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Genetics of prion diseases

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Prion diseases are transmissible, fatal neurodegenerative diseases that include scrapie and bovine spongiform encephalopathy (BSE) in animals and Creutzfeldt–Jakob disease (CJD) in human. The prion protein gene (*PRNP*) is the major genetic determinant of susceptibility, however, several studies now suggest that other genes are also important. Two recent genome wide association studies in human have identified four new loci of interest: *ZBTB38-RASA2* in UK CJD cases and *MTMR7* and *NPAS2* in variant CJD. Complementary studies in mouse have used complex crosses to identify new modifiers such as *Cpne8* and provided supporting evidence for previously implicated genes (*Rarb* and *Stmn2*). Expression profiling has identified new candidates, including *Hspa13*, which reduces incubation time in a transgenic model.

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Introduction

Prion diseases or transmissible spongiform encephalopathies are fatal neurodegenerative diseases characterised by long incubation periods, accumulation of abnormal prion protein (PrP^{Sc}), spongiosis, gliosis and neuronal loss [1]. They include scrapie and bovine spongiform encephalopathy (BSE) in animals and Creutzfeldt–Jakob disease (CJD) in human. Sporadic CJD typically presents in late middle-old age as a rapidly progressive multifocal cortical dementia with additional neurological features including cerebellar ataxia, pyramidal and extrapyramidal motor dysfunction, myoclonus and dysfunction of the visuoperceptual system. Despite increasing ascertainment, these remain rare conditions, with typical incidences in the developed world of 1–2 cases/million/year. Variant CJD (vCJD), resulting from the human transmission of BSE mainly through dietary exposure, has steadily declined in incidence in the UK since 2000, with a total 176 cases [1,2]. Although the decline in vCJD is most welcome, the prevalence of subclinical infection indicated by anonymous surveys of appendiceal tissue, remains a significant concern at around 1:2000 in the UK (http://www.hpa.org.uk/hpr/archives/2012/news3212.htm#bnrmlprn). Subclinically infected individuals may never convert to clinical cases, however they pose risks for iatrogenic transmission by blood or blood product transfusion, by dentistry and surgery.

PrP is central to the disease process with its misfolded form thought to be the principal component of the infectious particle. Mutations in the prion protein gene (*PRNP*) are causative for inherited prion diseases [3,4] and a common polymorphism (M129V) has a significant effect on susceptibility and phenotype [5,6].

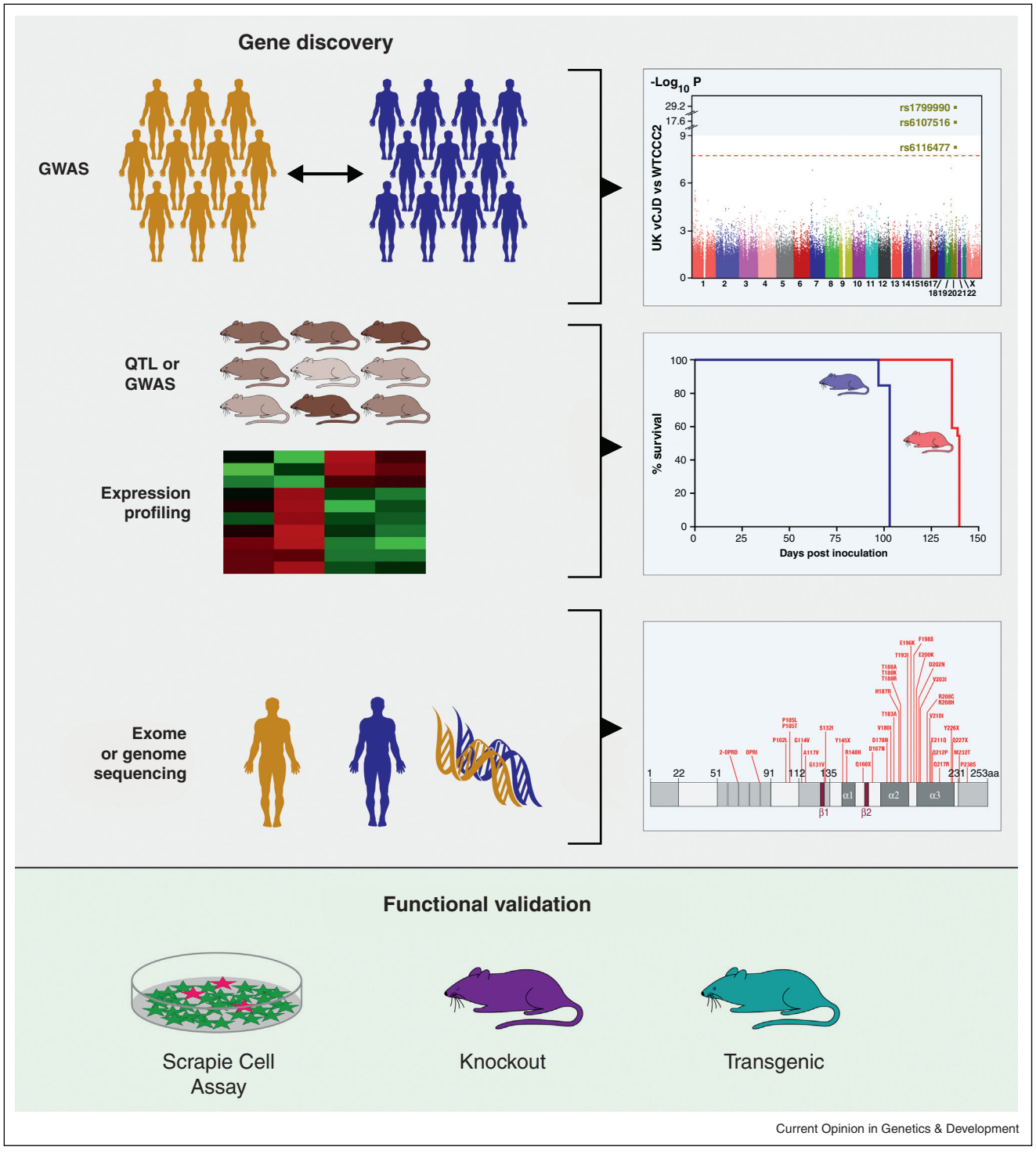
In this review we highlight progress since 2010 in determining genetic susceptibility to prion diseases. The use of human genome-wide association studies (GWAS) and complementary mouse studies reinforce the key role of *PRNP* and identify new genetic modifiers. We outline the challenge of verifying the role of putative modifiers and propose a way forward for gene identification and validation (Figure 1).

Human genetics

Recent work has focussed on the collection of large patient cohorts for GWAS, which has necessarily been an international collaborative endeavour given that human prion diseases are rare. As a generality from common diseases, genetic risk factors discovered by GWAS have been modest in their effects (odds ratios 1–1.2) requiring sample sizes of several thousand to have the statistical power required for unequivocal detection of significant variants. Two collaborative groups are working in prion disease GWAS. The UK MRC Prion Unit in collaboration with the Universities of Munich, Gottingen and Perth has conducted a GWAS of sporadic CJD, variant CJD, iatrogenic CJD, inherited prion disease, and kuru involving over 2000 samples [7,8••]. A Europe-wide collaboration led by Dutch and Spanish investigators published a GWAS of vCJD involving 93 samples [9••]. In these studies, the *PRNP* locus was unequivocally and strongly associated with risk of prion disease, driven by the known coding variation at *PRNP* codon 129.

In the European vCJD GWAS two single nucleotide polymorphisms (SNPs) (rs4921542 and rs7565981) reached genome-wide significance after pooling discovery and replication populations. Rs4921542 ($p = 1.6 \times 10^{-8}$) is an intronic variant in the myotubularin

Figure 1



From modifier gene discovery to functional validation. Current strategies for prion disease susceptibility gene discovery include both human and mouse studies. These include human GWAS case–control studies and complementary QTL and GWAS studies in advanced mouse crosses. GWAS results can be displayed as a Manhattan plot as shown here with highly significant hits shown for *PRNP* SNPs. Expression profiling of key tissues for example comparing short (blue) and long (red) incubation time mice has also revealed new pathways and candidates. Next generation sequencing of patients can now be used to identify high risk alleles at novel genes to generate an allelic mutation series as shown here for *PRNP*. Options for functional validation of candidate genes include both *in vitro* (scrapie cell assay) and *in vivo* approaches (mouse models). GWAS – genome-wide association studies; CJD – Creutzfeldt–Jakob disease; QTL – quantitative trait loci; SNP – single nucleotide polymorphism.