Background: An expanded hexanucleotide repeat in the C9ORF72 gene has recently been identified as a major cause of familial frontotemporal lobar degeneration (FTLD) and motor neuron disease. Here we present a detailed analysis of the epidemiological, clinical, neuroimaging and histopathological features of a C9ORF72 mutation case series in relation to other forms of genetically determined frontotemporal lobar degeneration ascertained at a specialist centre. Methods: The UCL FTLD DNA cohort (n = 223 probands) was screened for the C9ORF72 mutation. Eighteen probands (19 cases in total) were identified, representing 35% of FTLD cases with identified mutations. A retrospective review of case notes was carried out extracting clinical features, disease duration, and family history. Biomarker data was also obtained for analysis including volumetric and tractographic MR imaging. Longitudinal data was obtained where available. Detailed histopathological assessment was carried out on six cases with the C9ORF72 mutation. Results: Families showed wide variation in clinical onset (43-68 years) and duration (1.7-22 years). Behavioral variant frontotemporal dementia was the commonest clinical syndrome. 60% of cases developed clinical features consistent with motor neuron disease during the period of follow-up. Anxiety, agitation and memory impairment were prominent features (between a half to two-thirds of cases), and dominant parietal dysfunction was also frequent. 33% of those with C9ORF72 had no identified relevant family history. MRI findings were highly variable. The group as a whole showed extensive thinning of frontal, temporal and parietal cortices, subcortical grey matter atrophy including thalamus and cerebellum, and involvement of long intrahemispheric, commissural and corticospinal tracts. Neuropathological examination identified histomorphological features consistent with either type A or B TDP-43 deposition; however, p62 positive (in excess of TDP-43 positive) neuronal inclusions were not seen in this group.

## Table 1

| Case | Final Diagnosis | AAO (Y) | Dur (Y) | Han d | Early symptoms | Neuropsychology profile |
|------|-----------------|--------|--------|-------|----------------|-----------------------|
| 1    | bvFTD 51        | 6.0    | R      | 5     | Anxiety, disinhibition, episodic memory impairment, speech dysarthric | 80 89 <5 <1 50-75 <1 >5 ++ Norm |
| 2    | bvFTD 60        | 7.0    | R      | 6     | Anxiety, delusions, disinhibition, episodic memory impairment, hyperorality | 100 113 5-10 <5 95 <50 >5 ++ Norm |
| 3    | bvFTD 56        | 8.0    | R      | 5     | Anxiety, empathy loss, obsessionality, prosopagnosia | 82 77 <5 10-25 <5 5-10 >5 ++ Norm |
| 4    | FTD-MND 55      | 7.7    | L      | 5     | Disinhibition, obsessionality, speech effortful, weakness upper limbs | 71 75 <5 <5 <5 >5 ++ Norm |
| 5    | bvFTD 45        | 8.4    | R      | 6     | Disorganisation, episodic memory impairment, obsessationality | 87 78 <5 <5 5-10 >5 ++ Imp |
| 6    | bvFTD 55        | 16.6   | R      | 7     | Disorganisation, empathy loss, episodic memory impairment, prosopagnosia | 103 95 50-75 <1 75 25-50 >5 ++ Norm |
| 7    | bvFTD 43        | 1.7    | R      | 8     | Anxiety, apathy, disinhibition, prosopagnosia, topographical memory impairment | UT UT UT 5 <5 >5 ++ Norm |
| 8    | FTD-MND 64      | 5.4    | L      | 9     | Apathy, delusions, prosopagnosia, speech effortful, topographical memory impairment | 84 82 5-10 <1 <5 <5 >5 ++ Norm |
| 9    | FTD-MND 54      | 5.0    | R      | 10    | Depression, disinhibition, speech effortful, weakness limbs | 69 80 5-10 1.5 10-25 <5 >5 ++ Imp |
| 11   | bvFTD 58        | 8.0    | R      | 11    | Anxiety, disinhibition, hyperorality, topographical memory impairment | 85 69 10-25 50-75 10-25 <5 >5 +++ Imp |
| 12   | bvFTD 61        | 5.7    | R      | 12    | Episodic memory impairment, hyperorality, falls, somatic symptoms, weakness limbs | 78 76 <1 <1 <5 10-25 >5 +++ Imp |
| 13   | bvFTD 68        | 7.1    | R      | 13    | Anxiety, episodic and topographical memory impairment, speech dysarthric | 73 78 <5 <5 10-25 10-25 >5 ++ Imp |
| 14   | bvFTD 53        | 14.8   | R      | 14    | Anxiety, disinhibition, episodic memory impairment, prosopagnosia | UT UT <5 <5 <1 UT >5 ++ Imp |
| 15   | PNFA 55         | 5.0    | R      | 15    | Comprehension impairment, disinhibition, speech effortful | 55 70 25-50 <1 <5 <1 >5 +++ Norm |
| 16   | bvFTD 46        | 22.0   | R      | 16    | Anxiety, disorganisation, episodic memory impairment, obsessionality, prosopagnosia | 116 113 75-95 50-75 75-90 >90 >5 ++ Norm |

Individual clinical and neuropsychological data available for C9ORF72 cases (16 of 19 cases). *Percentile scores are shown. ++/+++ = defective performance on at least one/two/three tests of executive function (Weigl sorting test; Wisconsin Card Sorting Test; STROOP colour interference; Verbal Fluency). \(^\dagger\)Current duration for living cases. Blank cells indicate testing not performed. AAO = Age at onset; Calc = Calculation; Dur = Total/current disease duration; Exec = Executive functions; GNT = Graded Naming Test; Hand = handedness data available; Norm = Normal; Imp = Impaired; Percep = Perception; PIQ = Performance IQ; RMTF/W = Recognition Memory test for faces / words; UT = untestable; VIQ = Verbal IQ.
cytoplasmic inclusions in hippocampus and cerebellum were a consistent feature of these cases, in contrast to the similar frequency of p62 and TDP-43 deposition in 53 control cases with FTLD-TDP. **Conclusions:** These findings corroborate the clinical importance of the C9ORF72 mutation in FTLD, delineate phenotypic and neuropathological features that could help to guide genetic testing, and suggest hypotheses for elucidating the neurobiology of a culprit subcortical network.

**O1-05-02** | FTLD REPEAT EXPANSIONS IN C9ORF72: EVIDENCE FOR VARIABILITY IN THE REPEAT SEQUENCE
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**Background:** Repeat expansion mutations of an intronic GGGGCC hexanucleotide repeat in C9orf72 have recently been shown to be a major cause of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). These expansions can routinely be detected using a repeat-primed PCR assay but southern blotting is needed to measure the exact size of the mutation as these can consist of up to 1500 repeats, whereas up to 23 repeats are seen in controls. Analysis of 392 cases of the Manchester FTLD cohort detected expansions in ~8% of all cases. Screening of a small family with type A TDP-43 pathology and FTLD+ALS but also with the cerebellar pathology, which is thought to be specific to cases with the expansion, failed to detect an obvious expansion with the PCR assay. However, there was a suggestion of a very low signal of up to 30 repeats. We, therefore, investigated this family further to establish if a repeat expansion was present or not. **Methods:** We extracted genomic DNA from brain and performed a southern blot of C9orf72. In addition we sequenced the primer binding site for the repeat-primed PCR to look for variation. **Results:** We detected an expansion of approximately 17kb in this family using southern blotting and the primer binding sequence for the PCR assay was normal. **Conclusions:** We have confirmed the presence of a mutation expansion in a family with FTLD+ALS using southern blotting. However, the repeat-primed PCR assay appears to be very inefficient in detecting this, unlike other expansions in our cohort. One explanation for this is the presence of a SNP on the mutant allele affecting the binding of the anchor primer, however, we ruled this possibility out using sequencing. Therefore, the only explanation for the low efficiency of this assay in this case is that the repeat-primed primer specific to GGGGCC is not annealing well. This suggests there is a difference in the repeat sequence i.e. it is not GGGGCC. This change in repeat sequence may also explain why the pathology in this family is of type A when type B is normally seen in cases with the GGGGCC expansion.

**O1-05-03** | NEURONAL EFFECTS OF PROGRANULIN DEFICIENCY CONTRIBUTE TO FRONTOTEMPORAL DEMENTIA INDEPENDENT OF NEUROINFLAMMATION
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**Background:** Frontotemporal dementia (FTD) is a fatal neurodegenerative disease characterized by changes in social and emotional behavior. The disease can be caused by mutations in GRN that result in haploinsufficiency of the neuronal and microglial protein progranulin. Recent findings using Grn-/- mice have directed attention to progranulin’s function in microglia and its contribution to neuroinflammation. Grn-/- mice have FTD-related behavioral deficits and gliosis similar to the human disease, however they do not model progranulin haploinsufficiency. We sought to determine the relative effects of progranulin insufficiency on neurons and microglia in mouse models. **Methods:** In this study we tested the behavior, physiology, neuropathology, inflammatory mediators, and neuronal morphology in Grn+/+/- mice at different ages to investigate the relationship between neuroinflammation and neuronal dysfunction in FTD. **Results:** Grn-/- mice displayed FTD-related behavioral deficits, similar to Grn+/+/- mice, without neuroinflammation. We found reduced social behavior in Grn+/+/- and Grn-/- mice using the three-chamber sociability test. This social deficit was constant between multiple cohorts on two separate genetic backgrounds and appeared to be age-dependent, with deficits emerging after 4 months. In addition to the three-chamber test, we observed abnormal social behavior in Grn+/+/- mice using the tube test of social dominance. We also found emotional impairments in Grn+/+/- and Grn-/- mice, evident by decreased freezing in a classical fear-condition paradigm. Whereas social/emotion impairment was clear, we found no hippocampal-dependent behavioral or electrophysiological impairment in Grn-/- mice. This is consistent with the relative preservation of other cognitive domains early in FTD. Gliosis and increased TNF-I ± mRNA levels were not observed in Grn-/- mice, unlike Grn+/+/- mice, demonstrating a dissociation of neuroinflammation and neuronal dysfunction. Therefore, we analyzed neuronal morphology and found that Grn+/+/- mice, as well as Grn-/- mice, displayed abnormal dendritic architecture in the amygdala, a region that controls social/emotional behavior and is implicated in FTD. **Conclusions:** Our results demonstrate that neuroinflammation and microglial involvement are not a driving force in FTD due to progranulin haploinsufficiency and suggest a vital role for progranulin in neurons. Also, Grn+/+/- mice are a useful tool in studying the behavioral deficits in FTD.

**O1-05-04** | PROGRESSIVE NEURODEGENERATIVE APHASIAS TARGET DISTINCT NODES OF THE LANGUAGE NETWORKS
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**Background:** Primary Progressive Aphasia (PPA) has been hypothesized to target distinct nodes of the dominant-hemispheric perisylvian language network. We sought to test this hypothesis using contemporary structural and functional neuroimaging techniques. We further sought to test the hypothesis that the topography of normal language networks predicts progression of atrophy in PPA. **Methods:** Two types of MRI data were used: structural MRI scans from PPA patients (generating cortical thickness measures) and functional MRI scans from normal adults (generating network-connectivity measures). Seeds for functional connectivity analysis were derived from regions of focal cortical thinning generated from PPA patient data, as well as coordinates of regions previously known to be activated in fMRI studies of language tasks. **Results:** When analyzed as a single group compared to controls, the progressive aphasic patients demonstrate dominant hemisphere cortical thinning in perisylvian and temporopolar regions. Yet focused analyses demonstrate three distinct subgroups that fit with clinical diagnostic subcategories: agrammatic, semantic, and logopenic variants. Agrammatic PPA is associated with atrophy in inferior prefrontal and super temporal regions with sparing of the temporal pole. Semantic PPA is associated with atrophy of the temporal pole