



Figure 1 Cumulative number of clinical staff in our unit with serological H1N1 influenza over a 7-day period.

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First independent replication study confirms the strong genetic association of *ANXA11* with sarcoidosis

Sarcoidosis is an inflammatory disease characterised by the presence of granulomas that can affect the skin, lungs, heart, brain and nervous system, eyes and various other tissues and organs.¹ The disease can present in an acute or subacute form and is often self-limiting, but in many cases it is chronic with variable disease activity over many years.² A genetic association between sarcoidosis and a truncating splice-site mutation in the gene *BTNL2* (butyrophilin-like 2, a member of the immunoglobulin gene family) has been confirmed in different studies and populations.^{3–5}

Very recently the first whole-genome association study (WGAS) reported a strong association between sarcoidosis and *ANXA11* (annexin A11) on chromosome 10q22.3, a member of the annexin family of calcium-dependent phospholipid-binding proteins involved in structural organisation of the cell, growth control, calcium signalling, cell division, vesicle trafficking and apoptosis.^{6,7} Different single nucleotide polymorphisms (SNPs) within and downstream of the *ANXA11* gene were strongly associated with sarcoidosis, including one non-synonymous SNP rs1049550 (c.688T→C, p.C230R) and several intronic or intergenic SNPs (rs1953600, rs2573346, rs2784773, rs2789679). The associated SNPs were in strong linkage disequilibrium.

To replicate the association in an independent cohort, we performed a case–control association study in 325 patients (mean age 52.1 years) and 364 healthy matched controls (healthy white German subjects, mean age 49.7 years). The diagnosis of sarcoidosis was based on evidence of non-caseating epithelioid cell granuloma in biopsy specimens and chest radiographic abnormalities. A chronic course was defined as disease over at least 2 years or at least two episodes in a lifetime. Acute sarcoidosis was defined as one episode of acute sarcoidosis which had totally resolved at the date of the examination. None of the individuals in the control group had a history of lung disease or showed any symptoms of

lung or other disease by chest radiography or laboratory blood tests.

The C allele frequency of rs1049550 was significantly increased in the patients with sarcoidosis (C=0.6504, T=0.3496 in cases; C=0.5479, T=0.4521 in controls; $p=0.00014$, table 1). It was significantly associated with an increased risk of sarcoidosis in the individuals carrying the CC genotype (OR 2.18, 95% CI 1.39 to 3.43; $p=0.00065$). The increased risk was present in both dominant and recessive models ($p=0.017$ and $p=0.0004$, respectively). The allelic and genotypic risk of rs2573346 with sarcoidosis was even stronger, as described previously (allelic $p=0.00008$ and genotypic $p=0.00022$). The calculated population attributable risk (PAR) for rs2573346 CC homozygotes and CT heterozygotes was 21%. These data independently confirm the strong association between variations in *ANXA11* and sarcoidosis and support the hypothesis that *ANXA11* represents a strong genetic risk factor for sarcoidosis.

In contrast to the previously reported difference in association to *BTNL2* in our patient cohort,⁵ there was no statistical difference between acute and chronic forms of sarcoidosis and rs1049550 or rs2573346 alleles, and both groups showed a significant allelic and genotypic association for both SNPs (table 1). However, this effect was slightly more pronounced in the chronic form, which was the larger subgroup with higher statistical power. All p values obtained in our study withstand a conservative Bonferroni correction for multiple testing.

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Table 1 Statistical analysis of the case–control study

SNPs		Controls	Cases	OR(95% CI)	p Value	Acute*	p Value	Chronic*	p Value	
rs1049550	Allele	T	283 (45%)	244 (35%)	1	82 (35%)		119 (34%)		
		C	343 (55%)	454 (65%)	1.54 (1.23 to 1.92)	0.00014	152 (65%)	0.0073	233 (66%)	0.0005
	Genotype	TT	65 (21%)	48 (14%)	1	18 (16%)		24 (14%)		
		CT	153 (49%)	148 (42%)	1.31 (0.85 to 2.03)	0.2245	46 (39%)		71 (40%)	
		CC	95 (30%)	153 (44%)	2.18 (1.39 to 3.43)	0.00065	53 (45%)	0.0143	81 (46%)	0.0018
rs2573346	Allele	T	303 (47%)	260 (37%)	1	86 (36%)		129 (35%)		
		C	341 (53%)	452 (63%)	1.55 (1.24 to 1.92)	0.00008	150 (64%)	0.0050	239 (65%)	0.00074
	Genotype	TT	71 (22%)	50 (14%)	1	18 (16%)		26 (15%)		
		CT	161 (50%)	160 (45%)	1.41 (0.93 to 2.15)	0.1097	50 (42%)		77 (43%)	
		CC	90 (28%)	146 (41%)	2.30 (1.47 to 3.60)	0.00022	50 (42%)	0.0131	76 (42%)	0.0027

Significant associations are shown in bold.

*Only patients with unequivocal classification were included.

Competing interests None.

Ethics approval This study was conducted with the approval of the University of Bonn 060/05.

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