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REVIEW ARTICLE

47, XYY Syndrome (Jacobs Syndrome): Real-World Data From Patient Associations Suggest an Integrated Multidisciplinary Model

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ABSTRACT

Background: 47, XYY syndrome (Jacobs syndrome) is a sex chromosome aneuploidy with an estimated prevalence of approximately 1:1000 live male births. Despite its frequency, 47, XYY syndrome remains largely underdiagnosed, with often late identification and the absence of structured and uniform care pathways.

Objectives: Here, we aimed to integrate the most recent scientific evidence with real-world descriptive data collected from two patient associations in Italy and Spain, in order to identify key clinical organizational challenges and propose an integrated model for multidisciplinary management.

Materials and Methods: Data obtained through structured questionnaires disseminated by two national patient associations were analyzed. The analysis was descriptive and comparative, integrating questionnaire-derived information with evidence from the published literature.

Results: The data suggest that 47, XYY syndrome is a multisystem condition that requires coordinated longitudinal monitoring.

Conclusion: Patient-reported opinions advocate for the development of an integrated multidisciplinary clinical pathway to enhance the continuity of care, equity of access to services, and endocrinological surveillance.

1 | Introduction

47, XYY syndrome is a sex chromosome aneuploidy affecting approximately 1 in every 1000 live male births [1]. It is most commonly caused by paternal meiotic nondisjunction, although mosaic forms can also occur [2]. Despite its prevalence, many cases remain undiagnosed due to the absence of distinctive dysmorphic features [3].

This syndrome presents a variable range of conditions mostly affecting neurodevelopment: language delay, attention-deficit/hyperactivity disorder (ADHD), executive difficulties, autism spectrum traits, and learning disabilities. Hypotonia (low muscle tone) is also frequently reported as a motor/neuromuscular feature [4–6]. In addition, a recent meta-analysis indicates that a proportion of adult patients may present with gonadal dysfunction [7]. Some individuals may additionally show physical

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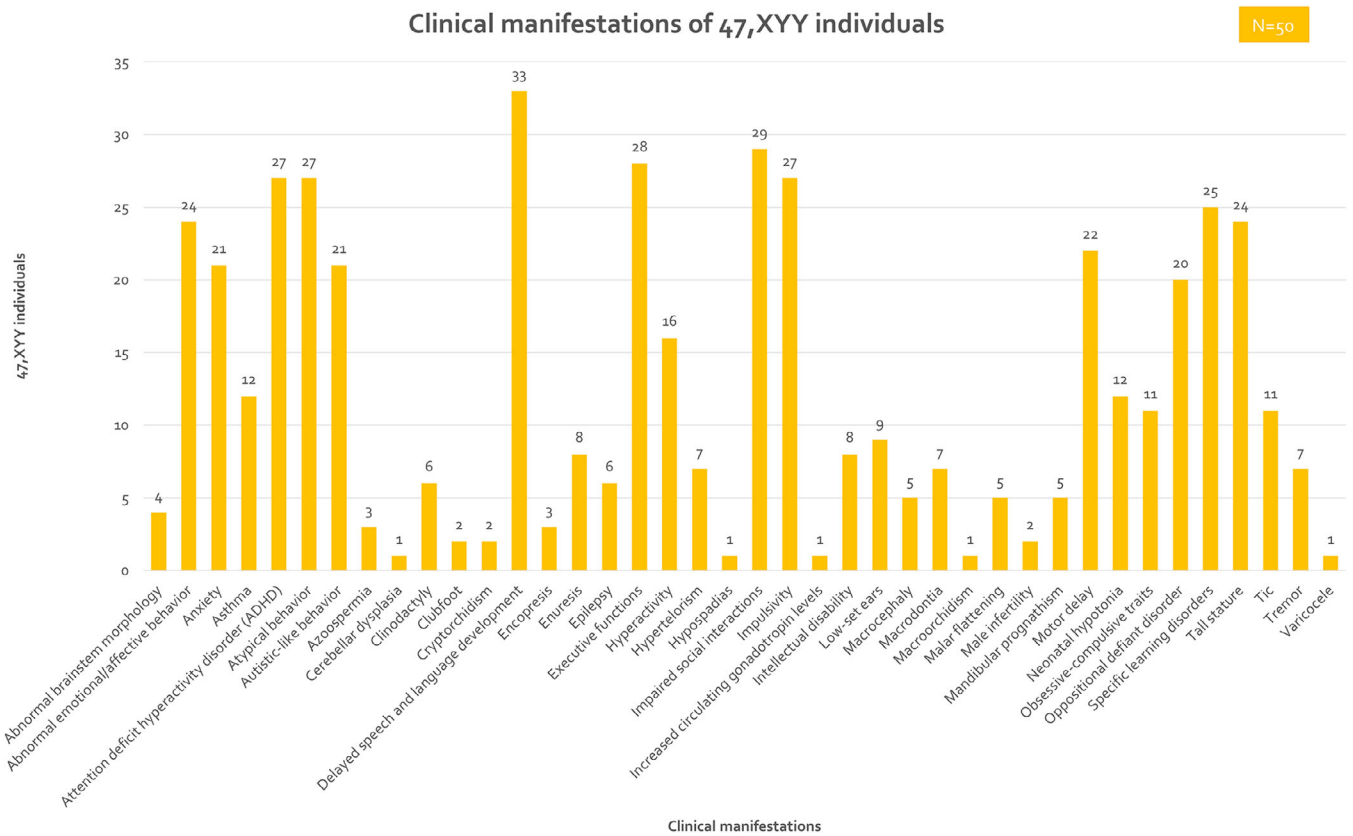


FIGURE 1 | Distribution of clinical manifestations reported by individuals with 47, XYY ($n = 50$). The figure shows the frequency of the main manifestations reported in the questionnaires, with the possibility of multiple answers.

TABLE 1 | Neurodevelopmental and behavioural challenges most frequently reported in individuals with 47, XYY ($n = 50$).

Neurodevelopmental and behavioral challenges	Frequency	Percentage
Language delay	33	66%
ADHD	27	54%
Atypical behavior	27	54%
Impulsivity	27	54%
Impaired executive functions	28	56%
Impaired social interactions	29	58%
Specific learning disorders	25	50%
Abnormal emotional/affective behavior	24	48%
ASD	21	42%
Anxiety	21	42%

TABLE 2 | Medical comorbidities and somatic features reported in individuals with 47, XYY (n = 50).

Medical comorbidities and somatic features	Frequency	Percentage
Neonatal hypotonia	12	24%
Epilepsy	6	12%
Asthma	12	24%
Enuresis	8	16%
Clinodactyly	6	12%
Hypertelorism	7	14%
Macrodontia	7	14%
Prominent jaw	5	10%
Azoospermia	3	6%
Motor delay	22	44%
Tall stature	24	48%

characteristics such as tall stature (above-average height), as a well-described feature of the syndrome [3–6]. In general, registry studies in subjects with sex chromosome aneuploidies document an overall increase in morbidity compared to the general population [8]. Real-world data corroborate the considerable neurodevelopmental burden and highlight the fragmentation of existing care pathways.

Recently, new evidence on the molecular mechanisms underlying sex chromosome aneuploidies has been published. In particular, iPSC models have shown global transcriptional dysregulation that cannot be fully accounted for by DNA methylation [9].

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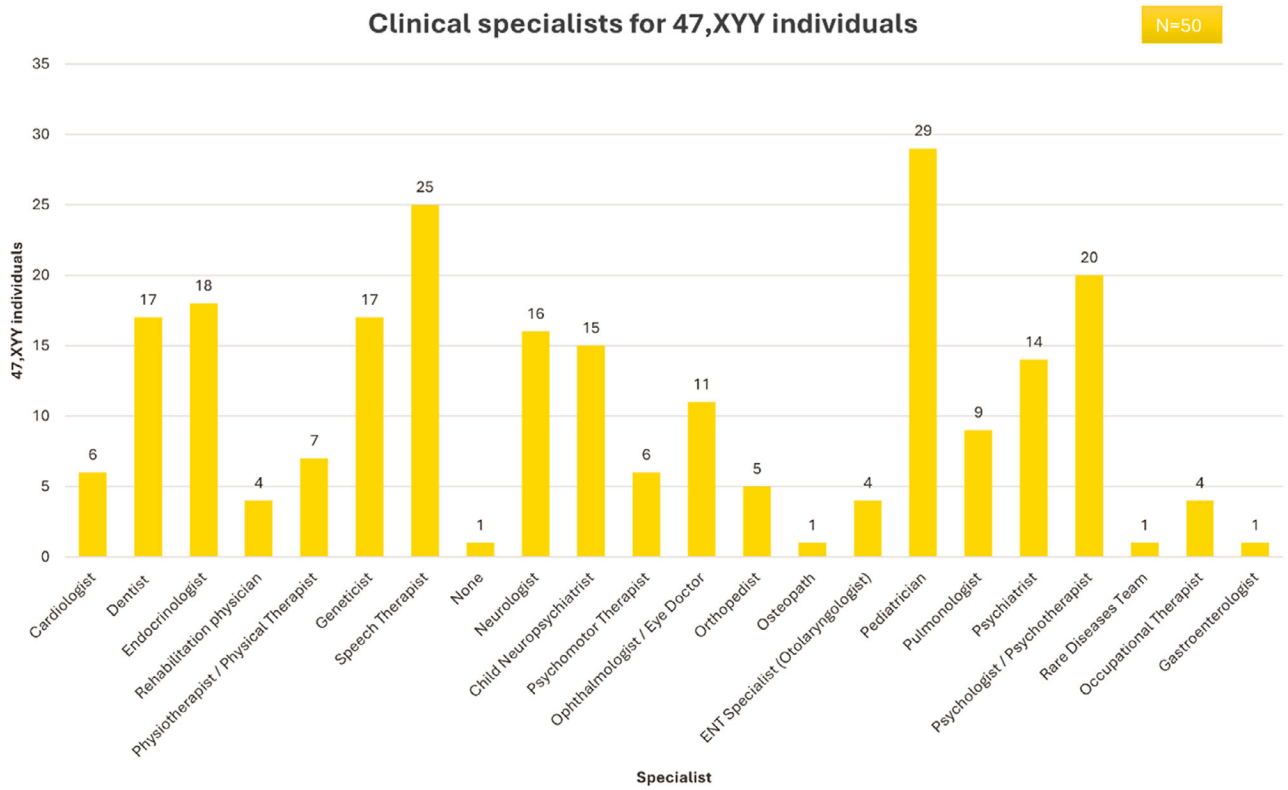


FIGURE 2 | Clinical specialists involved in the management of individuals with 47, XYY ($n = 50$). The figure illustrates the number of households reporting the involvement of different health specialists.

These iPSC-derived cellular models from individuals with 47, XYY have shown alterations in transcriptional networks involved in neuronal development [9]. Furthermore, neuroimaging studies in sex chromosome trisomies also suggest changes in cortical organization [10]. Prospective studies report an increased prevalence of neurodevelopmental problems, such as speech disorders, ADHD, executive difficulties, and social vulnerabilities in individuals with 47, XYY [3–6]. However, cognitive functioning shows wide inter-individual variability [10].

Regarding gonadal function, a recent meta-analysis of studies including individuals with 47, XYY reported elevated LH and FSH levels and reduced testosterone in a subset of adults, with cases of oligozoospermia and azoospermia [7]. These findings challenge the earlier assumption of invariably preserved fertility [11]. However, longitudinal studies in adulthood remain scarce. Despite these recent findings, 47, XYY syndrome remains under-recognized and under-diagnosed, and clear clinical management pathways are not defined.

The aim of this work is to integrate this evidence with self-reported data from patient associations to highlight key clinical and organizational challenges in the management of the syndrome and to propose an integrated model for multidisciplinary management.

2 | Methods

Data were collected through structured questionnaires distributed by two national associations. Participation ($n = 50$) was voluntary and anonymized. The questionnaire covered different areas: age and method of diagnosis, reported clinical manifestations, medical comorbidities, and specialists involved in follow-up

The term "clinical manifestations" is used to encompass phenotypic features, self-reported symptoms, observable physical features, and medically diagnosed comorbidities as reported by families.

The analysis was exclusively descriptive. This study does not constitute a classic scientific study; it describes the view of patients and families.

3 | Results

A wide spectrum of clinical, neurodevelopmental, and medical manifestations associated with 47, XYY syndrome was reported. The overall distribution of the reported symptoms is summarized in Figure 1.

A total of 484 symptom reports were recorded (with the possibility of multiple responses for each participant). Table 1 shows the most frequently reported symptoms in the sample, ordered according to their frequency.

In addition to neurodevelopmental manifestations, several medical comorbidities and somatic features associated with 47, XYY syndrome have been reported. The distribution of the main conditions reported in the sample is summarized in Table 2.

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Importantly, the patients described the involvement of multiple health professionals, reflecting the multisystem complexity of the condition (Figure 2).

4 | Discussion

The data collected here from two patient associations in Italy and Spain show novel findings, particularly interesting as they reflect the self-reported data and feelings from subjects with 47, XYY syndrome. The major information derived from this survey is the significant clinical heterogeneity, with neurodevelopmental disorder manifestations as the most frequent aspect, but also a significant endocrine component requiring specific monitoring [7]. Therefore, in light of emerging evidence [7], periodic endocrinological evaluation in adolescence and adulthood is suggested, with possible reproductive counselling.

Furthermore, the findings highlight the need for a multidisciplinary approach to this syndrome and the need for systematic studies addressing these aspects. The clinical management of this syndrome is often fragmented, with variable access to specialist services. Indeed, registry studies of subjects with 47, XYY document an increase in morbidity and contact with health services compared to the general population [8]. Similar data are also reported in other sex chromosome aneuploidies [12].

The findings of this survey suggest the need for an integrated model of management, which should include early genetic diagnosis, standardized neurodevelopmental assessment, endocrinological follow-up, multidisciplinary coordination, and structured transition to adulthood. These principles are consistent with the recommendations developed for other sex aneuploidies [13].

In conclusion, 47, XYY syndrome is a relatively frequent yet persistently and under-recognized chromosomal condition. Emerging molecular and clinical data confirm its biological complexity and substantial phenotypic heterogeneity. Although not constituting scientific experimental evidence, these real-world descriptive findings are consistent with the existing literature and reveal significant organizational gaps in current care pathways. They also highlight the importance of patient associations in data collection and the need to coordinate their activities with professionals, researchers and clinicians to develop evidence-based management protocols.

The establishment of an integrated multidisciplinary clinical pathway may strengthen continuity of care, ensure systematic monitoring of comorbidities, and improve equity of access. Further prospective multicenter studies and international registries are essential to define robust, long-term, evidence-based management strategies.

Author Contributions

R.Z. and J.G. contributed equally to the conception of the study, the collection and analysis of the data, the writing of the manuscript, and the critical revision of its content. A.F. critically discussed the data and revised the manuscript. All authors approved the final version of the manuscript.

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Ethics Statement

Only anonymized data obtained through voluntary questionnaires disseminated by patient associations were used in this study. As no identifiable health information was collected and no intervention was performed, the study did not require approval by an ethics committee in accordance with applicable regulations.

Conflicts of Interest

The authors declare no conflicts of interest.

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