

Index

- AD. *See* Alzheimer's disease
- ADE1, 76
- ADE2, 76
- AGD. *See* Argyrophilic grain disease
- Aging, [PSI+] maintenance, 111–113
- Ago2, 151
- Argyrophilic grain disease (AGD), pathology, 365
- ALS. *See* Amyotrophic lateral sclerosis
- α -Synuclein
- aggregation reaction, 25–26
 - atomic force microscopy of fibril formation, 23
 - knockout mouse, 312
 - lesion spread in Parkinson's disease, 386–392
 - prion bioassays, 404–405
 - synucleinopathy overview, 366
 - transgenic mouse studies, 311–312
 - transmission routes, 387
- Alzheimer's disease (AD)
- clinical features and diagnosis, 174–177
 - differential diagnosis, 179–180
 - economic impact, 18–19
 - epidemiology, 18, 174
 - genetics, 178, 219–221
 - history of study, 18
 - imaging, 177–178
 - laboratory testing, 178
 - management, 179
 - overview, 219
 - pathology, 178–179, 307, 360–362
 - positron emission tomography
 - amyloid- β , 338–339
 - tau ligands
 - lead compounds, 339–342
 - overview, 339
 - phenyl-butadienyl-benzothiazole compounds, 344–346
 - prospects, 351
 - Roche compounds, 350–351
 - Siemens-Avid/Lilly compounds, 346–350
 - THK compounds, 342–344
 - prion bioassays, 403–405
 - risk variants, 221–224
 - tau lesion spread, 379–385
 - tau prion initiation, 8–9
 - transgenic mouse studies
 - amyloid- β , 307–308
 - tau, 309–311
 - treatment prospects, 27–28
- Amyloid. *See also specific prions*
- amyloidoses overview, 358
 - cellular functions, 6
 - comparison with other aggregates, 56–57
 - cross- β -sheet motif, 50, 53–55, 57
 - fibril intrinsic properties, 20–22
 - formation and protein homeostasis loss, 23–24
 - history of study, 6
 - pathogenic consequences, 22–23
 - protein requirements, 57
 - sensor in yeast, 113
 - steric zipper hypothesis of fibril structure, 35–40
 - structural polymorphisms, 53–54
 - toxicity, 55–56
- Amyloid- β
- aggregation
 - inhibitors, 26–27
 - reaction, 25–26
 - A β 42 transgenic fruit fly, 24–25
 - positron emission tomography, 338–339
 - prion
 - bioassays, 403–405
 - inactivation, 411–412
 - transgenic mouse studies, 307–308
- Amyloid precursor protein (APP)
- gene. *See* APP
 - processing, 65
- Amyotrophic lateral sclerosis (ALS)
- C9orf72 poly-dipeptides, 167–168
 - genetics, 228
 - history of study, 288
 - overview, 287, 289
 - pathology, 370
 - superoxide dismutase 1 prions. *See* Superoxide dismutase 1
- APOE ϵ 4, 229–230
- Apolipoprotein A1, familial amyloid polyneuropathy
- pathophysiology, 7
- APP. *See* Amyloid precursor protein
- APP
- Alzheimer's disease genetics, 178, 220
 - knockout mouse, 309
- ARE, 430
- ASC
- advantages of prion-like polymerization in signaling, 145–146
 - filament structure, 141
 - functional prion, 9–10
 - functional prion identification, 141
 - HET-s comparison, 142
 - infectious properties of prion, 141–142
 - prospects for study, 146
 - PYRIN domain polymerization, 136–137
- Ataxin-2, 151
- ATF4, 64
- ATF6, 64
- ATP13A2, 194
- β -Solenoid model, yeast prions, 40–42, 52
- Bovine spongiform encephalopathy (BSE), prion inactivation, 406–407

Index

- Brain network mapping
 connectomics, 323
 intrinsic connectivity, 322, 324
 structural connectivity, 322–323
 structural covariance, 322
- BRICHOS, 27, 114
- BSE. *See* Bovine spongiform encephalopathy
- Btn2p, [URE3] curing, 83–84, 109
- C9orf72*
 frontotemporal dementia genetics, 226–227
 poly-dipeptides in amyotrophic lateral sclerosis, 167–168
- Calnexin, 61
- Cancer. *See* p53
- CARD, MAVS polymerization in RIG-I antiviral pathway
 signaling, 136–141
- CBS. *See* Corticobasal syndrome
- Central dogma, 1
- CF. *See* Cystic fibrosis
- CHMP2B*, frontotemporal dementia genetics, 227
- Chronic traumatic encephalopathy (CTE), pathology, 362–364
- Chronic wasting disease (CWD), 82
- CJD. *See* Creutzfeldt–Jakob disease
- CLR01, 430
- COQ2, 201
- Corticobasal degeneration, 190–192, 364–365
- Corticobasal syndrome (CBS), 175, 191–192
- CPEB
 aggregation regulation, 129–131
 Aplysia studies
 aggregation inhibition effects, 127
 identification and characterization, 124–125
 long-term memory maintenance, 122–125
 neuronal function studies, 125–127
 serotonin induction of aggregation, 127
 Drosophila studies of Orb2
 overview, 127–128
 prion-like state in memory persistence, 128
 functional prion, 9
 memory, 122–124
 mouse studies of CPEB-3 brain function
 overview, 128–129
 synaptic plasticity persistence and memory storage, 129
 structure of aggregates, 131
- CPEB3, 128–129, 153, 158
- Creutzfeldt–Jakob disease (CJD)
 aggregate deposition, 65
 history of study, 3
 pathology, 359
 prion
 direct assay, 410–411
 inactivation, 406, 409
 PRNP mutations. *See* *PRNP*
 spontaneous disease prion features, 244
 variants, 241–242
- Cross- β -sheet motif
 amyloid, 50, 53–55, 57
 low complexity domain polymerization
 C9orf72 poly-dipeptides in amyotrophic lateral
 sclerosis, 167–168
 fiber binding of disordered regulatory proteins, 166–
 167
 history of study, 164–165
 labile fiber formation, 165–166, 170
 molecular footprinting of nuclear polymers, 168–169
 prospects for study, 169–170
- CTE. *See* Chronic traumatic encephalopathy
- Cur1, [URE3] curing, 83–84, 109
- CWD. *See* Chronic wasting disease
- Cystic fibrosis (CF), Ivacaftor therapy, 71
- Dementia. *See* *specific diseases*
- Dementia with Lewy bodies (DLB)
 Alzheimer's disease differential diagnosis, 179
 clinical symptoms and diagnosis, 195–197
 differential diagnosis, 199
 epidemiology, 195
 genetics, 198, 229–230
 imaging, 198
 laboratory testing, 198
 overview, 194, 229
 pathology, 198, 367–368
 transgenic mouse studies, 311–312
 treatment, 199
- Diabetes type 2
 economic impact, 19
 epidemiology, 19
- Dialysis-related amyloidosis (DRA), 19
- DLB. *See* Dementia with Lewy bodies
- DRA. *See* Dialysis-related amyloidosis
- eIF2, 153
- eIF3, 154
- Endoplasmic reticulum-associated degradation (ERAD), 63, 68
- Endoplasmic reticulum-derived quality-control compartment
 (ERQC), 68–69
- ERAD. *See* Endoplasmic reticulum-associated degradation
- ERQC. *See* Endoplasmic reticulum-derived quality-control
 compartment
- EWS, 166
- Familial amyloid polyneuropathy (FAP), 7
- Familial fatal insomnia (FFI)
 clinical features, 241–242
 PRNP D178N mutation, 159–160
- FAP. *See* Familial amyloid polyneuropathy
- FAST, 153
- FFI. *See* Familial fatal insomnia
- FMRP, 151
- Frontotemporal dementia (FTD)
 Alzheimer's disease differential diagnosis, 180
 behavioral variant, 181, 185, 319
 diagnosis, 181–185
 differential diagnosis, 185
 epidemiology, 180–181
 genetics, 181, 224–228
 imaging, 185
 onset, 327–328
 overview, 180, 221, 223–224
 pathology
 FTLD-TDP, 370–371
 overview, 181
 primary progressive aphasia
 logopenic variant, 187–188
 nonfluent variant, 187
 overview, 185
 semantic variant, 185–187
 treatment, 188

- Frontotemporal dementia-motor neuron disease (FTD-MND), 188–189
- FTD. *See* Frontotemporal dementia
- FTD-MND. *See* Frontotemporal dementia-motor neuron disease
- FU-1 strain. *See* Fukuoka-1 strain
- Fukuoka-1 (FU-1) strain, 409
- FUS, 163, 166, 189, 228
- [GAR], 78
- GBA, 229
- Gelsolin, familial amyloid polyneuropathy pathophysiology, 7
- Gerstmann–Sträussler–Scheinker disease (GSS)
clinical features, 241–242
PRNP mutations
A117V, 262
F198S, 263–264
H187R, 264
overview, 260–261
P102L, 261–262
P105L, 264–265
- Get proteins, 113
- GRN, 226, 232, 328
- GSS. *See* Gerstmann–Sträussler–Scheinker disease
- HD. *See* Huntington’s disease
- HDMX, 419
- Heat-shock factor 1 (HSF-1), 63, 71
- Heat-shock response (HSR), 63, 65, 69
- HELLP, 144
- Het-s
ASC homology comparison, 142–145
function of prion, 81
Het-s(218-289) amyloid fibril structure, 52
[Het-s]/HET-s incompatibility, 92–93
NWD2 interaction, 143–144
prion, 7
prion domain structure and function, 93–96
prion variants, 80
programmed cell death
Nod-like receptor signaling, 97–99
pore-forming domain in execution, 96–97
 β -solenoid model, 40–41, 52
- HSF-1. *See* Heat-shock factor 1
- Hsp40
prion propagation control, 104–106
yeast versus higher eukaryote effects on amyloids, 114
- Hsp70
prion propagation control, 104–106
[PSI⁺] generation inhibition, 82–83
yeast versus higher eukaryote effects on amyloids, 113–114
- Hsp104
overproduction effects on yeast prions, 104–105
[PSI⁺] curing, 84, 104–105
prion propagation control, 104
TIA-1 aggregation inhibition, 157
yeast versus higher eukaryote effects on amyloids, 114
- HSR. *See* Heat-shock response
- Huntington’s disease (HD)
clinical symptoms and diagnosis, 202–203
differential diagnosis, 205
epidemiology, 202
genetics, 204
imaging, 203–204
laboratory testing, 204
management, 204–205
pathology, 204
unfolded protein response, 67
- HuR, 151
- Inactivation of prions. *See* Prion
- Inflammasome, ASC PYRIN domain polymerization, 136–137, 141–142
- Innate immunity, prions with unique properties, 142
- Insoluble protein deposit (IPOD), 68, 109–110
- IPOD. *See* Insoluble protein deposit
- IRE1, 64, 69
- IRF3, 122
- [ISP⁺], 78
- Ivacaftor, cystic fibrosis management, 71
- JUNQ. *See* Juxtannuclear quality control compartment
- Juxtannuclear quality control compartment (JUNQ), 68
- K18 repeat domain, 4, 8
- K-Ras, 425
- Kuru, 230, 304
- Las17, 111
- LC domain. *See* Low complexity domain
- Lewy body dementia. *See* Dementia with Lewy bodies
- Low complexity (LC) domain, 10
cross- β polymerization
C9orf72 poly-dipeptides in amyotrophic lateral sclerosis, 167–168
fiber binding of disordered regulatory proteins, 166–167
history of study, 164–165
labile fiber formation, 165–166, 170
molecular footprinting of nuclear polymers, 168–169
prospects for study, 169–170
overview of characteristics, 163–164
- LRKK2, 194
- Lsb1, 112
- Lsb2, 111–112
- Magnetic resonance imaging (MRI)
Alzheimer’s disease, 177
brain network mapping, 322, 324
Fast genetic prion diseases, 256
frontotemporal dementia, 188
Huntington’s disease, 203
multiple system atrophy, 200–201
progressive supranuclear palsy, 189
Slow genetic prion diseases, 263
- MAPT, 181, 201, 224, 226, 231, 309, 328
- MAVS
biochemical characterization, 138
CARD polymerization in RIG-I antiviral pathway signaling
advantages of prion-like polymerization in signaling, 145–146
MAVS filament structure, 139
modeling of signaling, 139–141
nucleation of prion conversion, 138–139
overview, 136
prospects for study, 146
functional prion, 9–10, 122
HET-s comparison, 142
history of study, 137
prion validation, 138
- MDM2, 418–419, 421

Index

- MDM4, 418
MDMX, 419
Memantine, Alzheimer's disease management, 179
Microtubule-organizing center (MTOC), 66–68
MLN51, 151
[MOD+], 78, 104
[MOT3+], 78, 82
MRI. *See* Magnetic resonance imaging
MSA. *See* Multiple system atrophy
MTOC. *See* Microtubule-organizing center
Multiple system atrophy (MSA)
 classification, 199
 clinical symptoms and diagnosis, 199–200
 diagnosis, 197–198
 differential diagnosis, 202
 epidemiology, 199
 genetics, 201
 imaging, 199–200
 laboratory testing, 201
 pathology, 201, 368–369
 prion bioassays, 404–405
 treatment, 201–202
Neurodegenerative disease. *See also specific diseases*
 clinicoanatomic convergence, 324, 326, 328–331
 onset, 321, 323, 325–329
 phenotypic diversity, 324–325, 328–331
 progression, 321, 323–324, 329–331
Neurofibrillary tangles (NFTs)
 pathology, 361–362
 positron emission tomography, 338–339
 tau lesion spread in Alzheimer's disease, 379–385
NFTs. *See* Neurofibrillary tangles
NLRC4, 144
NLRP3, 10, 136, 141–145
NMR. *See* Nuclear magnetic resonance
Nrp1, 109
NT219, 71
Nuclear magnetic resonance (NMR)
 Het-s(218-289) amyloid fibril structure, 52
 PRP^C structure, 31, 33, 40
NWD2, 97–99, 142–145
[OCT+], 78
Octapeptide repeat insertion/deletion. *See* PRNP
Orb2, 127–128, 158
p53
 amyloid aggregation and oncogenesis, 423–425
 family members and interactions, 425–426
 functional overview, 418
 gain-of-function mutants, 427–428
 mutations and misfolding in cancer development, 420–423
 ordered and intrinsically disordered domains in function,
 418–419
 therapeutic targeting of aggregation, 428–430
p63, 425–428
p73, 425–428
PABP, 151, 154
Parkinson's disease (PD)
 aggregate deposition, 65
 α -synuclein lesion spread, 386–392
 clinical features and diagnosis, 192–193
 differential diagnosis, 194
 epidemiology, 192
 genetics, 193–194
 imaging, 193
 laboratory testing, 193
 pathology, 193, 367–368
 transgenic mouse studies, 311–312
 treatment, 194
Parkinson's disease with dementia (PDD)
 clinical symptoms and diagnosis, 195–197
 differential diagnosis, 199
 epidemiology, 195
 genetics, 198
 imaging, 198
 laboratory testing, 198
 overview, 194
 pathology, 198
 treatment, 199
Parkinson's disease with dementia
 pathology, 367–368
 transgenic mouse studies, 311–312
PD. *See* Parkinson's disease
PDI. *See* Protein disulfide-isomerase
PERK, 64–65, 296
PET. *See* Positron emission tomography
Pick's disease, pathology, 365–366
[PIN+]
 ecology and evolution, 82
 history of study, 76
 variants, 81
Pin3, 110
PINK-1, 194
PK. *See* Proteinase K
PKA. *See* Protein kinase A
PKR. *See* Protein kinase R
PNT1, 144
Positron emission tomography (PET)
 Alzheimer's disease
 amyloid- β , 338–339
 overview, 177
 tau ligands
 lead compounds, 339–342
 overview, 339
 phenyl-butadienyl-benzothiazole compounds,
 344–346
 prospects, 351
 Roche compounds, 350–351
 Siemens-Avid/Lilly compounds, 346–350
 THK compounds, 342–344
 dementia with Lewy bodies, 198
 frontotemporal dementia, 185, 187–188
 Huntington's disease, 203
 multiple system atrophy, 201
PP1R15A, inhibitors, 295–296
Prb1p, 78
Presenilin 1 (PS1), aggregate deposition, 67
PRIMA-1, 429
Primary progressive aphasia. *See* Frontotemporal dementia
Prion
 discovery, 4
 inactivation
 human PrP prions, 409–410
 noncorrosive inactivation, 407
 non-PrP prions, 411–412

- overview, 405–407
- steel wire model, 408–409
- surface-bound prions, 407–408
- World Health Organization guidelines, 407
- milestones of mouse studies, 302–303
- replication, 5, 7–9
- size, 4–5
- Prion cloud model, 78–79
- Prionoid, 55
- PRNP*, 31, 230
 - familial fatal insomnia D178N mutation, 159–160
 - genetic CJD mutations
 - overview, 245, 253
 - A224V, 259
 - D178N, 255, 257
 - E200G, 259
 - E200K, 253–255
 - K194E, 258–259
 - M232R, 258
 - T188R, 258
 - V180I, 257
 - V210I, 257–258
 - Gerstmann–Sträussler–Scheinker disease mutations
 - A117V, 262
 - F198S, 263–264
 - H187R, 264
 - overview, 260–261
 - P102L, 261–262
 - P105L, 264–265
 - indel mutations
 - octapeptide repeat deletion
 - 2-OPRD, 266
 - overview, 265–269
 - octapeptide repeat insertion
 - nonrepeat insertion, 275
 - 2-OPRI, 266
 - 3-OPRI, 270
 - 4-OPRI, 270–271
 - 5-OPRI, 271
 - 6-OPRI, 272–273
 - 7-OPRI, 273
 - 8-OPRI, 273–274
 - 9-OPRI, 274–275
 - 12-OPRI, 275
 - overview, 265–269
 - knockout mouse, 306
 - missense mutations, 246–252
 - mutational spectrum, 242, 244
 - nonsense mutations, 275–278
 - structure, 242–243
- Programmed cell death, Het-s studies
 - Nod-like receptor signaling, 97–99
 - pore-forming domain in execution, 96–97
- Progressive supranuclear palsy (PSP), 189–191
 - pathology, 363–364
 - prion bioassays, 405
- Protein disulfide-isomerase (PDI), 62
- Protein kinase A (PKA), 123
- Protein kinase R (PKR), 153
- Proteinase K (PK), 244, 403
- Proteostasis, therapeutic targeting, 69–71
- PrP-A, mouse studies, 305
- PrP-B, mouse studies, 305
- PRP^C
 - gene. *See PRNP*
 - prion. *See PRP^{Sc}; specific diseases*
 - processing, 243
 - structure, 31–33, 243
- PrP^{Sc}
 - amyloid structural models
 - β -solenoid model of yeast prions, 40–42
 - oligomers, 42–43
 - steric zipper hypothesis of fibril structure, 35–40
 - bioassays
 - cell-free assays, 403
 - cultured cell assays, 403
 - incubation-time assay, 402
 - overview, 401–402
 - rodent transmission of scrapie, 402
 - transgenic and knockout mice, 402
 - inactivation, 409–410
 - PRP^C structure and sequence in conversion, 33–34
 - spontaneous CJD features, 244
 - structural models
 - β 2 strand and β 2– α 2 loop, 44–45
 - parallel in-register β -sheets, 44
 - short, compact fibrils with potential β -helix fold, 44
 - structural polymorphism, 43–44
 - structural requirements
 - infectivity and species specificity, 34–35
 - toxicity, 35–36
 - structure, 243
- PS1. *See Presenilin 1*
- PSEN1*, Alzheimer's disease genetics, 178, 220
- PSEN2*, Alzheimer's disease genetics, 178, 220
- [PSI+]
 - cytoskeleton as scaffold for prionogenesis, 109–110
 - ecology and evolution, 82
 - history of study, 76
 - Hsp70 inhibition of generation, 82–83
 - Hsp104 curing, 84, 104–105
 - maintenance during stress and aging, 111–113
 - overview, 7
 - protein quality control, 108–109
 - replication, 8
 - ribosome-associated chaperone effects, 106–108
 - strains, 8
 - variants, 78–79, 81
 - yeast species differences, 81
- PSP. *See Progressive supranuclear palsy*
- Pub1, 111
- Pumilio, 151
- PYRIN domain. *See ASC*
- QuIC assay, 411–412
- RecACp53, 430
- RHBDL4, 63
- RIG-1 antiviral pathway, MAVS CARD polymerization in signaling
 - advantages of prion-like polymerization in signaling, 145–146
 - MAVS filament structure, 139

Index

- RIG-1 antiviral pathway, MAVS CARD polymerization in signaling (*Continued*)
 modeling of signaling, 139–141
 nucleation of prion conversion, 138–139
 overview, 136
 prospects for study, 146
- RIP1, 98, 144
RIP3, 98, 144
Rnq1, 106
Rpb4, 151
RuvbL1, 114
RuvbL2, 114
Scrapie
 history of study, 2–3
 prion bioassays
 cell-free assays, 403
 cultured cell assays, 403
 incubation-time assay, 402
 overview, 401–402
 rodent transmission of scrapie, 402
 transgenic and knockout mice, 402
- Sec61p, 61
Sephin1, 296
Serotonin, induction of CPEB aggregation, 127
Sgt2, 113
Signal recognition particle (SRP), 61
Sis1, 109
Sla1, 110
Sla2, 110
Slow virus hypothesis, 2
SNCA, 194, 198, 201, 229, 231
SOD1. *See* Superoxide dismutase 1
Spc42, 109
SRC3, 11
SRP. *See* Signal recognition particle
Ssa proteins, 105–106
Ssb proteins, [PSI⁺] inhibition, 82–83, 106–108
Ssz1, 106
STAND proteins, 97
Staufen, 151
Steel wire model, 408–409
Strain, prion
 molecular basis, 7–9
 [PSI⁺], 8
Stress, [PSI⁺] maintenance, 111–113
SUP35, prion validation assay, 138, 141
Sup35p
 prion. *See* [PSI⁺]
 prion domain, 9, 76–78
Sup45, 109
Superoxide dismutase 1 (SOD1)
 amyotrophic lateral sclerosis rational therapeutics, 294–296
 functional overview, 289
 mutations, 290
 prion-like properties
 cell-to-cell transfer, 292–293
 overview of evidence, 294
 propagation, 290–292
 seeding by preformed aggregates, 291–292
 transmission in vivo, 293
 uptake of aggregates, 291
 structure, 289–290
[SWI⁺], 78
Syrian hamster, prion studies, 304–306
TAF15, 166
TARDBP, frontotemporal dementia genetics, 227–228
Tau
 Alzheimer's disease lesion spread, 379–385
 knockout mouse, 311
 positron emission tomography ligands
 lead compounds, 339–342
 overview, 339
 phenyl-butadienyl-benzothiazole compounds, 344–346
 prospects, 351
 Roche compounds, 350–351
 Siemens-Avid/Lilly compounds, 346–350
 THK compounds, 342–344
 prion bioassays, 403–405
 prion initiation, 8–9
 tauopathy overview, 361
 transgenic mouse studies, 309–311
 transmission routes, 381
 trimer prions, 11
TDP-43, 163, 320, 369–370
Tetrabenazine, Huntington's disease management, 204
Tia1, 111
TIA-1
 aggregation
 regulation, 153–154
 structural determinants, 154
 brain function, 131–132
 functional prion evidence, 10–11, 154–158
 prospects for study, 158–159
 RNA metabolism function, 154
 stress granule function, 150–153
 structure, 150
TIA-1-related protein (TIAR), 153
TIAR. *See* TIA-1-related protein
TMEM106B, frontotemporal dementia genetics, 228
TP53. *See* p53
Transthyretin (TTR)
 amyloid fibril structure, 21–22
 familial amyloid polyneuropathy pathophysiology, 7
TTR. *See* Transthyretin
Tumor suppressor. *See* p53
Ubc4, 106
Unfolded protein response (UPR), 63–65, 67, 69
UPR. *See* Unfolded protein response
Ure2p, prion domain, 76–78
[URE3]
 Btn2p curing, 83–84, 109
 ecology and evolution, 82
 history of study, 75–76
 variants, 78, 81
 yeast species differences, 81
VCP, frontotemporal dementia genetics, 228
VP16, 169
X-ray crystallography
 β -solenoid model of yeast prions, 42
 peptide amyloids, 50–51
 PRP^C structure, 33
 steric zipper hypothesis of fibril structure, 36–37