up to 10% ALS and up to 30% of FTD in European populations. We, and others, have shown that this variant can also be associated with a range of neurological and neuropsychiatric phenotypes including bvFTD, psychosis, Huntington disease phenocopies, obsessive-compulsive disorder and bipolar affective disorder[2-5].

Using a population-based case control cohort study, we previously demonstrated increased aggregation of schizophrenia / psychotic illness and suicidal behaviour in ALS cohorts[6]. While this was associated with the presence of the *C9orf72* variant in ALS probands, in some cases, higher rates of psychosis and suicidal behaviour were also noted in relatives of probands who did not carry the *C9orf72* repeat expansion. It remains unclear as to whether this overlap with neuropsychiatric conditions is mediated by other pleiotropic genes of major effect within individual kindreds, or occurs as a consequence of shared polygenic risk

across the entire ALS spectrum. In favour of the latter, we have recently reported 14% shared polygenic risk between ALS and Schizophrenia using summary statistics from a combined ALS/Schizophrenia GWAS analysis[7]. However, we, and others, have also demonstrated that the genetic architecture of ALS seems to differ from schizophrenia, and that rare variants and private mutations are likely to account for a higher proportion of ALS, providing an explanation for the "missing heritability" in ALS [8-10]. An additional explanation for missing heritability is the likely presence of genetic pleiotropy, in which a pathogenic gene variant is associated with more than one phenotypic expression within a kindred. In this instance, the presence of ALS within a kindred would be interpreted as either sporadic or familial with incomplete penetrance, as the definition of familial disease purely based on a recurrence of ALS within the pedigree would be excessively narrow.

The purpose of this study was to explore the possibility of genetic pleiotropy within ALS kindreds using a case control design. We have expanded our previous familial aggregation study of ALS kindreds[6] by examining a second incident based cohort of patients with ALS to determine the extent to which other DSM-IV axis I and II disorders might occur in individual family members of patients with ALS. The objective was (1) to establish whether these traits are distributed uniformly across all ALS kindreds and (2) whether they segregate within individual kindreds suggesting the presence of single/oligogenic pleiotropic gene variants.

Methods

A population-based, case–control family aggregation study was designed. All patients included in the Irish ALS Register between January 2012 and January 2014 with definite, probable, or possible ALS by El Escorial criteria were invited to participate.

For each patient, an age- and gender-matched control was recruited at random from the records of the patient's general practitioner, or if this proved impossible, from the records of a general practitioner in the same area. The presence or absence of neuropsychiatric disease did not form part of the recruitment criteria. The family history questionnaire was administered only after proband recruitment.

Written consent for the study was obtained from ALS patients and matched controls. The study was approved by Beaumont Hospital Research Ethics Committee.

Data Collection

ALS probands and matched controls were asked to complete a family history questionnaire in which details of neurological and neuropsychiatric conditions reported by all first and second degree relatives were ascertained. This was followed by a semi-structured interview with the proband or another family member, where possible. This semi-structured interview ensured accuracy of the material recorded on the questionnaire, and addressed missing data where possible. An identical methodology was used for patients and controls. Details included questions about medical conditions in parents, siblings and children (first degree relatives) and grandparents, uncles, and aunts (second degree relatives), aged over 18 years. All respondents were asked specifically about the occurrence among their immediate relatives of psychiatric conditions (defined by DSM-IV at the time of this study's inception) including major psychotic illness (schizophrenia, bipolar disorder), suicide, autism or autistic spectrum disorder, obsessive compulsive disorder, addiction and alcohol dependence.

C9orf72 Genotyping

DNA samples were screened using repeat-primed PCR for the presence of a GGGGCC

hexanucleotide repeat expansion in *C9orf72*. Representative DNA from positive and negative controls was also analysed by Southern blot to confirm the sensitivity and specificity of the analysis. PCR products were analyzed on an Applied Biosystems 3130xl genetic analyzer and visualized using GeneMapper software (version 4.0). Patients with the characteristic appearance of the expanded hexanucleotide repeat on repeat-primed PCR consisting of a decaying series of 30 or more peaks in duplicate were regarded as having a pathologic expansion as described previously[11].

Statistical Analysis

Baseline characteristics were tested for difference using the chi-square test for independence. The relative risk (lambda), used in the majority of previously reported family aggregation studies, was calculated by comparing the risk of developing a disease in the relatives of ALS patients, compared to the risk in relatives of controls. K-means clustering was employed as a non-hierarchical method to quantify the presence of psychiatric diagnoses. Chi-square compared the distribution of ALS kindred to healthy control within the k-means clusters. Statistical analysis was carried out using SPSS v24 (SPSS Inc, Chicago, IL). All statistical testing was performed at the conventional 2-tailed a level of 0.05.

Results

127 incident ALS patients, diagnosed between 2012-2014, who agreed to complete the questionnaire on family history, were included in the study. There were no significant differences in age of diagnosis, gender, site of onset, or the proportion reporting a positive family history of ALS between this cohort and our previously cohort of 172 ALS patients[6]. In

addition, there were no significant differences in gender, El Escorial criteria at first assessment, site of onset, or the proportion reporting a positive family history between those who agreed to inclusion in the study and were able to provide a comprehensive family history compared to those who either declined inclusion or were unable to complete a family history (Table 1). As in a previous study[6] patients who declined to participate, or who were included in the study were significantly older at symptom onset and diagnosis.

Reported data from 2116 relatives of patients with ALS included 924 first-degree relatives and 1128 second-degree relatives. Data from controls comprised 829 first- and 1310 second- degree relatives. There was no statistical difference between the kindreds of ALS probands and controls with respect to the number of first and second degree relatives. Our previously observed increased risk of neuropsychiatric disorders including schizophrenia / psychotic illness, and suicide observed in first and second degree relatives of patients with ALS compared to relatives of controls was replicated (Table 2). Specifically, the relative risk of developing schizophrenia or other psychotic illness among first and second degree relatives of ALS probands compared with control was 3.4, p= 0.015, while the relative risk of death by suicide in first- or second-degree relatives of ALS probands was 3.3, p=0.037.

The reported frequency of OCD, personality disorders, addiction and alcoholism and autistic spectrum disorders) was also assessed in patients and controls. DSM criteria for each of these conditions was applied by the interviewer, and only those cases reporting to fulfil the criteria, or in whom a confirmed psychiatric diagnosis could be verified were included. Higher rates of autism, alcohol dependence and other conditions associated with personality rigidity (obsessive compulsive disorder, and personality disorder) were reported

196 in the kindreds of ALS probands compared with controls (Table 2).

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198

199 *Clustering of neuropsychiatric disease in ALS within kindreds.*

200 Of the 127 ALS probands, 77 (61%) had at least one sibling, parent, uncle, aunt or adult child
201 with a history of schizophrenia / psychosis / suicide / depression / alcoholism / autism /
202 other neuropsychiatric condition, compared with 51 (39%) of controls. K-means clustering
203 identified two distinct subgroups within the data. These subgroups have been defined as an
204 *expected rate*: 0-2 affected family members (45% ALS; *X*= 0.58±0.711; Min= 0; Max =2) and a
205 *high rate* of psychiatric illness: ≥3 affected family members (71% ALS; *X*=4.29±1.41; Min=3;
206 Max=7). Within the high rate of psychiatric illness group, ALS kindreds represented a
207 significantly higher rate when compared to health control kindreds (p=.001). This significant
208 clustering of neuropsychiatric disease within the kindreds of ALS probands was independent
209 of kindred size, and there was no significant difference between ALS probands and controls
210 in this regard. ALS probands with higher reported rates of neuropsychiatric disease reported
211 a mean number of 16 (range 6-32) first and second degree relatives, whereas controls
212 reported a mean of 21 (range 15-27) first and second degree relatives.

213

214 *Neuropsychiatric disease and C9orf72 status*

215 *C9orf72* genotyping was available in 111 of the 127 ALS patients (87%). Of these, 19% (21) of
216 probands carried the repeat expansion, while 81% (90) had a normal *C9orf72* repeat
217 expansion profile. A history of dementia affecting at least one other family member was
218 reported in 100% of kindreds of probands carrying the *C9orf72* expansion. This contrasted
219 with kindreds of ALS probands who were negative for the repeat expansion, in whom 27.5%

(33) reported a diagnosis of dementia in FDRs and SDRs and in controls, where 10% reported the presence of dementia in FDRs and SDRs.

The majority of *C9orf72* positive ALS kindreds (19 of 21, 90%) also reported at least one family member with a history of neuropsychiatric disease. The commonest neuropsychiatric conditions associated with *C9orf72* included depression and alcoholism. However, of the 29 kindreds reporting more than 3 first or second degree relatives with a neuropsychiatric condition, only 17% (6) of the ALS probands carried the expanded genotype. The remaining 23 (83%) of ALS probands did not carry any of the known pathogenic gene variants.

Discussion

This study confirms our previous epidemiologic observations of an association between ALS and schizophrenia in Irish kindreds, and extends the finding to other neuropsychiatric conditions characterized by impulse dyscontrol, addiction, alcoholism and rigid / autism spectrum disorder, as defined by DSM-IV. Our data support the hypothesis that family members of ALS probands are more likely to exhibit a neuropsychiatric endophenotype that recapitulates in part the extra motor changes reported in ALS.

We have shown than 58% of ALS probands reported at least one relative with a history of schizophrenia, psychosis, suicide, depression, alcohol dependence or autism, compared with 39% of control kindreds ($p=0.002$). While neuropsychiatric conditions are common within the general population as demonstrated by their presence within our control cohort, our data clearly suggest that kindreds of ALS probands are enriched for these disorders. Of the participants who clustered in the high rate of familial psychiatric illness (≥3 family members

with psychiatric illness), over 70% were ALS patients (p=.001), with the same mean number of relatives. Major psychiatric disorders that were specifically over-represented within these ALS kindreds included schizophrenia / psychosis (p=0.015), suicide (p=0.037), autism (p=0.027), rigid personality disorders (p=0.02) and alcohol overuse (p=0.045).

In patients with progressive neruodegenerative disease, the impact of psychological stressors on the caregivers and wider family network is well recognised. A higher than expected rate of neuropsychiatric disease in ALS kindreds may well be anticipated as simply a function of disease-induced stress on the family. However, this study was specifically designed to address this point as we identified those with neuropsychiatric symptoms that had been present prior to any knowledge of ALS within kindreds, in which case the diagnosis would be expected to have no impact on neuropsychiatric presentations within extended kindreds. Moreover, the absence of evidence of increased rates of depression, which would be anticipated were the presence of ALS a factor, suggests that the findings are not related to the presence of ALS within kindreds.

Our findings suggest the presence of the *C9orf72* repeat expansions does not fully account for the observed overlap between ALS and neuropsychiatric conditions. While 17% of probands from kindreds reporting high rates of neuropsychiatric conditions (>3 affected relatives) carried the *C9orf72* repeat expansion, the remaining 83% of probands carried the normal variant.

Consistent with our previous study, there was no reported difference in the presence of risk

of underlying depression in the kindreds of the ALS probands compared with controls. Given that depression is common within the general population and might be expected to be over-represented in ALS kindreds due to a bias in reporting, this finding supports the robustness of our finding of a relationship between specific neuropsychiatric conditions and ALS.

Indeed, the absence of an association between depression and ALS, despite the presence of higher rates of reported suicide among first and second degree relatives of ALS probands may reflect an underlying dysregulation of impulse control, rather than a specific alteration in mood. While further prospective family studies are required to confirm, the dichotomization of depression and suicide was also noted in our previous study[6]. This observation is congruent with the emerging concept of network disruption in ALS leading to a range of behavioural changes including increasing disinhibition, impulse dyscontrol, and in some cases increased personality rigidity[13-16].

This study was unable to demonstrate a significant association between behavioural change in ALS probands and the presence of a psychiatric endophenotype among first and second degree relatives. This was most likely due to the low power of our study, and the relative insensitivity of the employed behavioural screening tools.

Our study is limited by design. The neuropsychiatric signal among first and second degree relatives was obtained by report rather than by direct examination of family members, and verification was limited to a series of confirmatory questions by the interviewer. Verification

questions included clarification that the diagnosis had been made by a suitably qualified medical practitioner. It is therefore possible that some of the diagnostic categorization is incomplete. However, this limitation applied to ALS kindreds from probands with and without the *C9orf72* repeat expansion and controls equally, and is therefore unlikely to have substantially biased our findings. Secondly, it is possible that ALS probands over-reported the presence of psychiatric disorders. We consider this to be unlikely, as a possible association between ALS and neuropsychiatric conditions is not commonly known to the majority of ALS probands. Moreover, the absence of a significant increase in depression among family members supports the veracity of our findings. Our study cohort was slightly enriched by kindreds of probands carrying the *C9orf72* repeat expansion – this is likely an artifact of our collection method, as some families carrying the *C9orf72* expansion have knowledge of ALS, and more likely to agree to participate in this type of study. Notwithstanding, our study confirms our previous observation of higher rates of neuropsychiatric conditions within ALS kindreds. We have shown that this aggregation is driven primarily by kindreds enriched for particular neuropsychiatric conditions that recapitulate the cognitive and behavioural subphenotypes described in ALS, and that this effect is not primarily driven by the presence of the *C9orf72* expansion. Detailed suphenotyping and genotyping of members of informative kindreds from ALS probands will be required to further characterize this association which, if replicated, suggests the presence of a distinct subphenotype of ALS that shares pleiotropic genetic risk with some forms of neuropsychiatric illness.

K-means clustering was chosen as the process is a two-phase iterative heuristic, with data assignment, and centroid updating staggered successively[17,18]. K-means is a partitional

technique used to find clusters, whereby the clusters are represented by their centroids, e.g., the arithmetic means of data points within the respective clusters. The statistical convergence of these iterations, which are integral for clusters to be identified, further increased the integrity and robustness of these analyses alongside the close matched case and control cohorts.

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Authorship

M.O.B. assisted with study design, collected family data, carried out the statistical analysis, and wrote the manuscript. M.H. provided input with study design and collected family history data. A.V. provided input with study design and collected family history data, R.M. analysed genetic data, J.G. collected family data, S.B. designed the original study and questionnaires used, M.P.G. performed neurocognitive testing and analysed cognitive data, T.B. performed neurocognitive testing and analysed cognitive data, M.E. N.P. analyzed cognitive data, and contributed to writing the manuscript. O.H. was the principal investigator of this research, designed the study, wrote and edited the manuscript.

Potential Conflicts of Interest

The authors report no conflicts of interest.

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Characteristic	Not Included in Study (n=75)	Included in Study (n=127)	*P* value
Mean age onset, yr (SD)	67.2 (10.1)	62.8 (10.2)	0.004
Mean age diagnosis, yr (SD)	68.1 (10.1)	64.2 (10.7)	0.033
Sex, No. female (%)	30 (40%)	58 (45.6%)	0.47
Site onset, No. (%)	Bulbar, 30 (40); Limb 38 (50.7); other 7, (9.3)	Bulbar, 35 (27.5); Limb, 81 (63.7); other, 11 (9)	0.15
C9orf72 repeat status	Positive, 6 (8%); Negative, 35 (46.7%); Not available, 34 (45.3%).	Positive, 21 (16.5%); Negative, 90 (70.9%); Not available, 16 (12.6%).	0.64

389

390 Table 1. Comparison of the Demographic details of ALS patients included in the study and
391 those not included.

Disease	Relatives of Cases, n=2116	Relatives of Controls, n= 2139	Risk Ratio	*P*
Suicide	13	4	3.3	0.037
Schizophrenia / psychotic illness	17	5	3.4	0.015
Autism	10	1	10.1	0.027
Depression	35	31	1.14	0.59
Alcoholism	63	43	1.48	0.045
OCD and Rigid Personality Disorders	11	2	5.6	0.02

Table 2. Prevalence and relative risk of neuropsychiatric conditions in first and second degree relatives of ALS patients compared to controls relatives. ‘

Number of affected individuals per kindred	ALS Kindreds (n=127)	Control Kindreds (n=132)
0	50	81
1	32	31
2	16	14
3 or more	29	6

Table 3. Clustering of neuropsychiatric conditions in kindreds of patients with ALS compared to those of controls.