

<b>Characteristic</b>	<b>Classical scrapie</b>	<b>Atypical scrapie</b>
Age of cases	usually 2-3 years	usually older
Genetics, <i>PRNP</i> alleles	VLRQ, ALRQ	AFRQ, ALHQ, ALRR
Pathology, vacuolation and PrP <sup>D</sup> deposition	predominantly brain stem	predominantly cerebral and cerebellar cortices
Western blot profiles	triple banded pattern ~20kDa - ~30kDa, detected by many different anti-PrP antibodies eg 6H4	some cases show multiple bands but all have variable low molecular mass (~7-12kDa) band(s) detected only with antibodies to N terminal regions of PrP molecule eg P4
Protease sensitivity of PrP <sup>Sc</sup>	Resistant to high concentrations of Proteinase K	Much more sensitive to Proteinase K digestion
Transmission to mice	Variable transmission to wild type and transgenic mice depending on isolate	Does not transmit to wild type mice but will transmit to transgenic mice expressing sheep <i>PRNP</i> eg tg338

Table S1: Summary of the main differences between classical and atypical scrapie characteristics.

Inoculum	Scrapie type	Mouse scores for PrPd types and vacuolation				
		ITCL	PRTC	COAL	PLAQ	VACU
Scr2	Atypical scrapie	0	1	3	0.5	3
51x45	Atypical scrapie	0	1	3	0.5	2.5
68x81	Classical scrapie 21kD	1.5	1.5	1	3	1.5
SSBP/1	Classical scrapie 21kD, rapid	1.5	1.5	0	0	0.5
J2916	CH1641 classical scrapie, 19kD	2	2	0	0	0.5
L4824	Unusual case	0	0.5	3	0.5	3
L4823/4*	Unusual case	0	1	1.5	1.5	3
L4823/9*	Unusual case	0.5	1	1	3	0.5
H800	Unusual case	1.5	1.5	0	3	0.5
13X85	Unusual case	1.5	2	2	0	3

Table S2: Immunohistochemistry detected of PrPd in tg338 mice following transmission of unusual sheep scrapie cases and controls. Values are group average from 4 mice per inoculum except for inoculum L4823 where 2 single mice (L4823/4 and L4823/9) were examined. ITCL, intracellular; PRTC, fine particulate; COAL, coalescing; PLAQ, plaques; VACU, overall vacuolation score.

# Sheep sample selection process

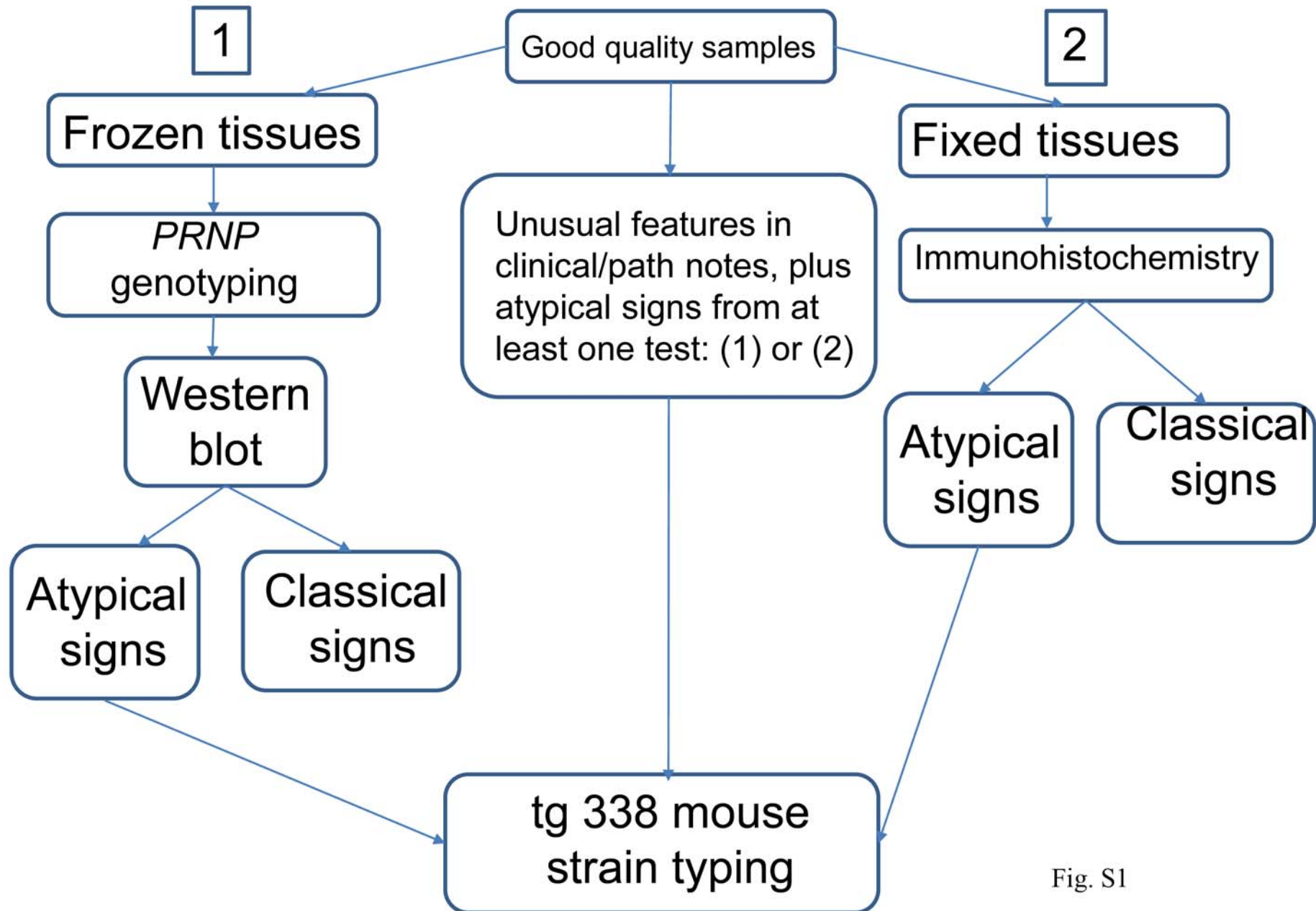


Fig. S1

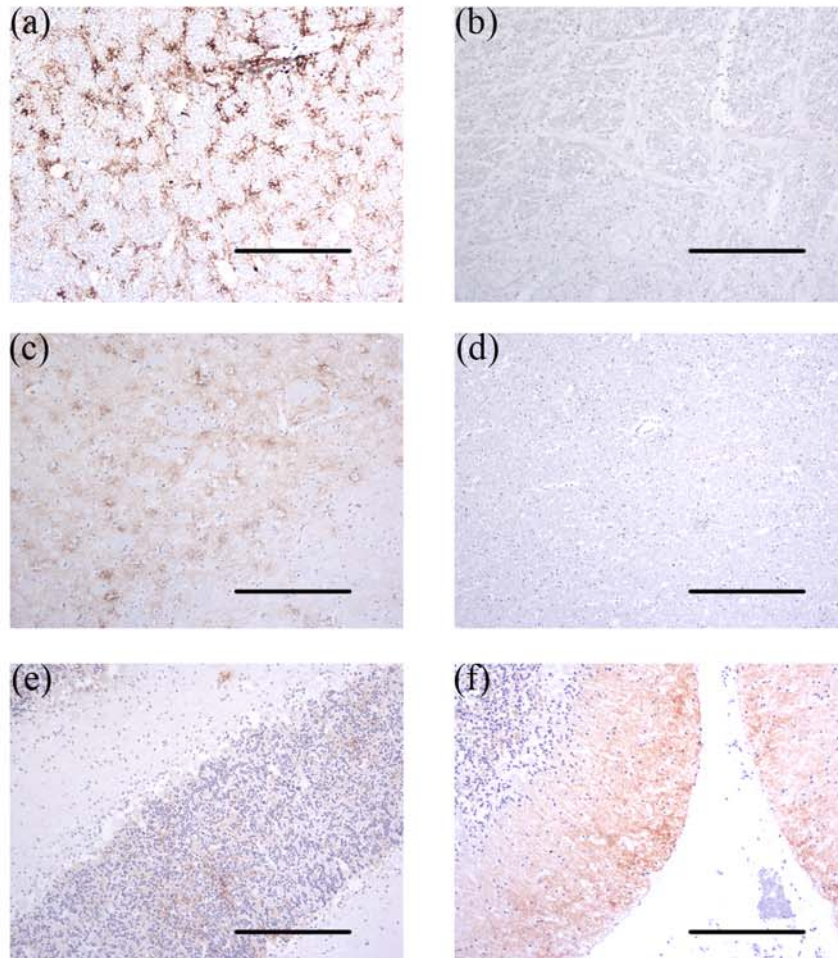


Fig. S2

**Fig S1:** Flow chart of process of selecting candidate atypical scrapie cases from archive samples dating back to 1960s.

**Fig. S2:** Immunohistochemistry using BG4 of brain sections from scrapie case L4823 (a, c, e) and its unusual scrapie case flockmate L4824 (b, d and f). Obex (a) and (b), basal ganglia (c) and (d), cerebellum (e) and (f). Size bars=500 $\mu$ m.