

The Italian Registry for Angelman Syndrome (RISA): an innovative patient-driven initiative in a rare neurological condition genetically determined



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Summary

Angelman syndrome (AS) is a **rare neurodevelopmental disorder** caused by dysfunction of the **maternally inherited UBE3A gene on the chromosome 15q11-13**, caused by four known genetic mechanisms: deletion, uniparental disomy, imprinting defect or mutation, while 10% of cases remained unknown on the genetic changes.

Treatments are symptomatic with no therapy that addresses the underlying etiological mechanisms by which UBE3A deficiency results in AS. Low prevalence and lack of disease knowledge in AS justify a need for different research strategies. In this perspective, a **patient-centered research** may shed light on symptom severity, functionality, treatments and health-related quality of life. In February 2018, the Italian Registry on AS (RISA) started as data repository for the collection of comprehensive **clinical, genetic and therapeutic information about AS patients living in the Italian territory**.

- **Aims:** to improve the understanding of disease mechanisms and natural history, to develop further studies, to inform families about research progress.

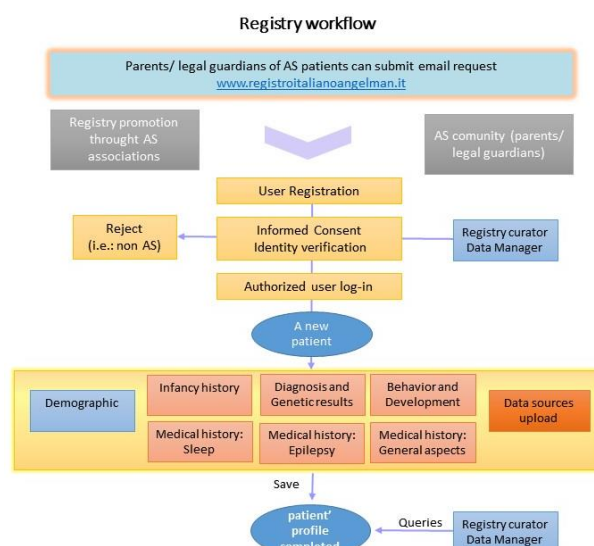
The involvement of parents and legal guardians contribute to improving the robustness, comprehensiveness, quality and quantity of data collected.

This poster details the key operation procedures, the methodology and the current status of the RISA.

RISA is compliant with the Data Protection Regulation (EU) 2016/679 by ensuring patient pseudonymization, secure data storage, user authentication and audit trail. All Italian patients with a genetic diagnosis of AS are potentially eligible. Parents/legal guardians interested to participate can submit data via a secure internet connection.

By the cut-off date (February 15, 2020), there were 64 participants enrolled in the RISA. Overall 93 registration requests have been sent (69% completed the registration process). Patients come from 14 Italian regions, the majority of patients are actually **aged ≤12 years (64%)**.

Most of them present a **deletion (63%)**, with the remaining showing uniparental disomy, imprinting defect or mutation.



Demographic	
Age (≤12yrs / > 12yrs)	41/23
Sex (male/ female)	29/35
Origin (Caucasian), n(%)	63(98)
Genotype, n(%) (n=43)	
Deletion	27(63)
Uniparental paternal disomy	7(16)
Imprinting defect	2(5)
Mutation	4(9)
Unknown	3(7)
Symptoms, n(%) (n=48)	
Epilepsy	37(77)
Sleep disorders	41(85)
Gastrointestinal problems*	34(71)
Strabismus	19(39)
Hearing problems	18(37)
Pneumonia others respiratory problems	9(19) 17(35)
Movement disorders**	33(69)

Demographic and clinical information among included patients. Data are relative to validated data. Defined as at least two symptoms among: *(drooling, reflux or vomiting with feeds); *(scoliosis, tight heels cords/ toe walking, no walk ability).

Epilepsy has been reported on **77%** of AS patients. Atypical absences, generalized/ tonic-clonic seizures, febrile seizures and convulsions are described. Among those **84%** received a specific **treatment**. Severe epilepsy with drug resistant seizures occurred in the 7% of patients, in the remaining seizures are controlled by anti-epileptic drugs.

Sleep disorders have been described on **85%** of patients, of which **37%** received a specific **treatment**. The median numbers of parent-reported nocturnal awakenings is 4.6.

Conclusion

From this report, we have the opportunity to demonstrate:

- the successful deployment of the first Italian patient-driven registry for AS
- a better characterization of AS patient profile
- the reliability of parent/ caregiver data reporting

The data generated from the Registry will be crucial in identifying patients suitable for clinical trials and in informing research that will identify treatments for AS and ultimately to improve the lives of individuals and their families living with AS.

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References: Angelman H. Puppet children. A report on three cases. Dev Med Child Neurol 1965;7:681-8; Clayton-Smith J, Laan L. Angelman syndrome: a review of the clinical and genetic aspects. J Med Genet 2003;40:87-95; Horsler K., Oliver C. The behavioural phenotypes of Angelman syndrome. J Intellect Disabil Res. 2006;50:33-53; Slade A. et al., Patient reported outcome measures in rare diseases: a narrative review. Orphanet J Rare Dis. 2018;13:61; Tones M. et al., Research protocol: The initiation, design and establishment of the Global Angelman Syndrome Registry. J Intellect Disabil Res. 2018;62:43; Christos Tsagkaris et al., Gene Therapy for Angelman Syndrome: Contemporary Approaches and Future Endeavors. Curr Gene Ther 2020

RISA had been registered at www.clinicaltrials.gov (ID: NCT03650569) and listed on Orphanet.

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