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The Italian Angelman Syndrome Registry (IReAS): a tool for standardized data collection and genotype-phenotype analysis

Giorgia Buoncuore [a], Marco Salvatore [a,*], Adele Rocchetti [a], Lorenzo Facciaroni [a], Edvige Veneselli [b], Maurizio Elia [c,d], Silvia Russo [e], Michelina Armando [f], Michele Germano [g], Tommaso Prisco [h], Stefano Sartori [i], Gemma Marinella [j], Roberta Battini [j,k], Giuseppe Gobbi [l], Paola Torreri [a], Angelman Syndrome Registry working group

[a] Undiagnosed Rare Diseases Interdepartmental Unit, National Center Rare Diseases Istituto Superiore di Sanità, Viale Regina Elena 299, 00161, Rome, Italy
[b] Dipartimento Scienze Medico-Pediatriche U.O.C. Neuropsichiatria Infantile IRCCS Istituto Giannina Gaslini, Genova
[c] Department of Medicine and Surgery, Kore University of Enna, Enna, Italy
[d] Oasi Research Institute-IRCCS, Troina, EN, Italy
[e] Research Laboratory of Medical Cytogenetics and Molecular Genetics, IRCCS Istituto Auxologico Italiano, Milan, Italy
[f] Department of Neuroscience and Neurorehabilitation, Pediatric Hospital Bambino Gesù, Rome, Italy
[g] Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, Italy
[h] Organizzazione Sindrome di Angelman Onlus (OR.S.A.), Italy
[i] Pediatric Neurology and Neurophysiology Unit, Department of Women's and Children's Health, University of Padua, Padua, Italy
[j] Developmental Neuroscience Department, IRCCS Fondazione Stella Maris, Italy
[k] Department of Clinical and Experimental Medicine, University of Pisa, Italy
[l] Infantile Neuropsychiatric Unit – IRCCS – Institute of Neurological Science, Bologna, Italy

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ABSTRACT

Background: Angelman syndrome (AS) is a rare and heterogeneous genetic disorder characterized by intellectual and psychomotor delay, speech deficits, seizures and behavioural issues. To evaluate the feasibility of collecting data by many Italian centers involved in pathology management, and to investigate the relationship between various symptoms and genotypes, a dedicated AS registry was developed.
This study aims to present preliminary findings from the Italian AS registry (IReAS), with a specific focus on exploring genotype-phenotype correlations.
Materials and methods: The IReAS, established in 2020, aims to collect information from 14 different Italian referral. It includes demography, diagnosis and genetic, patient status, therapeutic interventions and mortality data collection.
Results: 213 patients (55.4 % female *vs* 44.6 % male) were included in the IReAS during the 2020–24 period. Average age at genetic diagnosis was 3.8 years; 63 % of patients was paediatric; 70.4 % of subjects had maternal deletion. Most patients exhibited global developmental delay (100 %), movement disorders (94.8 %), behavioral abnormalities (96.2 %), and a total lack of language development (95.8 %). Epilepsy is also highly prevalent (80.3 %), with a significantly higher incidence in patients with maternal deletion compared to non-deletion groups (88 % *vs* 61.9 %).
Conclusions: The IReAS provides comprehensive data on the diagnosis, genetic subtypes and clinical features of AS patients. It can facilitate genotype-phenotype correlation analyses, offering insights into the AS natural history and potential implications for research on targeted therapies.

* Corresponding author. Undiagnosed Rare Diseases Interdepartmental Unit National Center Rare Diseases Istituto Superiore di Sanità, Viale Regina Elena 299, Rome, Italy.
E-mail address: marco.salvatore@iss.it (M. Salvatore).

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1. Introduction

Angelman syndrome (AS) is a rare disease that causes intellectual and developmental disabilities, significant delays in language acquisition, gait ataxia and musculoskeletal anomalies, distinct facial features, hyperactivity, epilepsy and a characteristically cheerful demeanor. The population prevalence of AS is estimated to range between 1 in 10,000 and 1 in 62,000 individuals (Wheeler et al., 2017). However, the exact prevalence or incidence of AS is not available in Italy yet.

This syndrome arises from genetic disruptions in the 15q11-13 region of chromosome 15, where the ubiquitin–protein ligase E3A (UBE3A) gene resides. In approximately 70–75 % of cases, the disorder is caused by deletions on the maternal copy of the chromosome. However, other genetic mechanisms, such as paternal uniparental disomy, imprinting errors, and point mutations can also trigger AS (Dagli et al., 1998).

Characterizing genetic subtypes is crucial, as several studies have demonstrated that the clinical phenotype varies across different genotypes. Typically, individuals with a deletion variant exhibit a more severe phenotype, whereas those with uniparental disomy or imprinting defects present a milder phenotype (Yang et al., 2021a). Understanding genotype-phenotype correlations is necessary for advancing a precision medicine approach to AS. Specifically, gene therapy is an emerging therapeutic option for AS, since it corrects the genetic defect and restores the activity of the gene UBE3A. In this sense, patient genotype characterization is determining for both selecting eligible patients for specific treatments and developing innovative treatment strategies for AS (Tesi et al., 2023).

No specific pharmacological therapies exist for AS right now. Treatments are focused primarily on managing symptoms such as epilepsy and sleep disturbances (Keary and McDougle, 2023). Non-pharmacological approaches, including physiotherapy, speech interventions and occupational therapy play a critical role in improving the quality of life of people living with AS (Duis et al., 2022).

The multifaceted nature of AS and the absence of targeted treatments often complicate patient management, requiring the coordination of care across multiple specialists (Fehr and Prütz, 2023) highlighting the need for a complete understanding of the AS syndrome's clinical and genetic relationship. Promising disease-modifying strategies are under investigation, particularly antisense oligonucleotide (ASO) therapies aimed at reactivating the paternal UBE3A allele. Ongoing trials include GTX-102 (Ultragenyx), ION582 (Ionis Pharmaceuticals), and Rugonersen (RO7248824) evaluated in the TANGELO study (Roche/Oak Hill Bio) (Ultragenyx Pharmaceutical Inc.; Ionis Pharmaceuticals and Inc, 2025; Hipp et al., 2025).

The use of disease registries in rare diseases has become essential in recent years i) serving as a very useful tools to collect, in a standardized way, clinical and demographic data, ii) supporting scientific research to improve understanding of the disease and iii) facilitating the development of new treatments and therapies (Kodra et al., 2019).

Previous experience on Angelman syndrome data collection (Napier et al., 2017; Krey et al., 2021; Carriero et al., 2024) showed how important it is to foster and speed up this process involving the clinicians, researchers and patients' associations.

In 2016, a national digital platform (RegistRare) was developed by the Italian Institute of Health's (ISS) with the final aim of providing rare disease Patient's Association the opportunity to develop a registry for their condition, benefiting from significant economic advantages (the platform used is customizable and can be adapted for all requirements at costs that are truly affordable for everyone). RegistRare is supported by IT technologies that ensure data security, privacy and reliability, fostering high-quality research while protecting patient privacy in accordance with European regulations (Salvatore et al., 2023).

The Italian AS registry (IReAS) was developed within RegistRare platform in 2020 establishing a formal collaboration among the Italian AS Patient Association (OR.S.A), fourteen different AS Italian referral centers[1] and ISS.

The IReAS aims to enhance clinical and genetic understanding of AS, improving patient management, providing better epidemiological data at national and international levels, and supporting clinical research for drug development. In this study, we analyze data from 213 AS patients enrolled during July 2020–December 2024 period.

2. Materials and methods

2.1. Registry scope

The registry collects comprehensive clinical and genetic information about people diagnosed with AS in Italy managed at most (N = 14) of the Italian Referral centers for Angelman Syndrome, to achieve the widest national coverage possible.

Specific aims of the registry are i) to evaluate the clinical history of people with AS, ii) to investigate any eventual genotype-phenotype correlation, iii) to improve and to standardize patient care throughout Italy, iv) to speed up research and to support the development of novel treatments by assessing long-term patient outcomes. IReAS data are also compared to those from the AS Consensus Statement criteria (Duis et al., 2022; Williams et al., 2006).

2.2. Registry design and protocol

1. Study Design

Fourteen different Italian paediatric and adult referral centers have voluntarily enrolled in the study and contributed to registry activities. Clinicians from these referral centers are responsible for information inclusion within the registry. Incident and prevalent cases are currently collected. Center participation is on a voluntary basis and, for patient inclusion, the completion and signing of a specifically developed informed consent (IC), established in accordance with the relevant regulations and approved by the local institutional ethics committee, is mandatory.

2. Governance

Activities are supervised by a specific Scientific Committee (SC) overseeing and coordinating the registry, preparing an annual report and handling requests for both internal and external data analysis. The members of the Scientific Committee include the presence and close collaboration of clinicians, geneticists, statisticians, and researchers in the socio-health field.

3. Registry datasets and data entry

The clinical variables included in the registry are agreed upon by all members of the Scientific Committee, establishing clear units of measurement, coding systems, and the specific meanings of each variable used. The IReAS includes variables from the "Set of Common Data Elements for Rare Diseases Registration", provided by the Joint Research Centre (JRC).

Data collection is organized into *enrolment* and *visit* categories including, information about demography, sex, date of birth, diagnostic details, genetics (including exact pathogenic variants), informed consent, follow-up visits, clinical characterization and ongoing treatments.

[1] A referral hospital is a specialized hospital that provides advanced (tertiary or quaternary) care for complex, rare, or specialized cases requiring specialized equipment and specialists. It receives referrals from primary care physicians or smaller hospitals, and often also carries out teaching and research.

The dataset of the Registry was defined by the clinicians and experts of the Registry SC, in accordance with the recommendations provided by international consensus documents (Duis et al., 2022; Williams et al., 2006; Beygo et al., 2019). Data collection and entry are performed by the clinicians working in the participating hospital centers, under a specific collaboration agreement. Data are entered during, or immediately after, patient follow-up and control visits. Follow-up of data is scheduled once-a-year. The data included in the registry are entered by each clinician using the information already available in the patients' hospital medical records. The patients are not involved in the data-entry process, but their signature (or that of a legal guardian) on a specific informed consent form developed for the purposes of the registry is mandatory.

4. Registry ethics, privacy and security

The Registry complied with Directive 95/46/EC (General Data Protection Regulation) on data protection and received appropriate ethical approval from the National ethics committee for clinical trials of public research bodies (EPR) and other national public institutions (CEN) and a Data Protection Impact Assessment (DPIA) is provided. Local ethics committees of clinical partners can contribute to the registry whenever required.

The IReAS is housed within the secure IT Italian National Pathology Registry Platform infrastructure named "RegistRare". All data are stored within this secure infrastructure and can only be accessed by authorized personnel. Web access is only possible for authorized users with a two-factors authentication. Patients can access the registry exclusively using qualified e-signature. Data is pseudonymized by the site entering the data. Data is used (and shared) in an aggregated form.

2.3. Data quality controls and data curation

The data in the Registry are curated by the Registry Coordinator (Istituto Superiore di Sanità, ISS) in collaboration with a dedicated Scientific Committee. The curation process involves a multidisciplinary team including clinicians, geneticists, statisticians, researchers, and IT managers, who jointly ensure data accuracy, consistency, and completeness.

Several validation processes are in place to guarantee the quality of the data upon entry. The first check is based on the use of default data types and predefined response options; to distinguish between *not answered* and *unknown* entries, the register IT team developed an algorithm preventing free text entry. This results in a reduction of errors associated with manual data input and standardization through predefined selectable options. Each case included in the registry is carefully reviewed by a multidisciplinary team of experts (mainly clinicians, geneticists, and researchers in the field) capable of identifying any potential anomalies or discrepancies between the reported data (e.g., diagnoses, clinical signs) and the patient's genetic findings. Any discrepancies or anomalies identified are addressed through targeted data queries sent back to the participating centers for clarification. Cases with unresolved inconsistencies are definitively excluded from the analyses.

Finally, an additional check has been introduced at genetic level to assure appropriateness of performed genetic analysis with clinical indications to validate *consistency* among clinical, genetic and molecular AS diagnosis. In this process, the geneticist's review is based on an evaluation of the genetic testing results (specifically, the type of pathogenic variant reported in the laboratory report) in relation to the patient's clinical diagnosis, as documented in the anonymized medical report uploaded to the platform by the responsible clinician at the participating center.

2.4. Patients' inclusion criteria

All individuals of any age living in Italy and with a diagnosis (evidenced by genetic tests) of AS are included. For this study individuals assessed by molecular testing, were selected on the basis of the AS multidisciplinary approach and consensus statement (Duis et al., 2022), the European Molecular Quality Network (EMQN) and the Association for Clinical Genomic Science (ACGS) best practice guidelines (Williams et al., 2006; Beygo et al., 2019). The inclusion criteria comprise male and female subjects of all ages characterized by: i) maternal deletion of chromosome 15q11–13, ii) UBE3A mutations, iii) paternal uniparental disomy of chromosome 15, iv) imprinting defects.

The register includes patients with a diagnosis performed before MS-MLPA was set up. In these cases, the presence of the deletion was ascertained by karyotype and FISH, and the microsatellite segregation confirmed the parental origin of the chromosome. In the past the diagnosis was confirmed in presence of a 15q11.2-q13 deletion, if clinical signs were concordant with the diagnosis.

"Angelman-like" patients, individuals presenting clinical features of AS without genetic confirmation, are also included in the IReAS but not among the cases analyzed in the present study.

Finally, although it cannot be ruled out a priori that factors such as extreme prematurity and/or concomitant presence of other syndromes (e.g. Down syndrome) may have contributed to the developmental delay and other medical complications observed in these participants we didn't exclude these patients from our registry and analyses.

2.5. Statistical analysis

The statistical analyses of the IReAS data involved descriptive analyses and, in the second phase, focused on determining any potential association between the cohort subgroups - namely AS deletion and AS non-deletion. The demographic information was described using median and interquartile range as indices of position and dispersion for quantitative variables and absolute and percentage frequencies for qualitative ones. After stratifying the sample into subgroups, statistical significance was assessed for differences across subgroups: the Chi-Square Test was used to evaluate associations between qualitative variables, while the Mood's test was applied to compare medians of quantitative variables. Specifically, a p-value lower than 0.05 was considered indicative of statistical significance. The statistical software used is R-Studio 4.5.0.

3. Results

3.1. Participating centers

Between July 2020 and December 2024, a total of 213 people with AS from a total of 14 different Italian centers were included in the Italian Registry of Angelman.

Fourteen Italian referral centers are involved in IReAS activities (Supplemental data); theyare distributed in most regions of Italy, thus representing a broad, nationally representative and multicenter sample data of Angelman patients.

3.2. Diagnosis

Male versus female percentage distribution was 44.6 % vs 55.4 %. Five patients were born very prematurely: one at 26 weeks of gestational age, two at 30 weeks, one at 31 weeks, and one at 32 weeks. Age at neurodevelopmental onset was on median 1.0 year with a 1.5-0.7 interquartile range (IQR), while age at genetic diagnosis was 2.0 years (IQR = 3.8-1.3); 37 % of patients were adults (>18 years old) and 63 % of patients were pediatrics (≤18 years old). Form a genetic point of view, most patients (70.4 %) had maternal deletion, 15 % carried pathogenic variants in the UBE3A gene, and 12.7 % had paternal uniparental disomy of chromosome 15 (UDP15). Additionally, imprinting center defects (ICD) in the 15q11–q13 region were identified in 4 cases.

Clinical Characteristics Data from Italian IReAS show a cohort of AS

patients resembling the following characteristics.

Table 1 summarizes clinical features of patients included within Italian IReAS accordingly to AS updated consensus (Duis et al., 2022; Williams et al., 2006). Consistent findings show that 100 % of individuals with AS experience developmental delays, while 94.8 % exhibit movement or balance disorders, 96.2 % demonstrate behavioral uniqueness, and 95.8 % show delays in language development. Regarding frequent clinical characteristics (more than 80 %) microcephaly was present in 55.9 %, seizures in 80.3 % and abnormal EEG in 95.8 % of patients. Most frequently associated findings include hypotonia (39.4 %) and sucking difficulties (39.9 %), feeding difficulties during infancy (41.3 %), sleep-wake cycle disorders (77.9 %), scoliosis (59.6 %), and strabismus (47.4 %).

3.3. Genetic tests

Across AS cohort, 491 genetic tests were executed, indicating that many individuals underwent more than one type of analysis to confirm the diagnosis. Conventional karyotyping was performed in 123 patients (57.7 %), while array CGH was used in 125 cases (58.7 %). Additional analyses included FISH (30.5 %) and MLPA for the UBE3A gene (6.1 %). Methylation analysis was conducted in 139 individuals (65.3 %), specifically 13.3 % were tested using MS-PCR, 51.8 % a MS-MLPA technique and 37.8 % of cases the method was not specified. Sequencing analyses were performed in 26 patients (12.2 %). These included single-gene Sanger sequencing (23 %), NGS panels (23 %) and whole exome sequencing (WES) (11.5 %). In 42.3 % of cases, the sequencing method used was not specified.

Table 1
Clinical characteristics of patients included within Italian IReAS accordingly to AS updated consensus (Duis et al., 2022; Williams et al., 2006).

Consensus – clinical feature of AS	N (%) (out of 213 AS patients)
CONSISTENT (100 %)	
Developmental delay (evident by 6–12 months of age)[b]	213 (100 %)
Movement or balance disorders (ataxia of gait, and/or tremulous movement of limbs, movement disorder can be mild. May not appear as frank ataxia but can be forward lurching, unsteadiness, clumsiness, or quick, jerky motions)	202 (94.8 %)
Behavioral uniqueness (hyperactivity/excitability, happy demeanor with frequent laughter/smiling, stereotypies, signs of autism spectrum disorder)	205 (96.2 %)
Lack of language development[a,b]	204 (95.8 %)
FREQUENT (80 %)	
Microcephaly (by 2 years)[b]	119 (55.9 %)
Seizures (usually 3 years)[b]	171 (80.3 %)
Abnormal EEG (in the first 2 years)[b]	204 (95.8 %)
ASSOCIATED (20–80 %)	
Hypotonia, during neonatal period	84 (39.4 %)
Sucking difficulties, during neonatal period	85 (39.9 %)
Feeding difficulties, during infancy	88 (41.3 %)
Obesity	31 (14.6 %)
Constipation	73 (34.3 %)
Sleep-wake cycle disorders	166 (77.9 %)
Flat occiput	105 (49.3 %)
Wide mouth	126 (59.2 %)
Protruding tongue	55 (25.8 %)
Wide-spaced teeth	73 (34.3 %)
Frequent drooling	144 (67.6 %)
Mandibular prognathia	91 (42.7 %)
Strabismus	101 (47.4 %)
Hypopigmented skin, light hair, and eye colour	104 (48.8 %)
Scoliosis[b]	127 (59.6 %)

[a] *Lack of language development refers to a complete absence of language and excludes patients who have minimal word use.*
[b] Age dependant characteristics.

3.4. Genotype-phenotype correlations

To investigate the relationship between genotype and clinical phenotype, Angelman patients were divided into two groups based on genetic subtype: AS patients with a deletion (n = 150) and AS patients with a non-deletion (n = 63), this latter including patients with UBE3A pathogenic variants, paternal uniparental disomy of chromosome 15 and defects in 15q11–q13 imprinting center.

Several clinical differences were revealed between the two groups.

The first neurodevelopmental observation in AS with a deletion occurred at 0.8 years (IQR 1.2-0.6) compared to 1.4 years (IQR 2.0-1.0) in AS patients with a non-deletion ($p < 0.001$). Similarly, the age at genetic diagnosis was statistically significant between the two groups: 1.6 (IQR 2.1-1.1) in deletion AS and 3.4 (IQR 5.8–2.3) in non-deletion patients ($p < 0.001$).

There were no significant differences between groups in terms of sex, age (pediatric and adult), weight, length and head circumference at birth, pregnancy complications, or birth-related issues such as hypotonia and difficulty sucking (Table 2). No significant statistically association between sex and age groups was found (p-value 0.219).

Among neurological disorders, epileptic seizures were significantly more frequent in deletion compared to non-deletion cases (88 % *vs* 61.9 %; $p < 0.001$). Additionally, patients with deletion experienced their first epileptic seizure at an earlier age compared to non-deletion patients, with an age of seizure onset of 2 years (IQR 3-1) in the deletion group versus 4 years (IQR 6.5-2) in the non-deletion group ($p = 0.0019$).

Patients with maternal deletion were statistically more likely to have other neurological characteristics (Table 3), such as limb tremors (64 % *vs* 47.6 %) and lack of language development (99.3 % *vs* 87.3 %).

Of a total of 205 patients with unique behavioral phenotype, 143 were deletion AS, while 62 were non-deletion, without statistically significant differences between the two groups, as shown in Table 4. Although not the most common behavioral uniqueness, stereotypes emerged as the most specific to individuals with maternal deletion, occurring in 65 % of AS with maternal deletion compared to 43.5 % in the non-deletion group ($p = 0.006$).

Physical characteristics and abnormalities of the digestive system in AS patients are summarized in Table 5. A flat occiput was significantly more frequent in the deletion group (54 %) compared to the non-deletion group (38.1 %) ($p = 0.048$). Microcephaly was also significantly more prevalent in the deletion group (60.7 %) versus the non-deletion group (44.4 %) ($p = 0.04$). Excessive drooling was also more commonly reported in individuals with maternal deletion (72.7 %) than non-deletion AS (55.6 %) ($p = 0.022$).

Pigmentary traits also differed significantly between groups. Individuals with deletion more frequently exhibited the hypopigmentation phenotype, including blue eyes (41.3 % *vs* 22.8 %, $p = 0.023$), hypopigmented skin (38 % *vs* 15.9 %, $p = 0.002$), and blond hair (42 % *vs* 20.6 %, $p = 0.004$) compared to AS without deletion.

A significant borderline difference was also shown for deep-set eyes, present in 22 % of the deletion group compared to 9.5 % of the non-deletion group ($p = 0.05$).

Concerning the gastrointestinal symptoms, obesity was the only characteristic that differed significantly between genotypes, considerably more common in the non-deletion group (31.7 %) than in the deletion group (7.3 %) ($p < 0.001$). Other digestive problems, including feeding difficulties during early childhood, constipation, and gastro-esophageal reflux, showed no significant differences between the two groups.

The most significant differences in clinical features between the AS deletion and non-deletion groups are summarized and illustrated in Fig. 1.

Table 2
Demographic characteristics in AS patients with deletion and AS patients with non-deletion.

Demographic characteristics	Available data (n)	Total	AS patients with a deletion (n = 150)	AS patients with a non-deletion (n = 63)	*p*-value
Females (N)	213	118 (55.4 %)	82 (54.7 %)	36 (57.1 %)	*0.856*
Males (N)		95 (44.6 %)	68 (45.3 %)	27 (42.9 %)	
Pediatrics (age ≤ 18)	213	135 (63 %)	94 (62.7 %)	41 (65 %)	*0.858*
Adults (age>18)		78 (37 %)	56 (37.3 %)	22 (35 %)	
Age at enrollment (years) *median(IQR)*	213	13.7 (21.88-6.63)	13.6 (22.41-5.93)	13.9 (21.1-8.1)	*0.964*
Age at neurodevelopmental onset (years) *median (IQR)*	213	1.0(1.5-0.7)	0.8 (1.2-0.6)	1.4 (2.0-1.0)	*<0.001*[a]
Age at genetic diagnosis (years) *median(IQR)*	213	2.0(3.8-1.3)	1.58 (2.5-1.1)	3.4 (5.8–2.3)	<0.001[a]
Characteristics at birth					
Pregnancy complications (N)	204	56 (27.5 %)	[a]37 (25.9 %)	[a]19 (31.1 %)	*0.548*
Weight (*gr*) *median(IQR)*	199	3010 (3300-2740)	3020 (3250-2730)	2965 (3327.5-2750)	*0.468*
Length (*cm*) *median(IQR)*	171	49 (50-47.25)	49 (50-47)	49 (51-48)	*0.896*
Head circumference (*cm*) *median(IQR)*	165	34 (35-33)	34 (35-33)	34 (35-32.5)	*0.807*
Neonatal hypotonia (N)	190	84 (44.2 %)	[a]62 (46.3 %)	[a]22 (39.3 %)	*0.469*
Difficulty sucking (N)	195	85 (43.6 %)	[a]61 (44.2 %)	[a]24 (42.1 %)	*0.912*

IQR: interquartile.
Note: "available data" refers to the total number of patients per variable available in the registry database.
[a] The percentages for the deletion and non-deletion groups were calculated based on the number of responders within each respective cluster.

Table 3
Neurological disorders in AS patients with deletion and AS patients with a non-deletion and non-deletion AS.

Signs and Symptoms (Neurological disorders)	Available data (n)	Total	AS patients with a deletion (n = 150)	AS patients with a non-deletion(n = 63)	*p*-value
Seizures	213	171 (80.3 %)	132 (88 %)	39 (61.9 %)	<0.001[c]
Age onset of first seizure (years) *median(IQR)*	156	2 (1–3)	2 (1–3)	4 (2–6.5)	<0.001[c]
Abnormal EEG	213	204 (95.8 %)	145 (96.7 %)	59 (93.7 %)	*0.532*
Developmental delay	213	213 (100 %)	150 (100 %)	63 (100 %)	*0.887*
Age of onset developmental delay (years) *median(IQR)*	61	0 (0–1)	0 (0–1)	0.5 (0–1)	*0.090*
Limb tremors	213	126 (59.2 %)	96 (64 %)	30 (47.6 %)	*0.038*[c]
Myoclonus	213	101 (47.4 %)	76 (50.7 %)	25 (39.7 %)	0.188
Balance disorders[a]	213	190 (89.2 %)	131 (87.3 %)	59 (93.7 %)	0.265
Ataxia[b]	213	155 (72.8 %)	110 (73.3 %)	45 (71.4 %)	0.907
Hypotonia	213	90 (42.3 %)	61 (40.7 %)	29 (46 %)	0.568
Hyperreflexia	213	51 (24 %)	37 (24.7 %)	14 (22.2 %)	0.837
Intellectual disability	213	212 (99.5 %)	149 (99.3 %)	63 (100 %)	*1.0*
Lack of language development[c]	213	204 (95.8 %)	149 (99.3 %)	55 (87.3 %)	*<0.001*[c]
Sleep-wake cycle disorders	213	166 (77.9 %)	119 (79.3 %)	47 (74.6 %)	*0.563*

IQR: interquartile.
Note: "available data" refers to the total number of patients per variable available in the registry database.
[a] Motor instability refers to a compromised ability to maintain stable control over movement, leading to poor coordination, balance issues, weakness, tremors, or difficulty with fine motor skills.
[b] Alteration of movement or balance, causing a gait disturbance (gait ataxia) and tremor in limb movements. The movement disorder may be mild.
[c] Lack of language development refers to a complete absence of language and excludes patients who have minimal word use.

4. Discussion

Rare disease registries represent important tools for improving disease knowledge, monitoring patient outcomes and supporting clinical research and health policy. providing insights into natural history, clinical characterization and genetic variability, and contributing to the reduction of the information gap resulting from the limited data available from patients with rare diseases (Williams et al., 2010). Their role is especially valuable in rare conditions such as Angelman syndrome, where the low prevalence limits the availability of large and representative cohort.

Although some national and international studies (Napier et al., 2017; Krey et al., 2021; Carriero et al., 2024) have involved the direct participation of patients in data collection and provided a preliminary, albeit limited, overview of the Italian population, these experiences cannot be considered representative of the actual size and characteristics of the AS population in Italy. In this sense, the Italian AS registry represents a concrete attempt to create a national network to address the need to include most reference centers for AS, and to provide a concrete national epidemiological data, being the IReAS developed in strict collaboration with the Italian Angelman Syndrome Association (OR.S.A.) and Italian clinical referral centers. Between July 2020 and December 2024, it collected data from 14 specialized centers across the country, enrolling a total of 213 individuals with AS.

Our data confirm that the most common genetic cause of AS was due to maternal deletion of 5q11-13 region (70.4 %), mutations in UBE3A gene (15 %), UPD (12.7 %) and imprinting center defects (1.9 %), as largely described (Margolis et al., 2015; Buiting et al., 2016; Ramsden et al., 2010).

Unfortunately, it remains unclear how many UBE3A variants are inherited and how many cases can be considered familial. Few data from IReAS, indeed, referred to a total of only 30 reports in which this information was available. In 12 cases a *de novo* UBE3A mutation was reported; in 5 cases it was reported that the proband's mother was UBE3A carrier; in 13 cases it was reported the necessity of a genetic counselling and extension of genetic analyses to family members.

The analysis of the registry data confirms the consistency of most clinical features of AS patients with those reported in the Consensus

Table 4
Behavioral phenotype in AS patients with deletion and AS patients with a non-deletion.

Signs and Symptoms (Behavioral phenotype)	Available data (n)	Total (n)	AS patients with a deletion (n = 150)	AS patients with a non-deletion (n = 63)	*p*-value
Behavioral uniqueness[a]	213	205 (96.2 %)	143 (95.3 %)	62 (98.4 %)	*0.439*
Hyperactivity and/or excitability	205	173 (84.4 %)	121 (84.6 %)	52 (83.9 %)	*1.0*
Happy demeanor with frequent laughter/ smiling	205	127 (62 %)	95 (66.4 %)	32 (51.6 %)	*0.064*
Stereotypies	205	120 (58.5 %)	93 (65 %)	27 (43.5 %)	*0.006**
Signs of autism spectrum disorder	205	52 (25.4 %)	40 (28 %)	12 (19.4 %)	*0.259*

Note: "available data" refers to the total number of patients per variable available in the registry database.
[a] Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand-flapping, or waving movements; hypermotoric behaviour (Duis et al., 2022; Williams et al., 2006).

Statement (Duis et al., 2022; Williams et al., 2006). Specifically, for the variables classified as *"Consistent (100 %)"*, the Italian Registry shows values ranging from 94.8 % to 100 %. For *"Frequent (80 %)"* variables, the range is between 55.9 % and 95.8 %, with two notable deviations observed for *abnormal EEG*, likely related to the high proportion of patients with deletions and epileptic seizures, and for *microcephaly*. Finally, among the *"Associated (20–80 %)"* variables, only *obesity* shows a slight deviation (14.6 %), probably influenced by the limited sample size of patient with no deletion (N = 63). Data regarding genetic testing reflects the intricate process of genetic diagnosis of AS, which typically begins with DNA methylation analysis as the first-line test, followed by subsequent tests (microsatellites analyses, SNP/arrayCGH UBE sequencing or WES) according to consolidate guidelines (Beygo et al., 2019; Moncla et al., 1999). DNA methylation (65.3 %), array-CGH (58.7 %), and karyotype analysis (57.7 %) were among the most performed analyses, however our cohort includes a high percentage of adults (37 %) diagnosed by high resolution karyotype and FISH analyses (Lossie et al., 2001). The valuable and long-lasting cooperation between patients' associations, geneticists and clinicians allowed to collect information and clinical data in 78 patients from the diagnosis to the adult age, revealing aspects still not explored of the AS syndrome.Understanding the relationship between genetic characterization and clinical features can enhance the comprehension of the causes, signs and symptoms, outcomes and responses to treatment for various genetic disorders, including AS. In this respect, supporting comprehensive genotype-phenotype correlation analyses is one of the IReAS advantages.

In agreement with SC of the registry, we adopted the commonly used dichotomous classification (deletion vs. non-deletion) to ensure statistical robustness and facilitate comparison with previous studies. In agreement with SC of the registry, we adopted the commonly used dichotomous classification (deletion vs. non-deletion) to ensure statistical robustness and facilitate comparison with previous studies. This approach is supported by the fact that patients with deletion are reported with a more severe phenotype in several studies, probably due to the haploinsufficiency not only of UBE3A, but also of the flanking genes, thus giving us the possibility to be more confident and reliable in small cohort statistical analyses and enhancing comparability across studies using similar groupings. However, this simplification may mask genotype-specific differences within the non-deletion group, such as variability in cognitive or behavioural profiles, and that future studies with larger sample sizes may warrant a more detailed stratification of non-deletion subtypes.

Data from IReAS confirms that individuals with maternal deletion exhibited an earlier onset of clinical signs and are more frequently affected by neurological features such as seizures, limb tremors and complete absence of speech, if compared to non-deletion genotypes.

These findings align with literature, which indicates that maternal deletions are typically associated with a more severe phenotype due to the loss of multiple genes within the 15q11–q13 region (Varela et al., 2004; Tan et al., 2011; Gentile et al., 2010; Yang et al., 2021b; Fujimoto et al., 2024). As a result, individuals with maternal deletion more often displayed hypopigmentation traits, including blonde hair (42 % *vs* 20.6 %), blue eyes (41.3 % *vs* 22.8 %) and skin hypopigmentation (38 %

Table 5
Physical characteristics and abnormalities of the digestive system in AS patients with a deletion and AS Patients with non-deletion.

	Available data (n)	Total (n)	AS Patients with a Deletion (n = 150)	AS Patients with a Non-Deletion (n = 63)	*p*-value
Signs and Symptoms: Physical characteristics					
Flat occiput	213	105 (49.3 %)	81 (54 %)	24 (38.1 %)	*0.048**
Wide mouth	213	126 (59.2 %)	89 (59.3 %)	37 (58.7 %)	*1.0*
Protruding tongue	213	55 (25.8 %)	44 (29.3 %)	11 (17.5 %)	*0.102*
Bruxism	213	29 (13.6 %)	25 (16.6 %)	4 (6.3 %)	*0.074*
Wide-spaced teeth	213	73 (34.5 %)	56 (37.3 %)	17 (27 %)	*0.195*
Frequent drooling	213	144 (67.6 %)	109 (72.7 %)	35 (55.6 %)	*0.022*
Mandibular prognathia	213	91 (42.7 %)	67 (44.7 %)	24 (38.1 %)	*0.463*
Microcephaly	213	119 (55.9 %)	91 (60.7 %)	28 (44.4 %)	*0.04**
Brachicefalia	213	77 (36.2 %)	58 (38.7 %)	19 (30.2 %)	*0.306*
Strabismus	213	101 (47.4 %)	72 (48 %)	29 (46 %)	*0.91*
Myopia	213	23 (10.8 %)	19 (12.7 %)	4 (6.3 %)	*0.265*
Deep-set eye	213	39 (18.3 %)	33 (22 %)	6 (9.5 %)	*0.05**
Blue eyes	213	77 (36.2 %)	62 (41.3 %)	15 (22.8 %)	*0.023**
Skin hypopigmentation	213	67 (31.5 %)	57 (38 %)	10 (15.9 %)	*0.002**
Blonde hair	213	76 (35.7 %)	63 (42 %)	13 (20.6 %)	*0.004**
Scoliosis	213	127 (59.6 %)	89 (59.3 %)	38 (60.3 %)	*1.0*
Signs and Symptoms: Abnormalities of the digestive system					
Feeding difficulties, during infancy	213	87 (41 %)	63 (42 %)	24 (38.1 %)	0.706
Obesity	213	31 (14.6 %)	11 (7.3 %)	20 (31.7 %)	<0.001*
Constipation	213	73 (34.3 %)	49 (32.7 %)	24 (38.1 %)	0.546
Gastroesophageal reflux	213	85 (39.9 %)	63 (42 %)	22 (34.9 %)	0.418

Note: "available data" refers to the total number of patients per variable available in the registry database.

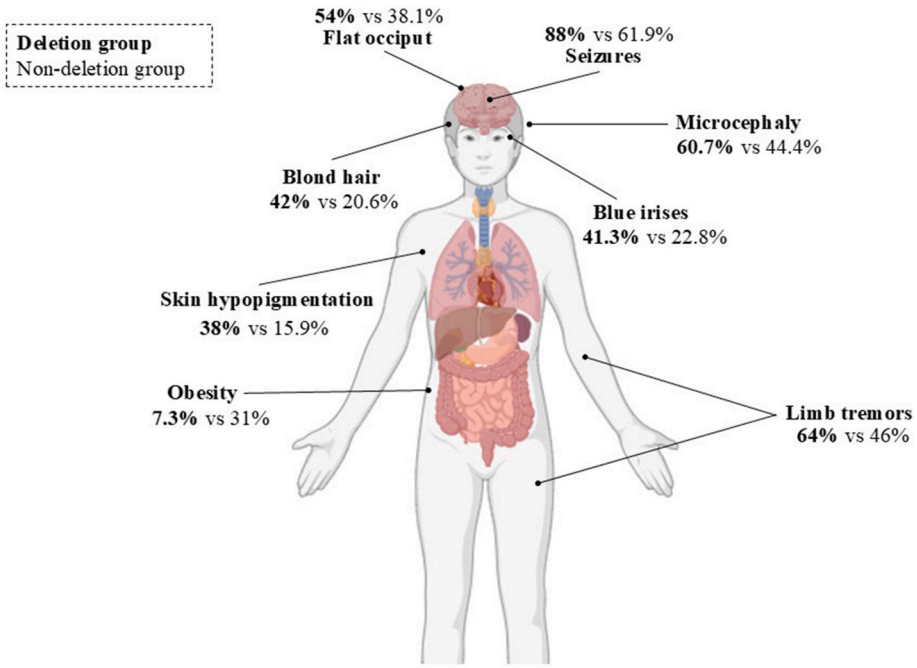

Fig. 1. AS Patients with a deletion vs with a non-deletion representation of signs and symptoms.

vs 15.9 %). Fridman and colleagues reported that tyrosinase-positive oculocutaneous albinism (OCA, type II; OCA2) was associated with both Angelman and Prader-Willi diseases caused by maternal/paternal deletion (Fridman et al., 2003).

Conversely, individuals with non-deletion AS tend to exhibit a milder phenotype with later onset, characterized by fewer neurological manifestations and physical anomalies. Nevertheless, patients with UBE3A mutations or UPD and imprinting defects were associated with higher rates of obesity (7.3 % in deletion *vs* 31.7 % in non-deletion group). A possible hypothesis of increased rates of obesity in cases characterized by non-deletion genotypes may be overexpression of paternally expressed genes (Brennan et al., 2015).

This study presents the first results of four years activities (2020-24) of the Italian Angelman Syndrome Registry on the diagnosis, genetic data and clinical history of people with AS collected during this period. Moreover, it evaluated correlations between genetic subtypes and clinical features in AS with the final aim of advancing both clinical management and research in the context of precision medicine (e.g. gene therapy). Despite facing challenges such as limited financial and human resources and organizational variability across centers, the IReAS represents a valuable tool for collecting clinical and genetic data, evaluating clinical management, enhancing patient care and promoting research to discover novel therapeutic options. Inclusion of data from a large number of existing AS referral centers distributed across Italy, offers a nationwide representation of this pathology at national level.

Interestingly, one of the key strengths emerging from the analyses of IReAS data is the relatively large number of adults with Angelman syndrome (N = 78; 37 % of the total) whose medical complications have not yet been thoroughly investigated or well characterized, particularly within the Italian population, where such aspects have not been systematically explored, including through the use of a dedicated registry. In the future, it will be valuable to focus on studies specifically aimed at highlighting the health status and characteristics of this population subgroup.

Finally, managing of this platform within a public health Italian Institute, ensures high standards of data privacy, security and quality, as well as long-term efficiency and sustainability.

Nevertheless, the Registry currently includes a relatively small number of patients, and its development is not mandated or institutionally supported; rather, it relies on a project-based initiative and the voluntary participation and commitment of the contributing clinicians.

Submission declaration

The work described has not been published previously. It is not under consideration for publication elsewhere. The article's publication is approved by all authors. If accepted, the article will not be published elsewhere in the same form, in English or in any other language.

Declaration of generative AI in scientific writing

Generative AI technologies have been used during the writing process exclusively to improve the readability and language of some few sentences in the manuscript.

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CRediT authorship contribution statement

Giorgia Buoncuore: Data curation, Formal analysis, Investigation, Writing – original draft. **Marco Salvatore:** Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Adele Rocchetti:** Data curation, Formal analysis, Methodology. **Lorenzo Facciaroni:** Data curation, Formal analysis. **Edvige Veneselli:** Investigation, Writing – review & editing. **Maurizio Elia:** Conceptualization, Investigation, Writing – review & editing. **Silvia Russo:** Data curation, Investigation, Writing – review & editing. **Michelina Armando:** Investigation, Writing – review & editing. **Michele Germano:** Investigation, Writing – review & editing. **Tommaso Prisco:** Conceptualization, Writing – review & editing. **Stefano Sartori:** Investigation, Writing – review & editing. **Gemma Marinella:** Conceptualization, Investigation, Writing – review & editing. **Roberta Battini:** Investigation, Writing – review & editing. **Giuseppe Gobbi:** Conceptualization,

Investigation, Writing – review & editing. **Paola Torreri:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2026.105067.

Data availability

Data will be made available on request.

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