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GENOTYPE-PHENOTYPE LINKS IN FRONTOTEMPORAL LOBAR DEGENERATION

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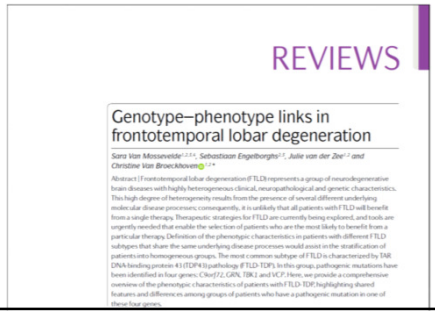
REVIEWS

Genotype–phenotype links in frontotemporal lobar degeneration

Sara Van Mossevelde[1,2,3,4], Sebastiaan Engelborghs[3,5], Julie van der Zee[1,2] and Christine Van Broeckhoven[1,2,4]

Abstract | Frontotemporal lobar degeneration (FTLD) represents a group of neurodegenerative brain diseases with highly heterogeneous clinical, neuropathological and genetic characteristics. This high degree of heterogeneity results from the presence of several different underlying molecular disease processes; consequently, it is unlikely that all patients with FTLD will benefit from a single therapy. Therapeutic strategies for FTLD are currently being explored, and tools are urgently needed that enable the selection of patients who are the most likely to benefit from a particular therapy. Definition of the phenotypic characteristics in patients with different FTLD subtypes that share the same underlying disease processes would assist in the stratification of patients into homogeneous groups. The most common subtype of FTLD is characterized by TAR DNA-binding protein 43 (TDP-43) pathology (FTLD-TDP). In this group, pathogenic mutations have been identified in four genes; C9orf72, GRN, TBK1 and MCP. Here, we provide a comprehensive overview of the phenotypic characteristics of patients with FTLD-TDP, highlighting shared features and differences among groups of patients who have a pathogenic mutation in one of these four genes.

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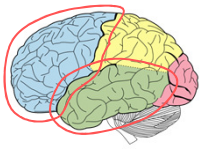
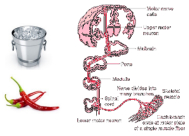
FTLD

- Behaviour/personality changes (*bvFTD*)
- Language deficits (*PPA*)
- Initial relative preservation of memory function



- Extrapiramidal symptoms

- Motor neuron signs



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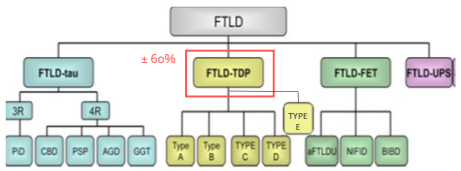
Histopathology of FTLD

- protein inclusions in degenerating neurons



Adapted from Mackenzie IRA and Neumann M. J. Neurochem. 2016; Lee et al. Acta Neuropathol. 2017.

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Genetics of FTLD-TDP

- *C9orf72* (2011): 4-29%
- *GRN* (2006): 1-12%
- *TBK1* (2015): 0.2-1.3%
- *VCP* (2004): 1.2%

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C9orf72: phenotype

CLINICAL symptoms and signs

complex repetitive
irrational, bizarre
bvFTD 65-100%
disinhibition = apathy

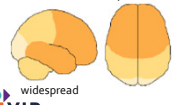
bulbar onset 20-89%
MND

disease anticipation

anxiety
psychiatric 21-56%
hallucinations

NEUROIMAGING

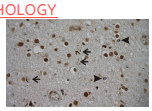
symmetric



widespread

NEUROPATHOLOGY

TDP B > A



TDP-43 - , p62+ inclusions
cerebellum and hippocampus

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GRN: phenotype

CLINICAL symptoms and signs

PNFA
language 21-91%
amyloid negative LPA

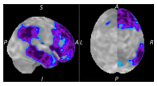
parietal lobe dysfunctions 82%
CBS
unilateral apraxia

bvFTD 50-75%
apathy

parkinsonism 30-90%

no MND

NEUROIMAGING



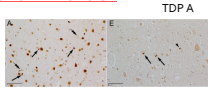
frontotemporal +/- parietal

white matter hyperintensities

asymmetric

NEUROPATHOLOGY

TDP A



nucleus caudate atrophy

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TBK1: phenotype

CLINICAL symptoms and signs

apathy 75%
disinhibition 60%
bvFTD 65%
stereotyped behaviour 55%

parkinsonism 25-30%

predominant UMN 28% > LMN 14%

MND

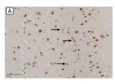
NEUROIMAGING

asymmetric > symmetric

hippocampal atrophy 25-30%

frontotemporal +/- parietal

NEUROPATHOLOGY



TDP B > TDP A

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VCP: FTD phenotype… *few cohort studies*

CLINICAL symptoms and signs

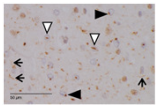
myositis
IBMPFD
Paget disease
apathy
emotional blunting
early behavioural changes
loss of initiative and spontaneity
left- and right-lateralized SD
language problems
anomia
early psychotic signs and schizophrenia

NEUROIMAGING

variable…

rarely asymmetric

NEUROPATHOLOGY



TDP D

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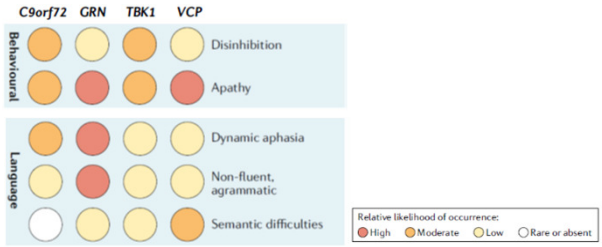
Comparative: CLINICAL symptoms and signs



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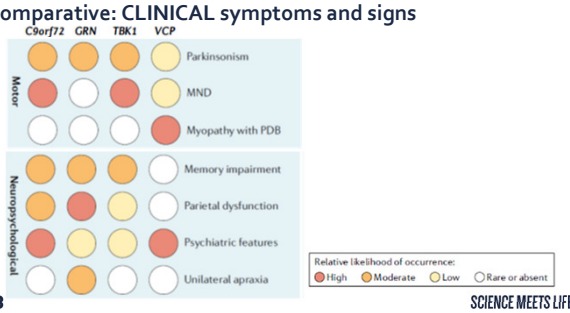
Comparative: CLINICAL symptoms and signs



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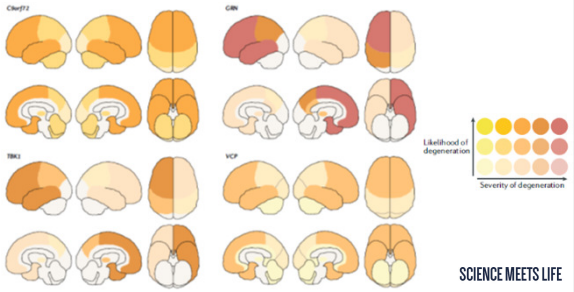
Comparative: neuroimaging and atrophy



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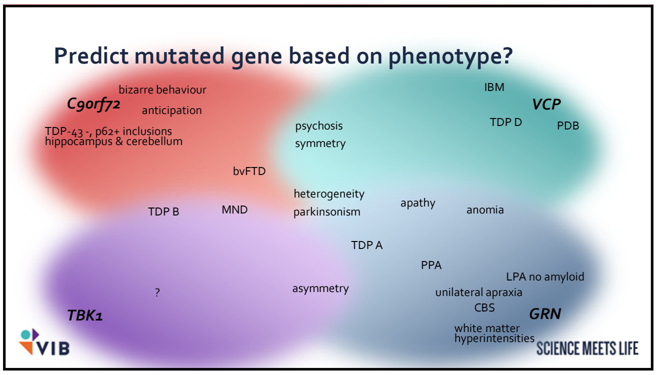
Predict mutated gene based on phenotype?
C9orf72
bizarre behaviour
anticipation
TDP-43 -, p62+ inclusions
hippocampus & cerebellum
IBM
VCP
TDP D
PDB
psychosis
symmetry
bvFTD
heterogeneity
parkinsonism
apathy
anomia
TDP B
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TDP A
PPA
LPA no amyloid
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asymmetry
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CBS
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GRN
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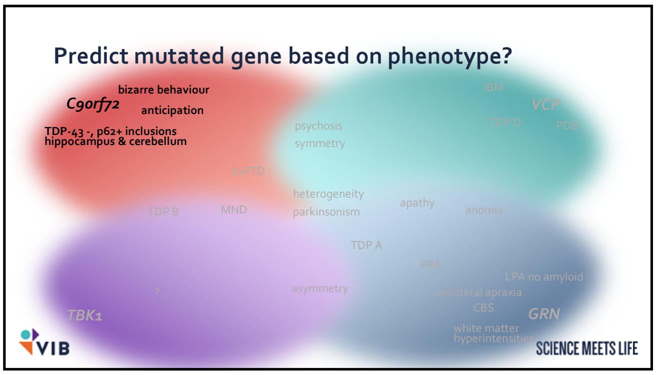
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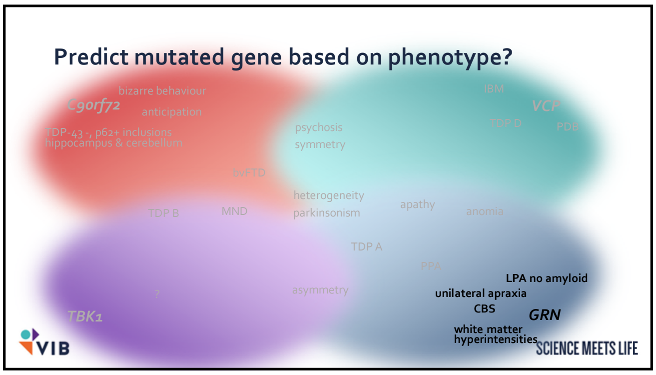
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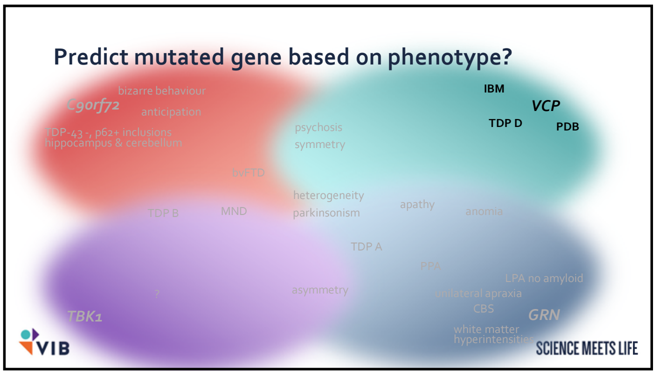
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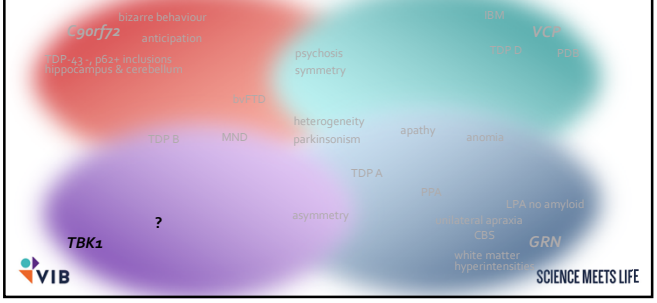

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