Index

A

AAB-003. *See* Bapineuzumab
ACC-001, 621–622
AD. *See* Alzheimer's disease
ADAM10, 517
ADARβ2, 485
AEF. *See* Amyloid enhancement factor
Affitope, 621–622
AGD. *See* Argyrophilic grain disease
α-Synuclein, 655
  brain expression
    cytoskeleton, 287
    endoplasmic reticulum, 287
    Golgi, 287
    mitochondria, 286–287
    nucleus, 287
    overview, 285
    synapse, 286
  cell studies of prions, 308–310
  cellular pools, 279, 283
  conformational change in disease, 307–308
  degradation, 288
  functions
    chaperone activity, 290–291
    dopamine synthesis and transport, 291
    lipid transport and packaging, 290
    neurotransmitter release and synaptic plasticity, 291–292
    overview, 289–290
    vesicle trafficking, 291
  history of study, 277–279
  intracellular trafficking, 334–337
  intracerebral injection of brain samples from dementia with Lewy bodies and multiple system atrophy patients, 312–314
  multiple system atrophy
    aggregation modeling in vitro, 322–324
    glial cytoplasmic inclusions, 321–322
    mutations, 2–3, 15, 348
    neuropathology, 322
    prion propagation in cell culture, 324–325
    prion transmission in mice, 325–327
  mutation in disease
    overview, 305–306, 343–344
    Parkinson's disease
      copy number mutations, 345–346
      genotype–phenotype correlations, 346–347
      heredity, 344
      neuropathology, 345
      sporadic disease, 347–348
  phosphorylation in disease, 306–307
  posttranslational modifications
    acetylation, 283
    glycation, 284
    glycosylation, 284
    nitration, 284
    oxidation, 284
    phosphorylation, 283
    proteolysis, 284–285
    sumoylation, 283
    ubiquitination, 284
  prions
    spread in Parkinson's disease, 288–289
    strains, 52–53
    structure, 13
    transmissibility studies, 15–17
  sequence, 305–306
  structure, 279
  transcellular propagation, 332–334
  transgenic mouse studies, 310–312
ALS. *See* Amyotrophic lateral sclerosis
Alzheimer's disease (AD), 655. *See also* Amyloid-β; Amyloid precursor protein
  epidemiology, 1, 189
  familial disease mutations, 9
  familial versus sporadic, 203
  immunotherapy targeting of amyloid-β
    active immunization, 620–622
    overview, 9, 619–620
    passive immunization, 622–625
    prospects, 625–626
  mouse models, 191–193
  neuropathology, 175–176, 190, 617–618
  progression and prion accumulation, 199
  transmissibility studies, 3–4, 11
  unifying hypothesis, 9–10
2-Aminothiazole (AMT)
  chronic wasting disease studies in cell culture, 103
  prion strain resistance, 51–52
AMT. *See* 2-Aminothiazole
Amylin. *See* Islet amyloid polypeptide

Amyloid-β, 655
  Alzheimer's disease pathogenic cascade, 177
  antibody-mediated clearance, 619–620
  binding sites for oligomers and synaptic toxicity
    ephrin receptors, 247–248, 252–253
    epidermal growth factor receptor, 250, 252–253
    FcγRIIb, 248, 252–253
    functions of receptors, 251–253
    insulin receptor, 250, 252–253
    LilrB2, 249, 252–253
    nAChRα7, 245, 252–253
    NgR1, 247, 252–253
    overview, 241–243
    p75NTR, 246–247, 252–253
    PrPc, 243–245, 252–253
    RAGE, 245–246, 252–253
    reversibility of binding, 253–254
    selectivity for oligomers versus monomers, 251–252
    σ_2 receptor/PGRMC1, 251, 252–253
    SorLA, 249, 252–253
    sortilin, 250, 252–253
  cascade hypothesis of Alzheimer's disease, 191, 210
  clinical implications of prions, 19–20
  Creutzfeldt–Jakob disease, 183
  host factor interactions, 179–180
  immunotherapy targeting
    active immunization, 620–622
    overview, 9, 619–620
    passive immunization, 622–625
    prospects, 625–626
  mouse models of amyloidosis, 618–619
  plaque formation, 3–4, 8–9
  prion strains, 52, 196–198
  prion structure, 114–115, 120
  prion transmissibility
    monkey models, 3, 193–194
    transgenic mice, 8, 194–196
  seeds
    aggregation seeding, 177–179
    clinical evidence, 183
    PrP seed comparison, 183–184
    robustness, 180–181
    size and potency, 180
    trafficking
      brain, 181–182
      periphery to brain, 182
  structure of aggregates
    Aβ40 fibril polymorphs, 266–268
    brain tissue aggregates, 270–271
    fibrils, 259, 264–269
    history of study, 262–264
    nuclear magnetic resonance, solid-state, 263–270
    oligomers, 261
    techniques for study, 261–262
    transient and metastable aggregates, 269–270
    transmission electron microscopy, 260
    X-ray scattering, 261–262
Amyloid enhancement factor (AEF), 567–568
Amyloidosis, noncerebral
  biochemical characterization of proteins, 565
  fibril structure, 565–566
  islet amyloid polypeptide
    aggregation, 554–556, 573–574
    cross-seeding with other protein aggregates, 557–558
    history of study, 552–553, 572
    prion-like transmission, 556–557
    prospects for study, 558
    seeding, 573
    structure, 553
  overview, 563–565
  seeding, 566
  serum amyloid A amyloidosis
    cross-seeding in animal model, 569
    human studies of seeding, 569
    overview, 566–567
    transmissibility, 567–569
  transthyretin-related amyloidosis
    clinical features, 570–571
    hereditary amyloidosis, 436, 570–571
    transmission, 571–572
    treatment, 571
    wild-type protein amyloidogenicity, 570
Amyloid plaque, 655. *See also* Alzheimer's disease; Amyloid-β; Amyloidosis
Amyloid precursor protein (APP), 655
  defects in Alzheimer's disease
    overview, 191, 204
    Down syndrome, 191, 204–205
    duplication, 205–206
    autosomal-dominant missense mutations
      Aβ domain, 207
      amino-terminal domain, 207
      carboxy-terminal domain, 207
      neuropathological profile, 207, 209
      overview, 206, 208
    A673V mutation
      Aβ formation effects, 209
      neuropathological profile, 209
      protective recombinant mutant, 209–210
  gene, 203
  processing, 190, 204
  structure, 203–204
Amyotrophic lateral sclerosis (ALS), 656
  C9ORF72 disease
    clinical presentation, 414
    mutation distribution and effect, 414–415
    pathogenic mechanism, 415–416
    pathological findings, 415
  clinical phenotypes, 352–354
  epidemiology, 427

frontotemporal lobar degeneration association, 354, 360, 405–406, 461, 477–478, 499–500
FUS disease
  clinical presentation, 412–413, 461–463
  mutation distribution and effect, 413
  pathogenic mechanism, 413–414
  pathological findings, 413, 463–465
genetics
  angiogenin, 382
  C9ORF72, 381, 385
  CHCHD10, 379
  dynactin, 382–383
  FUS, 379–381, 385
  genome-wide association studies, 385–391
  genomic structural variation, 391
  hnRNPA1, 381
  hnRNPA2B1, 381
  juvenile-onset disease genes, 384–385
  matrin-3, 382
  modifying genes
    ARHGEF1, 394
    ataxin 2, 393
    chromogranin B, 394
    CX3CR1, 393
    DMT1, 393–394
    ephrin A4, 392–393
    MMP9, 393
    NIPA1, 393
    TMEM106B, 394
    TREM2, 394
  optineurin, 378–379
  overview, 368–376, 407–408
  profilin-1, 383
  prospects for study, 394–395
  SOD1, 370, 377
  TBK1, 378–379
  TDP-43, 379
  tubulinA4A, 383–384
  twin studies, 391–392
  valosin-containing protein, 378
inherited disease, 17
neuropathological heterogeneity, 354–356
overview, 351–352, 367–368
prion-like spread in progression, 418–419
progression, 356–359
SOD1 disease
  clinical presentation, 406, 410
  mutation distribution and effect, 410
  pathogenic mechanism, 410
  pathological findings, 410
  prevalence, 406
TDP-43 disease
  clinical presentation, 410–411
  mutation distribution and effect, 411–412
  pathogenic mechanism, 412, 433–435
  pathological findings, 412, 428
  therapeutic targeting, 436–439
AN1792, 620–621
Angiogenin, amyotrophic lateral sclerosis genetics, 382
Anle138b, 603, 607–608
APH1, presenilin complex, 218
APOE4, 203
APP. *See* Amyloid precursor protein
Argyrophilic grain disease (AGD), 158, 452, 656
ARHGEF1, amyotrophic lateral sclerosis modifying gene, 394
Ataxia, 656. *See also* specific diseases
Ataxin 2
  amyotrophic lateral sclerosis modifying gene, 393
  therapeutic targeting, 437
ATTR amyloidosis. *See* Transthyretin
Autophagy
  Huntington's disease, 521–522
  tau modulation, 646
Autosomal heredity, 656
Avagacestat, 227

B

Bapineuzumab (AAB-003), 622–623
Basophilic inclusion body disease (BIBD)
  FUS disease neuropathology, 469–469
  overview, 468
BDNF. *See* Brain-derived neurotrophic factor
BIBD. *See* Basophilic inclusion body disease
Bioluminescence imaging (BLI), 656, prion disease progression in mice, 588
BLI. *See* Bioluminescence imaging
BMS-869780, 230, 232
Bovine spongiform encephalopathy (BSE), 36, 579, 656
Brain-derived neurotrophic factor (BDNF), 517, 519
Brown–Vialetto-Van Laere (BVVL) disease, 385
BSE. *See* Bovine spongiform encephalopathy
BVVL disease. *See* Brown–Vialetto-Van Laere disease

C

C9ORF72, 656
  amyotrophic lateral sclerosis defects
    clinical presentation, 414, 478
    mutation distribution and effect, 414–415
    pathogenic mechanism, 415–416
    pathological findings, 415
  disease risk with intermediate repeat alleles and flanking region indels, 505
  double gene hits, 507
  frontotemporal lobar degeneration
    dipeptide repeat in neuropathology, 485–490
    overview, 478, 480–481, 499–500
    therapeutics and biomarkers, 490–491
  gene structure, 500

C9ORF72 (*Continued*)
loss of function, 479–482
promoter methylation, 505
protein structure and function, 414
repeat expansion
antisense oligonucleotides, 490
biomarkers, 490, 507
clinicopathological heterogeneity, 501–503
frequency of expansion, 500–501
history of study, 500
origins, 505–506
overview, 478–479
pathogenic mechanisms, 506–507
size variability, 503–505
transcript neurotoxicity, 482–485
splice variants, 479–481
C9ORF72, amyotrophic lateral sclerosis genetics, 381, 385, 428–429
CAA. *See* Cerebral amyloid angiopathy
CAG repeat. *See* Huntington's disease; Polyglutamine proteins
Caspase, inhibitors for Huntington's disease, 526
CBD. *See* Corticobasal degeneration
CDI. *See* Conformational-dependent immunoassay
Cerebral amyloid angiopathy (CAA), 177, 183, 656
CHCHD10, amyotrophic lateral sclerosis genetics, 379
CHF5074, 229–230
Chorea, 656. *See also* specific diseases
Chromogranin B, amyotrophic lateral sclerosis modifying gene, 394
Chronic traumatic encephalopathy (CTE), 657
blood–brain barrier disruption, 169
clinical presentation, 166–167
inflammatory response, 169–170
interstitial fluid clearing, 170
interventions, 171
latency and tau prion propagation, 168
neuropathology, 164–166
overview, 163–164
posttraumatic stress disorder association, 11
tau prion transmissibility, 11–12
traumatic injury cascade, 167–168
Chronic wasting disease (CWD), 657
cell culture models
prion quantification, 103–104
therapy studies, 103
economic impact, 98
epidemiology, 95–96
host range, 95–96
management, 98
mouse models, 99–100
pathogenesis, 96–97
prion propagation mechanisms
amino-terminus polymorphism effects, 100–101
β2–α2 loop interactions with α-helix 3, 101–102
prion strains, 104–105
prospects for study, 106–107
transmission
experimental, 98–99
natural, 97–98
zoonotic potential, 106
CJD. *See* Creutzfeldt–Jakob disease
Clusterin, 645
Compound B, 582–583, 587, 589, 604, 606–607, 622
Concussion, 657. *See also* Chronic traumatic encephalopathy
Conformational-dependent immunoassay (CDI), prion strain characterization, 47
Congo red, 150–152, 581–582
Copper, PrP binding, 6
Corticobasal degeneration (CBD), 133, 168, 452, 626, 657
CPEB, 432, 434, 542, 657
Crenezumab, 625
Creutzfeldt–Jakob disease (CJD), 657
amyloid-β lesions, 183
animal models, 580–581
clinical implications of prions, 20
familial disease, 4–6, 569, 658
iatrogenic disease, 660
clinical features, 83
diagnosis, 83
epidemiology, 83
neuropathology, 83–84
mouse models
A224V, 67
D178N, 67
E200K, 66–67
overview, 66, 68
T183A, 67
onset of neurodegeneration, 6
preclinical diagnosis, 608–609
prion protein mutations, 1–2, 58
prion strains
adaptation, 49
overview, 36–37
sporadic disease, 664
clinical features, 75
diagnosis, 75–76
epidemiology, 74–75
pathology, 76–80
types, 76–77
transmissibility in monkey models, 3
treatment
anle138b, 603, 607–608
combination therapy, 609–610
compound B, 604, 606–607
doxycycline, 603–605
flupirtine, 601, 603
historical perspective, 599–601
IND24, 603, 607
IND81, 603, 607
pentosan polysulfate, 603–604

preemptive intervention, 608
quinacrine, 601, 603–604
therapeutic targets, 605–606
variant disease, 665–666
clinical features, 84–85
diagnosis, 85–86
epidemiology, 84, 88–89
neuropathology, 86–88
transfusion transmission, 88
Crm1, 436–437
Cross-β motif, 260, 262–263, 265, 657
Cryo-electron microscopy, 218–219, 657
CSPα, 335
CTE. *See* Chronic traumatic encephalopathy
CWD. *See* Chronic wasting disease
CX3CR1, amyotrophic lateral sclerosis modifying gene, 393
CYP27A1, 391

D

Dbr1, therapeutic targeting, 437
DCTN1. *See* Dynactin
Dementia, 657. *See also* specific diseases
Dementia with Lewy bodies (DLB), 312–314, 657
Dextran sulfate 500 (DS500), 581
Diabetes type 2
epidemiology, 552
islet amyloid polypeptide
aggregation, 554–556, 573–574
cross-seeding with other protein aggregates, 557–558
history of study, 552–553, 572
prion-like transmission, 556–557
prospects for study, 558
seeding, 573
structure, 553
Dipeptide repeat, 483, 485–490, 506–507
DLB. *See* Dementia with Lewy bodies
DMT1, amyotrophic lateral sclerosis modifying gene, 393–394
Down syndrome (DS), Alzheimer's disease, 191, 204–205
Doxycycline, 603–605
DPP6, 391
DPR. *See* Dipeptide repeat
DS. *See* Down syndrome
DS500. *See* Dextran sulfate 500
Dynactin (DCTN1), amyotrophic lateral sclerosis genetics, 382–383

E

E2012, 230, 232
E2212, 230, 232
EGCG. *See* Epigallocatechin gallate
EGFR. *See* Epidermal growth factor receptor
eIF2α, 437–438
ELP3, 391
Ephrin A4, amyotrophic lateral sclerosis modifying gene, 392–393
Ephrin receptors, Aβ oligomer binding, 247–248, 252–253
Epidermal growth factor receptor (EGFR), Aβ oligomer binding, 250, 252–253
Epigallocatechin gallate (EGCG), 154
ESCRT, 335–336
Ewing's sarcoma
breakpoint region 1, 428, 436
protein, 470–471
EWS. *See* Ewing's sarcoma
EXPEDITION trials, 623–624

F

Fatal familial insomnia (FFI)
gene mutations, 6, 58
mouse models, 64–66
pathology, 58
prion strains, 46
Fatal insomnia, 2, 76, 79, 658
Fazio–Londe (FL) disease, 385
FcγRIIb, Aβ oligomer binding, 248, 252–253
FET proteins. *See* EWS; Fused in sarcoma; TAF15
FFI. *See* Fatal familial insomnia
FL disease. *See* Fazio–Londe (FL) disease
Fluorescence resonance energy transfer (FRET)
presenilin complex studies, 220
tau proteopathic seeding studies, 130–131
Flupirtine, 601, 603
FRET. *See* Fluorescence resonance energy transfer
Frontotemporal dementia (FTD), 658. *See also* Frontotemporal lobar degeneration
Frontotemporal lobar degeneration (FTLD), 658
amyotrophic lateral sclerosis association, 354, 360, 405–406, 461, 477–478, 499–500
C9ORF72 repeat expansions
DPR in neuropathology, 485–490
overview, 478, 480–481
therapeutics and biomarkers, 490–491
diagnosis, 10–11
FUS disease
atypical FTLD-U, 465–466
genetic analysis, 469–470
neuropathology, 466
overview, 465
subtypes, 469
gene mutations, 12
neurofibrillary tangles, 12
tau
immunotherapy targeting, 627–629
pathology, 626–627

FTD. *See* Frontotemporal dementia
FTLD. *See* Frontotemporal lobar degeneration
FUS. *See* Fused in sarcoma
Fused in sarcoma (FUS), 658
  amyotrophic lateral sclerosis defects
    clinical presentation, 412–413, 461–463
    genetics, 379–381, 385
    mutation distribution and effect, 413
    pathogenic mechanism, 413–414
    pathological findings, 413, 463–465
  basophilic inclusion body disease neuropathology, 469–469
  frontotemporal lobar degeneration
    atypical FTLD-U, 465–466
    genetic analysis, 469–470
    neuropathology, 466–467
    overview, 465
    subtypes, 469
  neuronal intermediate filament inclusion disease neuropathology, 466, 468, 470
  prion activity studies, 417–418, 472
  structure and function, 413, 462
FXN, 506

G

GADD34, 594
γ-Secretase. *See also* Presenilin complex
  inhibitors
    active site-directed inhibitors, 221–222
    Alzheimer's disease clinical trials, 222, 227–228
    exosite-targeted inhibitors, 221
    structures, 222–227
  modulators
    heterocyclic modulators, 230–233
    nonsteroidal anti-inflammatory drug-derived modulators, 228–231
    overview, 228
    structures, 229–230
Gantenerumab, 624
GCI. *See* Glial cytoplasmic inclusions
Genome-wide association study (GWAS), 248–249, 347, 385–392, 659
Gerstmann–Sträussler–Scheinker disease (GSS), 659
  gene mutations, 5–6, 58, 61
  mouse models
    A117V, 62–63
    GPI-anchorless PrP, 63
    9-OPRI, 63
    overview, 61
    P102L, 60, 62
    Y145X, 63–64
GFAP. *See* Glial fibrillary acidic protein
Glial cytoplasmic inclusions (GCIs), 3–5, 13–14, 320–324, 327, 659
Glycophosphatidylinositol (GPI), 57–64, 243, 659
Glymphatic system, 164, 168, 170, 659
GN8, 592–593
GPI. *See* Glycophoasphatidylinositol
GSK2606414, 438, 594
GSM-1, 229–230
GSM-2, 229–231
GSS. *See* Gerstmann–Sträussler–Scheinker disease
GWAS. *See* Genome-wide association study

H

HAP1, 522
HD. *See* Huntington's disease
HDAC6. *See* Histone deacetylase 6
Head trauma. *See* Chronic traumatic encephalopathy
Heat shock protein, 284, 336, 340, 438–448, 520, 543, 636–637, 641–645, 659. *See also* Tau
HGH. *See* Human growth hormone
High-throughput screening, prion disease therapeutics, 583–584, 592–593
Histone deacetylase 6 (HDAC6), 646
hnRNPA1, amyotrophic lateral sclerosis genetics, 381, 428, 436
hnRNPA2, amyotrophic lateral sclerosis genetics, 381, 428, 436
hnRNPA3, 428, 485, 506
HPA-23, 581
Human growth hormone (HGH), 81–84, 89, 659
Huntingtin, 659. *See also* Polyglutamine proteins
  aggregates
    aggregation, 518, 520
    interactions with other aggregate-prone proteins, 525
    transmission, 523–524
  cleavage into toxic fragments, 520
  function
    development, 517
    overview, 516–517
    scaffolding, 517
    synapse, 517–518
    transcriptional regulation, 517
  structure, 516
Huntington's disease (HD), 659–660
  clinical features, 515–516
  genetics, 515
  pathogenesis
    astrocyte and microglial dysfunction, 524–525
    epigenetics and noncoding RNA, 521
    huntingtin
      aggregation, 518, 520
      cleavage into toxic fragments, 520
      interactions with other aggregate-prone proteins, 525
      transcription dysregulation, 520
    mitochondrial dysfunction, 523
    synaptic plasticity alterations, 522–523

ubiquitin–proteasome system and autophagy, 521–522
prions and transmission, 17, 523–524, 541, 544–545
therapy
antioxidants, 526
antisense oligonucleotides, 526
autophagy upregulation, 526–527
caspase inhibitors, 526
clinical trials, 527
neuronal transplantation, 527
overview, 525–526
transglutaminase inhibitors, 526

I

IAPP. *See* Islet amyloid polypeptide
IDPs. *See* Intrinsically disordered proteins
IDRs. *See* Intrinsically disordered regions
IND24, 585, 588–589, 591–592, 603, 607
IND81, 585, 588–589, 591–592, 603, 607
IND125, 590
IND126, 590–591
IND28484, 587
IND114338, 590
IND116133, 587, 592
IND116135, 587, 592
IND162256, 587
Infectious unit, 608, 660
In silico screen, prion disease therapeutics, 593
Insulin receptor, Aβ oligomer binding, 250, 252–253
Interferon, 337–338, 660
Intrinsically disordered proteins (IDPs), 538
Intrinsically disordered regions (IDRs), 538
Islet amyloid polypeptide (IAPP), 660
aggregation, 554–556, 573–574
cross-seeding with other protein aggregates, 557–558, 573
function, 572
history of study, 552–553, 572
prion-like transmission, 556–557
prospects for study in diabetes, 558
seeding, 573
structure, 553
ISRIB, 438

J

JNJ-16, 230, 233
JNJ-42601572, 230, 232–233
JNK, 248, 522

K

KIF5, 522
Kuru, 580, 660
history of study, 81
neuropathology, 81–82
transmissibility in monkey models, 3

L

L-458, 221, 223–225
LAG3, 334
Latrepirdine, 527
Lewy body, 13–16, 279–280, 284, 288–289, 336, 344, 556, 660. *See also* Dementia with Lewy bodies
Lewy neurite, 284, 345, 660
LilrB2, Aβ oligomer binding, 249, 252–253
LIN5001, 592–593
Low-complexity domain, 17, 409, 411, 417–418, 505, 660
LY411575, 594

M

Mad cow disease, 20, 660. *See also* Bovine spongiform encephalopathy
Magnetic resonance imaging (MRI), Creutzfeldt–Jakob disease
sporadic disease, 75, 77
variant disease, 86
MAPT. *See* Tau
Mass spectrometry (MS), 281, 660–661
Matrin-3, amyotrophic lateral sclerosis genetics, 382
Matrix metalloproteinases (MMPs), MMP9 as amyotrophic lateral sclerosis modifying gene, 393
MB. *See* Methylene blue
Memantine, 1
Methylene blue (MB), 153
MicroRNA, Huntington's disease, 521
MK-0752, 227
MMPs. *See* Matrix metalloproteinases
MND. *See* Motor neuron disease
Motor neuron disease (MND), 661. *See also* specific diseases
MRI. *See* Magnetic resonance imaging
MS. *See* Mass spectrometry
MSA. *See* Multiple system atrophy
Multiple system atrophy (MSA), 661
α-synuclein
aggregation modeling in vitro, 322–324
glial cytoplasmic inclusions, 321–322
mutations, 2–3, 14–15, 348
neuropathology, 322
prion propagation in cell culture, 324–325
prion transmission in mice, 325–327
clinical features, 319–320
diagnosis, 321
genetics, 322
history of study, 320
mouse models, 322
prions, 13–15
transgenic mouse model, 2–3
transmissibility studies, 14, 53

Myotonic dystrophy type 1, 483
Myricetin, 154

N

N744, 154
nAChRα7, Aβ oligomer binding, 245, 252–253
NCI. *See* Neuronal cytoplasmic inclusions
Nedd4, 337
Neurofibrillary tangles (NFTs), 661. *See also* Tau
Neuronal cytoplasmic inclusions (NCIs), 12, 446–469, 489, 661
Neuronal intermediate filament inclusion disease (NIFID)
  FUS disease neuropathology, 466, 468, 470
  overview, 466
Neuronal intranuclear inclusion (NII), 470, 661
Neuropil thread (NT), 138, 142, 164, 621, 661
NFT. *See* Neurofibrillary tangles
NGP-555, 230–231
NgR1, Aβ oligomer binding, 247, 252–253
Nicastrin, presenilin complex, 217–218
NIFID. *See* Neuronal intermediate filament inclusion disease
NII. *See* Neuronal intranuclear inclusion
NIPA1, 391
NIPA1, amyotrophic lateral sclerosis modifying gene, 393
NMR. *See* Nuclear magnetic resonance
Notch-1, 594
NT. *See* Neuropil thread
Nuclear magnetic resonance (NMR), 661
  in vivo studies of α-synuclein, 280–281
  solid-state studies of Aβ aggregates, 263–270
Nucleolin, 484

O

Octapeptide repeat, 661
Oligodendrocyte, 662
Optineurin, amyotrophic lateral sclerosis genetics, 378–379

P

p53, 662
p75NTR, Aβ oligomer binding, 246–247, 252–253
Paired helical filaments, 10, 44, 149, 627, 635, 662
Parkinson's disease (PD), 662. *See also* α-Synuclein
  α-synuclein mutations
    copy number mutations, 345–346
    genotype–phenotype correlations, 346–347
    heredity, 344
    neuropathology, 345
    sporadic disease, 347–348
  clinical implications of prions, 20
  inherited disease, 13
  transmissibility studies, 4
Parkinsonism, 662. *See also* Parkinson's disease
Pbp1, 437
PCR. *See* Polymerase chain reaction
PD. *See* Parkinson's disease
PDK1, 594
PEN-2, presenilin complex, 218
Pentosan polysulfate (PPS), 581, 603–604
PERK, 438, 594
PET. *See* Positron emission tomography
PF-3084014, 227
PFN1. *See* Profilin-1
Phosphorothioate oligonucleotides, prion disease therapy, 593
Pick body, 468, 662
Pick's disease, 2, 11, 452, 626, 662
Pin1, 645
PMCA. *See* Protein misfolding cyclic amplification
Polyglutamine proteins. *See also* Huntingtin
  glutamine-rich domains, 539–540, 542
  homeostasis and aggregation, 538–539
  nonpathogenic prions, 542
  pathogenesis, 542–544
  prospects for study, 545
  transmission of aggregates, 541, 544–545
Ponezumab, 624
Positron emission tomography (PET), 155–156, 662
Posttraumatic stress disorder (PTSD), 662
  chronic traumatic encephalopathy association, 11
  epidemiology, 11
PPS. *See* Pentosan polysulfate
PRA1, 335
Presenilin complex. *See also* γ-Secretase
  functional anatomy, 220–221
  overview, 215–216
  structure of components
    APH1, 218
    nicastrin, 217–218
    PEN-2, 218
    presenilin, 216–217
  topology and structure, 218–220
Pridopidine, 527
Prion strain, 663
  adaptation, 48–50
  biochemical characterization, 47
  conformational stability versus replication rate, 47–48
  definition, 32
  diseases
    Alzheimer's disease, 52, 196–198
    bovine spongiform encephalopathy, 36
    chronic wasting disease, 104–105
    Creutzfeldt–Jakob disease, 36–37
    scrapie, 37
  drug resistance
    2-aminothiazole, 51–52

quinacrine, 50–51
swainsonine, 51
mixtures and consequences, 37–39
overview, 31–32, 46–47
properties, 34–36
tau, 133–134
TDP-43, 453–454
tropism, 32–34
PRNP, 2, 58, 663
Profilin-1 (PFN1), amyotrophic lateral sclerosis genetics, 383
Progranulin, 12, 250, 394, 663
Progressive supranuclear palsy (PSP), 11–12, 17, 138, 141, 635, 638, 663
Proteinase K, 11, 34, 47, 58, 77, 98, 113, 180, 313, 455, 580, 663
Protein misfolding cyclic amplification (PMCA), 34, 38–39, 86, 96, 100, 104–106, 592, 663
Proteostasis, 433, 439, 538, 644–646, 663
PrP, 663
amyloid-β seed comparison, 183–184
copper binding, 6
disease types, 2, 18, 58
mutation sites, 59
prion structure, 116–122
PrP 27–30, 663
PrP^{C}, 663, Aβ oligomer binding, 243–245, 252–253
PrP^{Sc}, 553–554, 579–580, 663
PSEN1, 203, 215
PSEN2, 203, 215
PSP. *See* Progressive supranuclear palsy
PTSD. *See* Posttraumatic stress disorder
PU.1, 524

Q

Quinacrine, 50–51, 582–583, 601, 603–604

R

Rab11, 334
RAGE, Aβ oligomer binding, 245–246, 252–253
RAN, translation, 485–490
Riluzole, 427
RNA stress granule, 439–440, 472, 485, 663–664
RO4929097, 227–228
RO5506284, 230, 233

S

SARM1, 385, 391
SARs. *See* Structure–activity relationships
SCA. *See* Spinocerebellar ataxia
ScN2a, 583–587, 590–591, 664
Scrapie, 37, 537, 664
Semagacestat, 222, 227
Shy–Drager syndrome, 320, 664
σ_2 receptor/PGRMC1, Aβ oligomer binding, 251, 252–253
SIGMAR1, 384–385
SLC52A3, 385
Slow virus, 3, 664
SMN1, 391
SNARE, 335
SNP. *See* Single nucleotide polymorphism
SOD1. *See* Superoxide dismutase
Solanezumab, 622–623
SorLA, Aβ oligomer binding, 249, 252–253
Sortilin, Aβ oligomer binding, 250, 252–253
SP-53, 230, 232
SP-1865, 230, 233
Species barrier, 37, 48, 99, 120, 312, 664
SPG11, 384
Spinocerebellar ataxia (SCA), 437, 470, 540, 664
Spongiosis, 58, 63, 67, 77, 97, 138, 355, 664
Steric zipper, 436, 539, 543, 565, 664
Strain, 664. *See also* Prion strain
Structure–activity relationships (SARs)
2-aminothiazoles, 584–585
aryl amides, 586–588
aryl piperazines, 585–586
Sup35, 8, 155, 436
Superoxide dismutase (SOD1), 664
amyotrophic lateral sclerosis defects
clinical presentation, 406, 410
genetics, 370, 377
mutation distribution and effect, 410
mutations, 17, 355
pathogenic mechanism, 410
pathological findings, 410
prevalence, 406
prion activity studies
template-directed misfolding and spread, 416
transmission in vivo, 416–417
structure and function, 410
Swainsonine, prion strain resistance, 51
Synucleinopathy, 665. *See also* α-Synuclein

T

TAF15, 428, 436, 471
Tafamidis, 436
TARDBP, 360, 507
Tau, 665
cell internalization of proteopathic seeds, 128–130
frontotemporal lobar degeneration
immunotherapy targeting, 627–629
pathology, 626–627
heat shock proteins
Hsp27 and tau reduction, 645
Hsp70 modulators, 643
Hsp90

Tau (*Continued*)
inhibitor studies of tau clearance, 644–645
stabilization, 643–644
stabilization of tau, 641–643
MAPT mutations, 12
neurofibrillary tangles, 9, 635–636
posttranslational modifications in disease, 150, 638–640
prion diseases
inherited tauopathies, 12–13
overview, 10–12, 137–139
transmissibility, 11–12
prion strains, 52, 133–134
protein–protein interactions
aberrant interactions, 636, 638
normal interactions, 636–637
proteopathic seeding, 130–132
reduction of levels
autophagy, 646
clusterin, 645
histone deacetylase 6, 646
Hsp27, 645
Pin1, 645
therapies, 646
small molecule studies
aggregation
agonists, 150–151
inhibitors, 152–154
reporters, 151–152
fibril remodeling, 154–155
positron emission tomography probes, 155–156
prospects, 157
structure and function, 636
therapeutic targeting, 640–641
transgenic mouse studies
aggregate formation, 143–144
prospects for study, 145
release of aggregates, 15
tau strains, 141–143
tauopathy induction and propagation, 139–141
uptake of aggregates, 143–145
transcellular propagation of aggregates, 132–133
Tauopathy, 665. *See also* specific diseases
TBI. *See* Traumatic brain injury
TBK1, 507
TBK1, amyotrophic lateral sclerosis genetics, 378–379
TDP-43, 665
amyotrophic lateral sclerosis defects
clinical presentation, 410–411
genetics, 355, 359, 429
mutation distribution and effect, 411–412
pathogenic mechanism, 412, 433–435
pathological findings, 412, 428
therapeutic targeting, 436–439
amyotrophic lateral sclerosis genetics, 379
misfolded protein reactivation, 438–439
nuclear transport modulation, 436–437
proteinopathy
neurotoxicity, 453
pathology, 452–453
prion activity studies, 417–418, 455
prion strains, 453–454
seeded aggregation in cell models, 454–455, 458
transmissibility studies, 455–457
stress granule targeting, 437–438
structure and function, 409, 411, 429–433, 452
suppressor targeting, 437
Tetrabenazine, 525
Thioflavin S (ThS), 151, 154
Thioflavin T (ThT), 150–152, 154
ThS. *See* Thioflavin S
ThT. *See* Thioflavin T
TMEM106B, amyotrophic lateral sclerosis modifying gene, 394
TNPO1, 472
Transglutaminase, inhibitors for Huntington's disease, 526
Transmissible spongiform encephalopathy (TSE), 551–552, 665
Transmission barrier, 62, 98, 101, 106, 665
Transthyretin
amyloidosis
clinical features, 570–571
hereditary amyloidosis, 436, 570–571
transmission, 571–572
treatment, 571
wild-type protein amyloidogenicity, 570
structure and function, 569–570
Traumatic brain injury (TBI), 11, 169–170, 665. *See also* Chronic traumatic encephalopathy
TREM2, amyotrophic lateral sclerosis modifying gene, 394
TRN, 472
TSE. *See* Transmissible spongiform encephalopathy
TubulinA4A, amyotrophic lateral sclerosis genetics, 383–384

U

UBQLN1, 385
UNC13A, 385
Unc119, 489

V

Valosin-containing protein (VCP), 665, amyotrophic lateral sclerosis genetics, 378
Variably protease-sensitive prionopathy (VPSPr), 78–81
VCP. *See* Valosin-containing protein
VPSPr. *See* Variably protease-sensitive prionopathy

X

X-ray scattering, Aβ aggregates studies, 261–262