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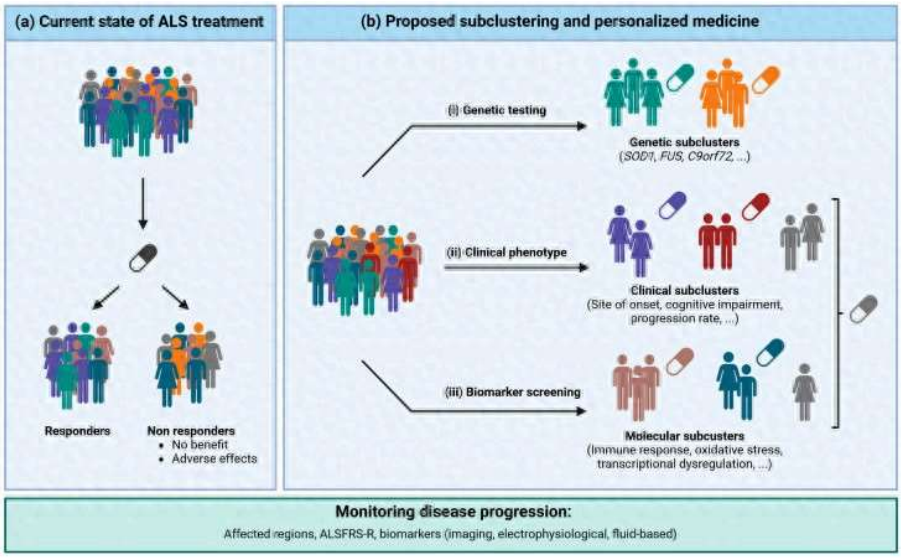
ALS heterogeneity and "stratified treatment" in clinical trials

2025-06-06 21:48 · Van Gogh's Jelly

Tzeplaeff L, Jürs AV, Wohnrade C, Demleitner AF. Unraveling the Heterogeneity of ALS-A Call to Redefine Patient Stratification for Better Outcomes in Clinical Trials. Cells. 2024 Mar 5;13(5):452. doi: 10.3390/cells13050452. PMID: 38474416; PMCID: PMC10930688.



I. Research basic information interpretation

1. Authors and institutions

- **Corresponding author** : Laura TzeplaeffAntonia F. Demleitner and I both work in the Department of Neurology at the Technical University of Munich in Germany. Our research focuses on the heterogeneity of neurodegenerative diseases and the development of precision medicine strategies.
- **Cooperation team** : including the University of Rostock, Germany"Albrecht Kossel" Translational Neurodegenerative Disease Research Group, Department of Neurology, Hannover Medical School, etc. The team integrates experts in genetics, neuroimaging, clinical epidemiology and other fields, and is committed to revealing the complexity of ALS across scales.
- **Research Orientation** : Based on multi-center clinical data and biobank in Europe , emphasis on " **clinical - genetic - molecular** " multi-dimensional integration to promote ALS patient stratification .

2. Journals and Academic Positioning

- **Journal** : Cells （Impact Factor 2023 : 6.6 , JCR Q2） is an open access journal of MDPI focusing on cell biology , molecular medicine , and disease mechanisms . It publishes reviews and original research integrating multi-omics data .

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Deputy Physician of Neurology, Zhongshan Hospital, Affiliated...

- **Publication significance** : As a key review in 2024 , this article is included in the " Neurodegenerative Diseases " topic , systematically summarizes the latest progress of ALS heterogeneity research , provides a " stratified therapy " theoretical framework for clinical trial design , and conforms to the current trend of precision medicine .

3. Topic Analysis

- **Key Terms** :

Heterogeneity （Heterogeneity） : Refers to **the genetic （e.g., C9orf72, SOD1 mutations）, pathological （e.g., TDP-43/FUS inclusions）, clinical （e.g., onset location, cognitive involvement）, and molecular （e.g., inflammation/oxidative stress pathway activation）** levels of great diversity.

Patients stratified （Patient Stratification） : By **genetic testing , pathological markers or molecular characteristics** , patients can be divided into different sub-groups to match targeted therapy to solve the problem of efficacy dilution caused by " one-size-fits-all " in traditional clinical trials .

- **Research Objective** : Critique " **ALS is a single disease** " and call for the inclusion of heterogeneity in basic research , drug development , and clinical practice to improve response rates .

II. In-depth interpretation of research content

1. Genetic heterogeneity: from single gene disease to multifactorial interplay

- **FamilialALS (fALS)** :

High-frequency mutations : C9orf72 hexanucleotide repeat expansion （33.7 % in European fALS）, SOD1 （14.8 %）, and FUS （2.8 %）. Mutations in these genes are associated with abnormal RNA processing or defects in nuclear-to-cytoplasmic transport .

Asian specificity : SOD1 mutations account for more than 30 % of fALS in Asia , suggesting the influence of genetic drift and regional environmental differences .

- **SporadicALS (sALS)** :

Polygenic risk : GWAS has identified more than 100 risk loci （e.g. STMN2 , UNC13A）, which are involved in pathways such as RNA splicing and immune response , reflecting the " polygenic-environment " model of synergistic pathogenesis .

Genetic load difference : Only 5.1 % of sALS patients carry C9orf72 mutations and 1.2 % carry SOD1 mutations , suggesting that sporadic cases are mainly caused by somatic mutations or epigenetic abnormalities .

2. Pathological heterogeneity: diversity and spatial distribution of protein diseases

.

- **Core Pathological Markers** :

TDP-43 inclusions : In 97 % of ALS cases , TDP-43 is co-expressed with p62 into 3 subtypes , of which subtype 2 （ TDP-43 + p62 + ） is associated with cognitive impairment .

FUS / SOD1-specific pathology : C-terminally truncated mutations （ e.g. p.R495 * ） in FUS cause inclusion bodies , while missense mutations （ e.g. p . R521C ） cause " neurofibrillary tangle-like " structures , which are directly related to the age of onset .

- **Accompanying neuropathology** :

20% of patients with sALS were associated with Haimer's disease-like pathology (such as β-amyloid deposition), suggesting a common pathogenic pathway for different neurodegenerative diseases.

3. Clinical heterogeneity: differences in phenotypic profile and prognosis

- **Incidence pattern** :

Early onsetALS : <45 FUS / SOD1 mutations are associated with a median age of onset of 40 years, with the most common symptoms in the medulla, and a median survival of < 3 years.

Late-onsetALS : >65 The age of onset is mainly spinal cord type, part of which is related to TDP-43 subtype 3, and the progress is slow.

- **Differences in functional involvement** :

Pure motor type : 60 % , involving only the upper and lower motor neurons ;

ALS-FTD overlapping : 30 % , with executive dysfunction , highly associated with C9orf72 mutation .

Electrophysiological characteristics : UMN-dominant patients have poor motor unit reinnervation , while LMN-dominant patients can maintain some function due to collateral sprouting .

4. Molecular heterogeneity: multiomics define subpopulations of biomarkers

- **Transcriptomic clustering** :

Inflammatory type （ALS-Glia） : Characterized by microglial activation （ CHIT1 upregulation ） and immune pathway activation, they had the shortest survival.

Oxidative stress type （ ALS-Ox ） : Mitochondrial dysfunction and synaptic signaling dysregulation may be sensitive to antioxidant treatment.

- **Body fluid markers** :

Neurofilament light chain （NfL）：Higher baseline NfL in C9orf72 mutation carriers was associated with disease progression.

Metabolic profile：Hypermetabolism （elevated REE） was present in more than 40 % of patients and was associated with LMN loss and weight loss , while hypometabolism was associated with longer survival .

III. Commentary from an evolutionary perspective

1. Genetic conservatism and the cost of mutation

- **Evolutionary constraints on core pathways**：Sequences of SOD1, FUS, etc. are more than 80% conserved in vertebrates, and their nuclear-cytoplasmic transport and RNA metabolic functions are essential for neuronal survival。Mutations resulting in functional loss (e.g. FUS nuclear positioning impairment) are strongly or negatively selected in evolution for disrupting underlying biological processes and manifest as rare diseases (e. g. Fus-ALS accounts for only 2.8% of familial cases).C9orf72 hexanucleotide repeat expansions are specifically enriched in the human genome and may be associated with genomic instability caused by chromatin remodeling during brain expansion in primates, but not in other species, suggesting a human-specific evolutionary risk.

2. Evolutionary trade off of phenotypic diversity

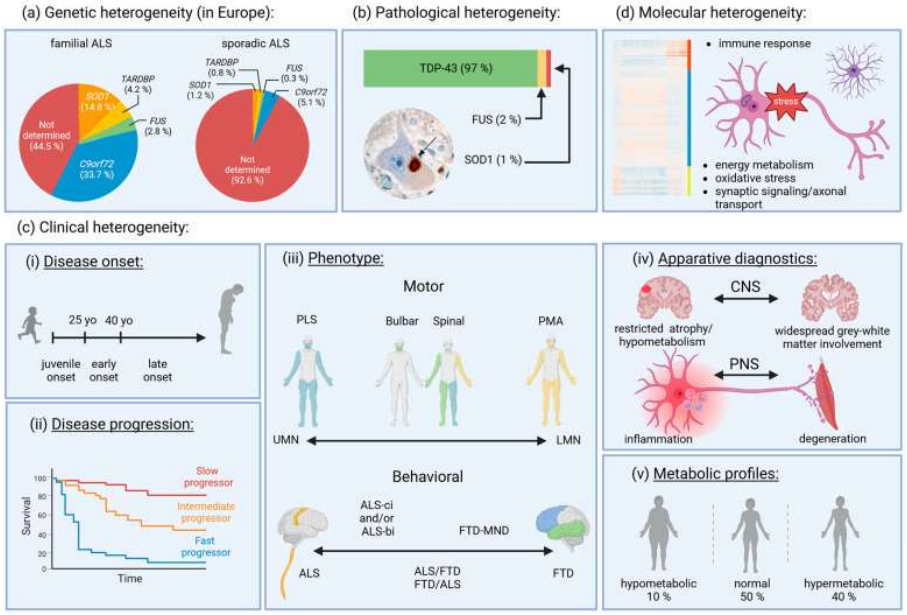
- **The price of brain complexity**：The expansion of the human prefrontal cortex enhances cognitive abilities, but also makes the dysfunction of RNA-binding proteins such as TDP-43 / FUS more likely to cause cortical neuronal degeneration, leading to ALS-FTD overlapping phenotypes, reflecting the "side effects of adaptive evolution."The high fatality rate of ALS in the medullary type is related to the specialization of the respiratory control center after human upright walking, in which the neurons are more sensitive to abnormal energy metabolism.

3. Evolutionary implications of therapeutic strategies

- **Limitations of cross-species models**：Mouse models （e.g., SOD1-G93A） can mimic motor neuron loss but lack the human-specific cortical cognitive phenotype because the rodent brain has not undergone the evolutionary pressure associated with cortical expansion。The mechanisms of ALS-FTD overlap should be studied in combination with organoids or non-human primate models.
- **Conservation of pathway targeting**：Therapeutics targeting RNA splicing （e.g. STMN2） or nuclear-cytoplasmic transport （e.g. importin inhibitors） may have cross-species efficacy due to highly conserved mechanisms in yeast to humans 。 For example, the successful targeting of SOD1 by the antisense oligonucleotide tofersen depends on the evolutionary stability of the gene's function.

IV. CONCLUSIONS

By integrating genetic, pathological, clinical and molecular data, we constructed a multidimensional analytical framework for ALS heterogeneity. The core conclusions are: **ALS is not a single disease, but a "clinical combination" driven by multiple genetic events, pathological processes and environmental factors.** 。 From an evolutionary perspective, its heterogeneity is the result of a combination of gene conservatism and human brain specificity - conservative pathway mutations become rare because of negative selection (e.g. FUS-ALS), while human-specific genetic variants (e. g. C9orf72) and neurostructural complexity magnify the risk of sporadic cases. Future research needs to integrate evolutionary genetics to develop **"Generic therapies based on evolutionary conservatism" and "Precision therapies for human-specific variation"** They also optimize drug screening through cross-species models, ultimately achieving clinical translation of "layered therapies."



Overview of different aspects of ALS heterogeneity

Overview of different aspects of ALS heterogeneity

(a) Genetic heterogeneity;

(b) Pathological heterogeneity;

(c) clinical heterogeneity, including: (i) age of onset; (ii) Disease progression; (iii) Motor and behavioral / cognitive phenotypes; (iv) diagnostic features of the instrument; (v) Metabolic profiles;

(d) Molecular heterogeneity.

Abbreviations Explained : ALS =Amyotrophic lateral sclerosis;SOD1 = superoxide dismutase 1;TARDBP = TAR-DNA binding protein;FUS = sarcoma fusion protein;C9orf72 = chromosome open reading box 72;TDP-43 = TAR DNA binding protein 43;PLS = primary ganglion hardening;PMA = progressive muscle atrophy;UMN = upper motor neuron; LMN = inferior motor neuron; FTD = anterior temporal dementia; MND = motor neuron disease; CI = cognitive impairment; Bi = behavioural disorder; BCI = behavioural and

cognitive impairment; CNS = central nervous system; PNS = Peripheral nervous system.
Made by Laura Tzeplaeff and Camilla Wohnrade using "BioRender.com"

to decipher

1. Genetic Heterogeneity (Genetic Heterogeneity)

- **Key features** : The genetic basis of ALS is highly diverse , encompassing familial （fALS） and sporadic （sALS） cases :

fALS : Approximately 10% are characterized by single-gene mutations, such as C9orf72 repeat expansion （33.7% in European familial cases）, SOD1 （14.8%）, and FUS （2.8%）, which affect conserved pathways such as RNA processing and nuclear-cytoplasmic transport.

sALS : Approximately 90% involve interactions between multiple genes （e.g., STMN2, UNC13A） and the environment, with only 5.1% carrying a C9orf72 mutation and 1.2% carrying a SOD1 mutation.

- **Clinical Significance** : The genetic background directly influences the pathogenesis （ e.g. FUS mutations cause cytoplasmic protein aggregation） and therapeutic response （ e.g. SOD1 mutations are sensitive to antisense therapy） . Genetic testing is the core basis for patient stratification .

2. Pathological Heterogeneity (Pathological Heterogeneity)

- **The diversity of proteinopathies** :

TDP-43 is dominant : it accounts for 97 % of cases and is co-expressed with p62 in 3 subtypes （ e.g. subtype 2 is associated with cognitive impairment） .

Specific pathological findings : In FUS mutation cases, truncated mutations （e.g., p.R495 *） form basophilic inclusion bodies, and missense mutations （e.g., pR521C） form "knotted" structures; SOD1 mutations account for only 1% and are characterized by oxidative stress damage.

- **Spatial distribution differences** : C9orf72 cases are often associated with widespread corticospinal tract TDP-43 aggregation , while FUS / SOD1 cases are mainly affected by the spinal cord or local cortex , suggesting different diffusion patterns .

3. Clinical Heterogeneity

- **Onset and progression** :

Early-onset （ < 45 years ） : associated with FUS / SOD1 mutations , prominent medullary symptoms , and survival < 3 years .

Late-onset （ > 65 years old ） : mainly spinal cord type , slow progression , partially related to TDP-43 subtype 3 .

- **Phenotypic spectrum** :

Motor phenotype : pure motor （ UMN / LMN affected ） , medullary , " flail arm / leg " （ limited weakness ） , PMA （ pure LMN ） , PLS （ pure UMN ） .

Cognitive-motor overlap : 30 % to 50 % of cases with FTD , highly associated with C9orf72 mutations , presenting with executive dysfunction .

- **Diagnosis and monitoring** : Electrophysiology （ e.g. motor unit number estimate MUNE ） and imaging （ e.g. MRI cortical atrophy ） can help to distinguish UMN / LMN-predominant and to predict prognosis .

4. Molecular Heterogeneity

- **Multi-omics features** : **Transcriptome** : ALS-Glia （ activated microglia ） , ALS-Ox （ mitochondrial dysfunction ） , ALS-TD （ transcriptional dysregulation ） . **Body fluid markers** : **NfL （ neurofilament light chain ）** : Levels were positively correlated with rate of neurodegeneration and were higher in C9orf72 cases . **Metabolic profile** : 40% patients showed hypermetabolism （increased resting energy expenditure REE） associated with LMN loss; Low-metabolism is associated with longer survival.
- **Therapeutic implications** : Molecular subtypes may guide targeted therapies . For example , patients with an inflammatory phenotype may benefit from immunomodulatory drugs , and patients with an oxidative stress phenotype may benefit from antioxidants .

5. Integration significance and research implications

- **Graphical function** : To **visualize the heterogeneity of genetic , pathological , clinical and molecular levels** , reveal the essence of ALS as a " syndrome " rather than a single disease , and emphasize the necessity of multidimensional data in patient stratification .
- **Clinical translation** : **Trial design** : Avoid " one-size-fits-all . " Design dual-targeting （ RNA / protein toxicity ） therapies for C9orf72 cases and gene-silencing strategies for FUS mutation patients . **Biomarkers** : Dynamic optimization of treatment regimens based on genetic mutations （ e.g. C9orf72 ） , pathological subtypes （ e.g. TDP-43 + p62 + ） , and molecular features （ e.g. CHIT1 inflammation marker ） .

6. Extending thinking from an evolutionary perspective

- **Conservancy and specificity** : evolutionary conservation of nuclear-cytoplasmic transport, RNA metabolism, etc. （e.g., FUS functionally conserved in yeast to humans） explains the ubiquity of single-gene mutations, while human-specific C9orf72 repeat expansions reflect the evolutionary cost of genome instability。The neural complexity caused by cortical expansion makes humans more vulnerable to TDP-43 / FUS dysfunction, reflecting "the fragility of brain evolution."

- **Model limitations** : Rodent models are difficult to simulate cognitive phenotypes due to the lack of human cortical specialization , and need to be combined with organoids or primate models to study the overlapping mechanisms of ALS-FTD .

summary

This figure systematically illustrates **the heterogeneity of ALS at the genetic , pathological , clinical , and molecular levels** , with the core values being :

1. Emphasizing " **Heterogeneity is the essence of ALS** " , precision medicine needs to be achieved through multidimensional stratification ;
2. Provide a framework for designing clinical trials, such as based on **genetic subtypes （e.g。SOD1 / FUS）** , **pathological markers （e.g. TDP-43 subtypes）** or **molecular pathways （e.g. inflammation / oxidative stress)** Screening of subjects ;
3. It suggests that basic research needs to focus on the balance between cross-species conservation mechanisms and human-specific risks to promote more transformative model development and drug discovery.

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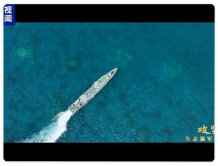

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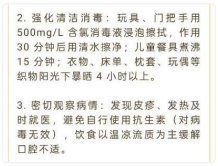
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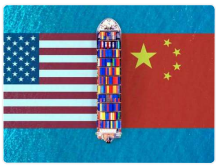

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