Autoimmune polyendocrine syndrome (APS1) in India: clinical aspects, *AIRE* mutations and functional analysis

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Introduction

- APS1 is an uncommon serious autosomal recessive disorder. It results from mutations in the *AIRE* gene and leads to impaired central tolerance
- Indians have a complex genetic background with ancestral gene populations, genetic admixture and communities with high consanguinity
- Awareness of APS1 is poor among physicians

Objectives

- To study clinical features, interferon-α antibodies (IFNA), *AIRE* mutations in 20 Indian APS1 patients and *in-silico* functional analysis of novel mutations

Patients and methods

- 20 patients (17 families) from 6 academic centers in India [including follow-up of 9 patients previously reported by us (Clin Genet 2009: 76:441)]
- IFNA measurement, bidirectional sequencing of *AIRE* gene, *in-silico* functional analysis of novel mutations were performed

Results

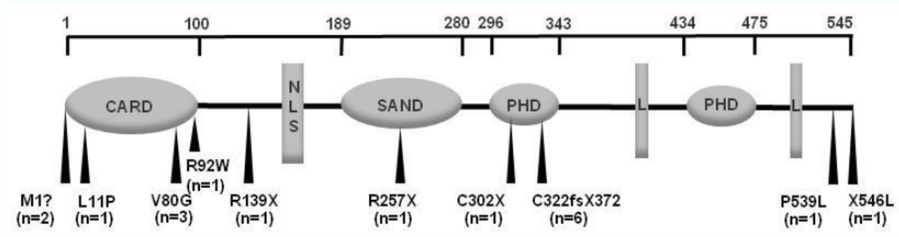
Clinical manifestations (n=20)

Age (yrs)	13 (4-30)
Age at first manifestation (yrs)	3 (0.5-15)
Consanguinity	9 (53%)
Major manifestations	
Muco-cutaneous candidiasis	19 (95%)
Hypoparathyroidism	18 (90%)
Primary adrenal insufficiency	13 (65%)
Number of manifestations/patient	5 (2-10)
Unusual features	Sjogren syndrome, chronic sinusitis, facial asymmetry/ptosis, absence of kerato-conjunctivitis
Elevated interferon α antibody	18/18 (100%)
Titer (normal <0.03)	2.0 (0.26-4.08)
	Median (range)

Mortality

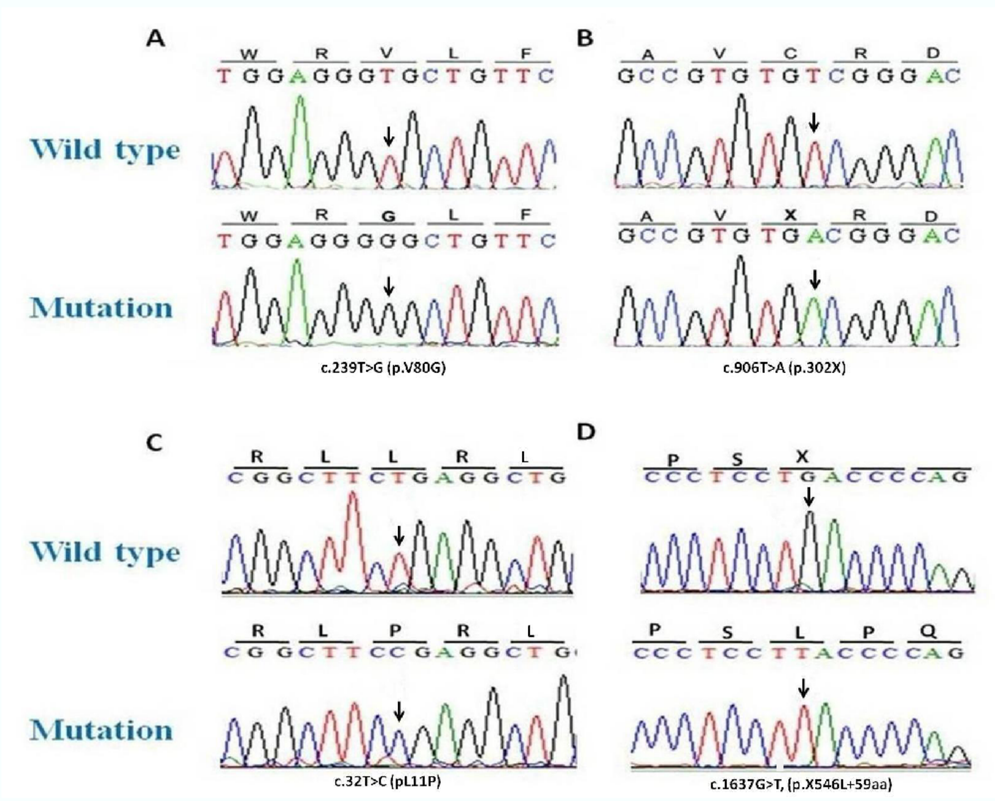
Frequency	6 (30%)
Age at death (yrs)	5 (4-23)
Cause	Septicemia (2), hepatic failure (1), unknown (1), poor compliance (2)
Mutations	C967_979del13 (4), L11P (1), R257X (1)

AIRE mutations (17 families)

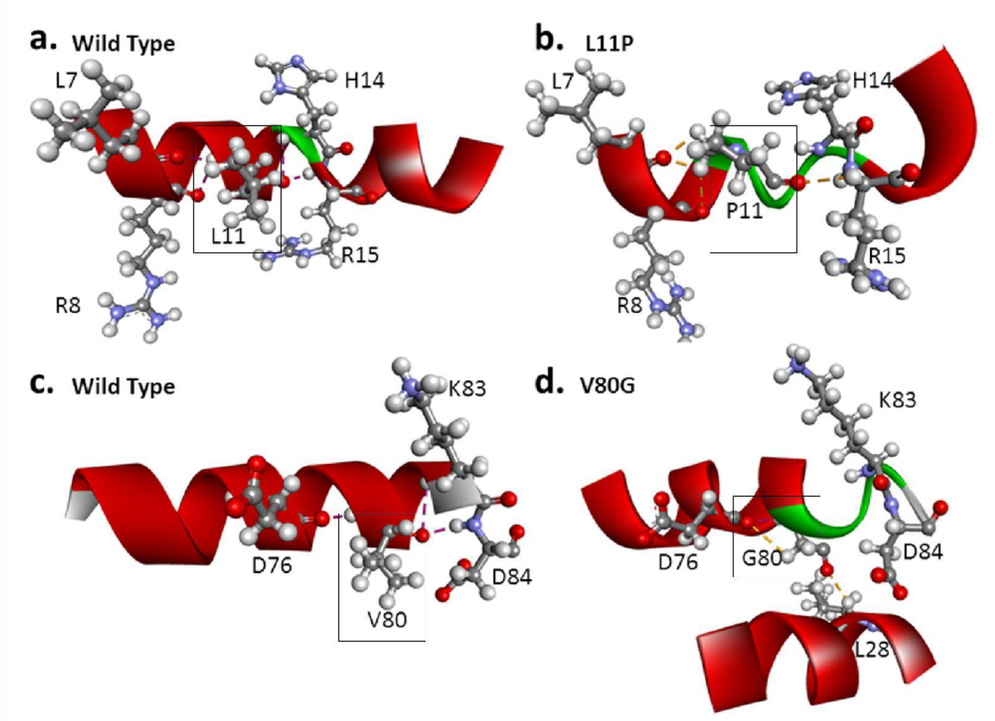


1 proband was heterozygous for R139X and M1?

Novel *AIRE* mutations



In-silico functional analysis



Novel missense mutations (V80G, L11P) in the CARD domain result in changes in intra-helical hydrogen binding, which are likely to cause protein instability

Conclusions

- APS1 had a wide spectrum; consanguinity was frequent; mortality was high and occurred at an early age
- Ten *AIRE* mutations were detected, including 4 novel mutations; the 13 bp deletion in exon 8 was found in 37%; V80G is likely to be a founder mutation in the small in-bred Vanika Vaisya community
- Functional analysis of novel CARD domain mutations revealed disruption of intra-helical hydrogen binding and increased instability

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