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University of Messina - Department of Pediatric Sciences

Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy: new insights into phenotype and genotype

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Background: Autoimmune-poly-endocrinopathy-candidiasis-ectodermal-dystrophy (APECED), also known as polyglandular syndrome type 1 (APS-1), is a rare disease of childhood, with a low overall prevalence and about 400 cases described worldwide. It is characterized by three main diseases: chronic mucocutaneous candidiasis (CMC), chronic hypoparathyroidism (HP) and Addison's disease (AD). In addition, many other autoimmune diseases or manifestations of ectodermal dystrophy may be present. APS-1 occurs worldwide but is most prevalent among genetically isolated Finnish, Sardinian and Iranian Jewish populations. The disorder is caused by mutation in the *AIRE* (AutoImmune REgulator) gene; more than 60 different mutations have been reported so far. In Sicilian population, only eight patients were identified to date, and described elsewhere. In 56% of the alleles the authors found the rare mutation of the Autoimmune Regulator (*AIRE*) gene named R203X, that has been considered to date as pathognomonic of Sicilian APECED patients.

Objectives: Aims of the present study are: a) to report seven additional Sicilian patients with APECED; b) to describe an *AIRE* gene mutation that had never been reported to now and to review clinical, genetic and immunological peculiarities of APECED in Sicily, on the basis of the overall population of 15 patients that our collaborative group has identified and investigated in the last years.

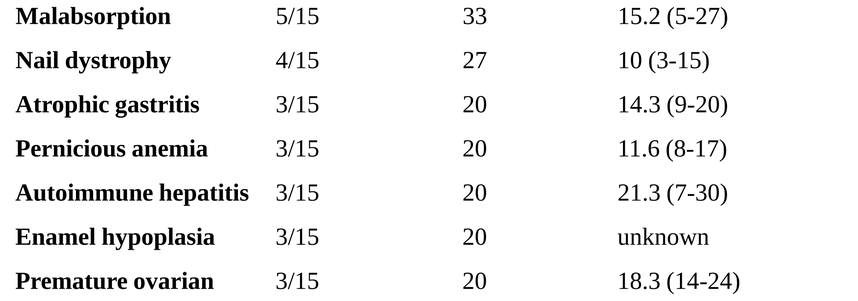
Clinical, genotypical and immunological features

Patient	Age at last visit	Age at CMC onset	Age at HP onset	Age at AD onset	Gene mutations	IFN ω Abs	Other Abs	References
1	**3.6**	**1**	**2.6**	**2.6**	**A21V/W78R**	**+**	**TPHAbs, AADC**	**This report**
2	**36**	**2**	**3.4**	**7.5**	**W78R/R257X**	**+**	**TPHAbs, AADC**	"
3[A]	**9**	**1**	**5**	**9**	**c.1566+2-1566+3insT/1566+2-1566+3insT**	**+**	**-**	"
4[A]	**15**	**1**	**11**	**-**	**c.1566+2-1566+3insT/1566+2-1566+3insT ***	**+**	**TPHAbs, AADC**	"
5[B]	**8.5**	**5**	**6**	**6**	**A21V/R257X**	**+**	**-**	"
6[B]	**13**	**-**	**10**	**-**	**A21V/R257X**	**+**	**-**	"
7	**32**	**-**	**11.2**	**20**	**A21V/C322fs/X372**	**+**	**TPHAbs**	"
8	38	1	5	-	R203X/R139X	-	-	J Endocrinol Invest 2012; 35:384-8
9	31	24	8	-	R203X/R203X	+	-	J Endocrinol Invest 2012; 35:384-8
10[C]	22	1	11	14	R203X/R257X	+	TPHAbs, AADC	Eur J Ped 2008; 167:1283-8 Eur IJ Ped 2009; 168:237-240
11[C]	18†	1	4	17	R203X/R257X	+	TPHAbs, AADC	Clin Endocrinol 2009; 70:421-428
12	33	12	10	22	R203X/R203X	+	TPHAbs, AADC, NALP5Abs	Clin Endocrinol 2009; 70:421-428
13	38	15	4	25	R257X/R203X	+	TPHAbs, AADC	J Endocrinol Invest 2012; 35:384-8
14	9	-	3	-	R203X/IVS9+5G>T	+	-	Clin Endocrinol 2009; 70:421-428
15	7	1	3	7	T16M/S107C/Q108sf	+	TPHAbs, AADC	Gene 2012; 499:343-6

Results

	N° of diseases/ total cases	Frequency	Median age at presentation (range)
Hypoparathyroidism	15/15	100	6.5 (2.6-11.2)
Addison's disease	10/15	67	7.2 (2.6-20)
Chronic candidiasis	12/15	80	5 (1-24)
Malabsorption	5/15	33	15.2 (5-27)
Nail dystrophy	4/15	27	10 (3-15)
Atrophic gastritis	3/15	20	14.3 (9-20)
Pernicious anemia	3/15	20	11.6 (8-17)
Autoimmune hepatitis	3/15	20	21.3 (7-30)
Enamel hypoplasia	3/15	20	unknown
Premature ovarian failure	3/15	20	18.3 (14-24)
Vitiligo	3/15	20	15.6 (6-27)
Autoimmune thyroiditis	2/15	13	24 (7-30)
Keratoconjunctivitis	2/15	13	14 (2-26)
Alopecia	2/15	13	7 (3-11)
Cholelitiasis	1/15	7	unknown
Chronic demielynating polyneuropathy	1/15	7	unknown
Constipation	1/15	7	8
Type 1 diabetes mellitus	1/15	7	22
Pulmonary disease	1/15	7	5

****New mutation***



Homozygous insertion T at IVS13+2

Conclusion:

On the basis of our experience we can infer that:

a) the clinical manifestation that can be considered as connotative of APECED in Sicilian patient is HP (100% of cases);
b) the most frequent mutation in Sicilian APECED patient is R203X, that is peculiar of our population, but other mutations could be present as W78R, typical of Apulian cases and A21V typical of Campania;
c) the triad of the syndrome may appear very early in the life as observed in one patient of our series; for this reason the clinicians should be vigilant in order to initiate treatment very early.