

Delivering the Diagnosis of Sex Chromosome Aneuploidy: Experiences and Preferences of Parents and Individuals

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Abstract

Increased prenatal diagnoses of sex chromosome aneuploidies (SCAs) amid limited knowledge of their prognoses heighten the need to understand how families contend with the implications of an SCA. To explore the experiences of parents and individuals who received a genetic diagnosis of an SCA (excluding Turner syndrome), we conducted semistructured qualitative telephone interviews with 43 participants affected by these conditions. Parents ($n = 35$) and individuals ($n = 8$) expressed almost unanimous interest in more optimistic portrayals of their condition from their providers, even when the prognosis is uncertain. While some participants reported success in receiving accurate information from their provider and identifying supportive resources, numerous families received outdated or misleading information about their condition and lacked direction in accessing follow-up care and support. Parents desire greater coordination of their child's medical care and access to care that approaches an SCA holistically. Opportunities remain to improve the diagnosis and care of individuals with SCAs.

Keywords

prenatal diagnosis, pediatric diagnosis, Klinefelter syndrome, trisomy X, Jacob's syndrome

Introduction

The integration of sex chromosome aneuploidy (SCA) detection into prenatal genetic screening protocols is positioned to increase prenatal diagnosis of SCAs. At present, only 10% or fewer of SCA diagnoses are detected prenatally and most pediatric diagnoses are secondary findings from other medical procedures.^{1–3} While the growing availability of clinical genetic services has increased the incidence of prenatal diagnosis of a variety of conditions with varying clinical significance, patient awareness and understanding of SCAs remains low compared with previous targets of screening, such as Down syndrome.^{4,5} In addition, the potential discovery of SCAs is not always included in routine pretest counseling discussions, leaving many parents to confront unexpected genetic diagnoses with uncertain prognoses.

While the karyotypes of SCAs vary, the most common conditions include Turner syndrome (45,X), trisomy X (47,XXX), Klinefelter syndrome (47,XXY), and Jacob's syndrome (47,XYY). As a group, SCAs are among the most common chromosomal aneuploidies, occurring in approximately 1:400 individuals. Individuals

in these groups typically present with varying physical, neurocognitive, behavioral, educational, psychological, and psychosocial needs, and decreased fertility or infertility are not uncommon.^{6–12} While phenotypes vary significantly between individuals, monosomy and trisomy conditions are typically less severe than tetrasomies. For many SCAs, a majority of individuals have a mild clinical presentation, normal life expectancy, and normal intelligence or mild cognitive impairment. Despite their frequency, there is a paucity of published treatment recommendations for SCAs, although published recommendations for Klinefelter syndrome and Turner syndrome exist.^{13,14}

Due to their variable expressivity and incomplete characterization, the prognosis of SCAs is often difficult to predict. The difficulty in anticipating their

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psychosocial impact on individuals and families makes the clinical management and counseling for SCAs particularly challenging.

Most SCAs are diagnosed postnatally in response to physical anomalies, developmental delays, learning disabilities, behavioral issues, or infertility.^{2,6,12} Individuals with mild phenotypes are frequently undiagnosed or misdiagnosed with a related condition; it is estimated that 65% to 85% of individuals with Klinefelter syndrome and XYY are never diagnosed.^{2,6,15} However, noninvasive prenatal testing (NIPT) has demonstrated the identification of sex chromosomal aneuploidies with reasonably high sensitivity and low false-positive rate, with the exception of Turner syndrome.¹⁶⁻¹⁸ While NIPT is currently reimbursed largely for pregnancies considered high risk only, it is gaining rapid clinical uptake and positioned to increase the number of prenatal genetic diagnoses, including SCAs.¹⁹⁻²¹ Though the prenatal discovery of an SCA with a variable prognosis may cause unanticipated dilemmas about termination, early diagnosis may also facilitate opportunities for earlier treatment and preventative therapies of indicated physical, educational, behavioral, and reproductive concerns. This study is a qualitative exploration of the experiences of families and individuals with the delivery of a genetic diagnosis of an SCA.

Methods

Participant recruitment was conducted in collaboration with advocacy, education, and support organizations for individuals with X or Y variations and their families. The nonprofit organizations Association for X and Y Variations (AXYS) Foundation and the XYY Project publicized announcements of our study in their primary repository of research opportunities for families and in other online platforms. We conducted telephone interviews with 35 parents of individuals with an SCA and 8 individuals diagnosed with an SCA. Participants discussed their experiences of receiving the diagnosis, their perceptions of the delivery process, the information and support they received, and the gaps they perceived in their care. Participants offered recommendations for medical providers and centers offering care to individuals with SCAs. Following transcription, a team of qualitative researchers developed a codebook to identify primary and secondary themes in the data. We present data on the reception of SCA diagnoses.

Participants

Participants in this study were the following: (1) individuals 16 years of age and older who had been diagnosed with

an X or Y chromosome variation or (2) parents of children of any age diagnosed with an X or Y chromosome variation. Inclusion criteria for X or Y variations included the trisomies of Klinefelter syndrome (47,XXX), Jacob's syndrome (47,XYY), and Trisomy X (47,XXX), as well as other sex chromosome variations including, 48,XXYY, 48,XXXY, various mosaicisms, and others. On the recommendation of community support group representatives, Turner's syndrome (45,X) was not included in the cohort as it has been more extensively studied and is relatively well known to clinicians, as well as due to a unique phenotypic profile distinct from the conditions studied here. Participants were enrolled in the study following receipt of their HIPAA (Health Insurance Portability and Accountability Act) authorization.

Interview Guide

The interview guide (see the appendix; available in the online version of the article) featured a series of open-ended questions asking participants about their (or their child's) genetic condition, how and when they learned about it, subsequent medical care and social services, their relationship with health care providers, and the support received from family and friends. A multidisciplinary research team—including representatives from genetic counseling, reproductive medicine, bioethics, sociology, and public health—informed the development of the interview guide and refined the sequence of question items for logical flow. During the course of the study, some interview items were lightly edited to provide clarification for participants, to simplify wording, or to incorporate novel content not previously anticipated.

Data Collection

Telephone interviews ($n = 38$) were conducted with parents, children, parent-child dyads, and parent-parent dyads between October 2016 and April 2017. Interviews were audio-recorded, transcribed verbatim, and anonymized. Each interview lasted 35 minutes on average. In keeping with standard qualitative methods, recruitment was conducted until thematic saturation was achieved.

Data Analysis

The software package NVivo Version 11 was used to facilitate data analysis. Anonymized interview transcript data were analyzed using a recursive thematic approach. The coding framework and resulting codebook for transcript analysis were developed by bioethics research assistants who had received training in qualitative methods based on inductively identified themes as well as

preexisting literature. We report here on the content of the following codes: Diagnosis, Pregnancy Termination, Emotional Responses, and Future Recommendations (see the online appendix).

To validate the codebook, 20% of the total interviews were coded to consensus by 2 separate researchers. Consensus on how and when codes should be applied was reached by discussion of 8 coded transcripts. The remaining 30 transcripts were divided between 2 coders, with frequent, recurrent discussion between coauthors to ensure coding consistency and resolve any discrepancies. Independently coded transcripts were exchanged twice over the course of the coding process for cross-review by the other coder to ensure similarity of code usage. Coded content was inductively analyzed to interpret participant responses and identify salient themes. Thematic analysis was conducted to detect patterns across the data in relation to the research questions previously outlined.

Results

Demographics

Diagnoses included in the dataset include trisomy X (47,XXX), Klinefelter syndrome (47,XXY), Jacob's syndrome (47,XYY), 48,XXYY, 48,XXXY, and 48,XXXX. Data collection represents participants from multiple US states, including New York, New Jersey, Florida, California, Minnesota, South Carolina, Maryland, Idaho, and Oregon, among others, as well as the United Kingdom, Canada, and Australia.

Mode of Delivery of Diagnosis

Parents who received pediatric diagnoses typically sought medical attention following notable behavioral and physical delays at home or at school, including difficulties with language, mobility, socialization, and cognitive function. Genetic testing in pediatric care was also pursued in response to specific symptoms or to clarify previous misdiagnoses (25 participants; Table 1). Prenatal diagnosis typically followed medically indicated genetic testing for advanced maternal age or NIPT for gender determination (12 participants).

She was reachin' her milestones a lot later than other children (. . .) She was quite delayed on everything, really, so that's what prompted the looking into if there was a cause behind it. (Mother of 3-year-old, Trisomy X; Pediatric diagnosis: 2-years-old)

Many pregnant women and couples experienced the delivery of a diagnosis as an unexpected event. Participants reported a range of negative and anxious responses to

Table 1. Participant Demographics.

Interviews	N = 38
Parents (on behalf of children any age)	n = 35
Individuals (age 16+)	n = 8
Mean age of affected individuals interviewed (range)	18.9 years (17 to 24 years)
Mean age of child at time of interview (range)	9.5 years (2 months to 24 years)
Mean age of child at time of diagnosis (range)	8.3 years (6 months to 17 years)
Participants with prenatal diagnosis, n (%)	12 (32%)
Participants with pediatric diagnosis, n (%)	25 (68%)

the delivery of diagnosis and emphasized that the method and tone of delivery had a significant impact on their emotional and mental state.

When we got this, we weren't prepared for that. I felt like I'd been kicked in the stomach, that's how I felt. Because all you hear is, "Your baby's not normal." (Mother of 15-year-old, Jacob's syndrome; Prenatal Diagnosis)

That's exactly what the doctor said to me. He's not gonna graduate from high school. He might turn to a life of crime, things like that. That was disheartening for me to hear. I mean I was a wreck that day. I didn't even go back to work. (Mother of 10-year-old, Jacob's syndrome; Pediatric diagnosis: 9-years-old)

Many participants reported first learning of their diagnosis via phone call or email. Few encountered optimistic outlooks from their medical providers. Several participants reported that one of the first things they were told was that their child was sterile. For those who received a diagnosis prenatally, many felt that the portrayal of the condition in question was predominantly negative and the diagnosis was frequently delivered as an unfortunate event.

"I hate to be the one to tell you this, but your son has a variation of Klinefelter's syndrome, and he's sterile." That's the first thing she tells me. I don't think that's—looking back, I'm like, that hits a father like a ton of bricks. (Father of 16-year-old son, 48, XXYY; Pediatric diagnosis: 9-years-old)

The genetic doctor looked it up and said, "Not to scare you, but your child will never leave home." He was 5 years old. He told that to a parent. (Mother of 8-year-old, 48, XXYY; Pediatric diagnosis: 5-years-old)

Individuals and families who received a pediatric or adolescent diagnosis unintentionally, usually as an

incidental finding to other testing, reported even more negative experiences and what they perceived as a strong lack of empathy on behalf of those delivering the result.

They just kind of threw out to [child] that you likely can never have children, you likely cannot [realize your career plans]. What was the other one? It was kind of like these two really big, I guess, whammies. (. . .) Hypogonadism is all they told us it was at that time. That was a very emotional day. (Mother of 18-year-old, Klinefelter syndrome; Pediatric diagnosis: 17-years-old)

Participants Reactions to Diagnosis and Remaining Questions

While most participants reported negative emotions following delivery of a diagnosis of an SCA, some families who received a pediatric diagnosis as the finale of a diagnostic odyssey reported experiencing relief having discovered an answer for previously unexplained physical, cognitive, and behavioral symptoms.

I think in general, it was, "Oh my gosh, now you know." Because we've all known that he struggled (. . .) That just really means that you now know why. There's a reason why he struggled. (Mother of 18-year-old, Klinefelter syndrome; Pediatric diagnosis: 17-years-old)

Participants reported unanswered questions on how and where to find support, what to expect, and whether they could have prevented the condition. Lack of confidence regarding what direction to take and concern about available interventions and services following the diagnosis appeared to contribute greatly to the experience of distress for many parents.

To be honest with you, I cried when I found out that they said that she wasn't autistic, because there are so many services for autism. All you have to do is say autism and people know what you're talking about. Nobody knows what Trisomy X is. (Mother of 7-year-old, Trisomy X; Prenatal diagnosis)

I think the biggest problem is the lack of specific available guidance on what to do because the symptoms of Klinefelter are fairly nonspecific and you can't definitely predict what's going to happen to any individual or not. (Father of 17-month-old, Klinefelter syndrome; Prenatal diagnosis)

Participant Perceptions of Provider Knowledge About SCAs

Many participants expressed low confidence in their providers' knowledge of the condition. Many parents

believed that the provider delivering the diagnosis had insufficient knowledge of the condition in question and was unable to answer their questions about the implications of the diagnosis. Participants often reported being "sent to Google" for information about the condition, where they found largely outdated, inaccurate, and disparaging results.

What she said was, "I'll be honest" The geneticist comes in the room at that point and said, "We don't have any experience diagnosing this." This guy had been a geneticist there at [hospital] for, whatever, 15 years, 20 years, and said, "I've never diagnosed it before, but we did a Google search, and this is what we found." (Father of 16-year-old, 48, XXY; Pediatric diagnosis: 9-years-old)

Parents reported that perceived lack of comprehensive counseling and support left them feeling "abandoned." Some parents reported mental and emotional trauma, sufficient to seek psychiatric care. Many parents turned to nonclinical sources including Internet sites and patient advocacy organizations for additional knowledge of their child's condition and for emotional support.

Medical Options Presented at Time of Diagnosis

Participants reported that the earlier the diagnosis, the greater the facilitation of their family's preparation for and access to early interventions for the child. Furthermore, earlier diagnoses appear to allow families to consider and plan for fertility preservation, when desired, as it is typically a procedure that can be completed within a limited timeframe. Moreover, some participants reported the desire for earlier diagnosis to maximize the potential benefit of hormone replacement therapy.

I certainly think that prenatal diagnosis is a Godsend because it means we know things to look for and can at least try to put extra effort and prevent the areas where there's likely to be trouble (. . .) If we hadn't had the prenatal diagnosis, it's possible we might not have discovered anything until after he was well into abnormal[ly] delay[ed] puberty and his sperm had already been killed off. (Father of 17-month-old, Klinefelter syndrome; Prenatal diagnosis)

Regarding prenatal medical options, participants explained that the option to terminate, when presented repeatedly, even after parents had declined, can be perceived as medical recommendation. Some expressed that the offer, and especially the repeated offer, of termination felt coercive and overtly judgmental about the potential quality of life of their child and their family.

We finally had to say, “Stop. We get we have the right to terminate. We are choosing not to.” That was difficult [be] cause when your doctor keeps harping on it, it makes you question [your] decision. (Mother of 10-year-old, Trisomy X; Pediatric diagnosis: 18-weeks old)

Discussion

Understanding familial and individual experiences of diagnosis with SCA is necessary to assess present challenges in the delivery of diagnosis and management of care for these conditions. While the majority of participants in this study ($n = 25$) received a pediatric diagnosis following clinical investigation into physical, cognitive, or behavioral symptoms, the experiences reported suggest that improvements can be made in the delivery of diagnosis and discussions about long-term care. Participants reported lack of confidence in their provider’s knowledge about SCAs and noted a predominantly negative tone in communication surrounding the diagnosis and its implications. Many recalled the diagnosis being delivered remotely, rather than in face-to-face encounters. These factors led to increased anxiety and uncertainty about their child’s condition. Parents expressed a strong desire to have the diagnosis presented in more positive terms as well as having the diagnosis delivered in person. These findings support a previous study suggesting great variation in provider knowledge of SCAs, with some health care professionals providing inaccurate or misleading information on prenatal diagnosis.²² Misperceptions of the clinical severity of SCAs may be influenced by ascertainment bias, as studies reporting on individuals diagnosed postnatally are biased toward describing individuals with more severe clinical involvement, but are not representative of the phenotypic range of SCAs.^{1,4,19} Based on these findings, improving medical provider’s knowledge of SCAs as well as delivering the diagnosis face-to-face may assist in mitigating parental anxiety surrounding an SCA diagnosis.²⁰

Several parents recalled being “sent to Google” for information regarding their child’s condition on delivery of the diagnosis. As online medical searches often return inaccurate, out-of-date, and biased results, patients should be provided materials or directed to specific trustworthy resources. Since many initial chromosomal analysis studies were performed in mental institutions and prison populations, leading some investigators to hypothesize a link between SCAs and violent or criminal behavior, online sources may contribute to heightened concern without the advantage of contextualizing these studies with discussion of their methodological errors and subsequent findings of population-wide studies. Providing standardized educational materials or

materials from patient advocacy organizations (eg, AXYS Foundation, the XYYY Project, and National Organization of Rare Disorders) may foster more complete outlooks and optimistic perceptions of their child’s future on delivery of diagnosis. Connecting patients to local or national patient advocacy groups may provide parents with the two-fold benefit of connecting their family with accurate resources and a community of support as they navigate the complexities of raising a child with an SCA.

Participants felt strongly that the use of apologetic language and pessimistic descriptions of the condition by providers presented the diagnosis as an overtly negative event, which parents retrospectively interpreted as a regrettable and unwelcome experience. In contrast, several participants who received a pediatric diagnosis experienced relief at finding an explanation for their child’s symptoms and the opportunity to access previously inaccessible educational, medical, and social services. While many providers emphasized infertility as the most prevalent impact of the condition, respondents felt that it was of secondary concern; their primary priority was in understanding how their child’s overall daily functioning could be improved in light of the diagnosis.

In the prenatal context, the mode and tone of delivery was perceived as even more important, given the possibility of termination. Participants recalled that repetition of the option to terminate was frequently interpreted as a medical recommendation or an attempt to coerce the participant to change their decision to continue with the pregnancy. To avoid perceptions of undue pressure, greater communication among team members—for instance, noting in the electronic medical record that the option of termination has been presented to the patient and declined—may eliminate the potentially harmful repetition of the option to terminate by multiple providers. The provision of accurate, comprehensive, and neutral information is necessary in this setting as it has been demonstrated that the decision to terminate pregnancy is influenced by clinical specialty and providers’ subjective perception of the quality of life of the affected individual, with pregnancy being more likely to continue if a genetic specialist provided the counseling.²³⁻²⁶

Many participants also expressed concerns over understanding their child’s prognosis and the desire for prognostic certainty. While this desire is understandable, SCAs have highly variable phenotypes and symptoms range in severity or may manifest in later childhood or adulthood, making it difficult to forecast outcomes based on a predictable phenotype. Of note, participants highly valued transparency about medical uncertainty, including providers’ acknowledgement of limited experience with SCA diagnoses or knowledge of SCA

phenotypes. Providers can assist patients and families by anticipating care at different stages of development and proactively referring patients to the appropriate medical disciplines for evaluation. It is also important to consider that requirements for individualized education plans vary from state to state and insurance coverage of specialty services may not include SCA diagnoses, adding to parental burden.

As NIPT expands, and the sex chromosomes are increasingly evaluated for the determination of fetal sex, the number of incidental diagnoses of SCAs is likely to increase. Participants of this study reported a strong preference for earlier diagnosis, as it allows for the introduction of therapies at an earlier developmental stage and for parental preparation. Some participants additionally noted that an earlier diagnosis facilitated the proactive implementation of hormonal therapies with potentially greater clinical benefit as well as the opportunity to consider fertility preservation. It is estimated that less than 10% of boys receive a diagnosis of Klinefelter syndrome before puberty, a period during which testosterone plays a crucial role in the development of bone, muscle, and secondary sexual characteristics.¹⁵ Presymptomatic diagnosis of an SCA will enable the timely implementation of hormonal therapies to improve reproductive outcomes and symptom management.^{27,28}

Conclusion

Although the sample size of the present study was fairly large for a qualitative study, there are limits to how far qualitative results may be generalized. Due to our recruitment mechanism, our participant pool may be biased toward high-functioning populations and/or families with high socioeconomic capacity to identify and access social services. As such, these participants may not be representative of the general population of parents and children in the SCA community. However, this study provided an opportunity to explore in-depth the attitudes and experiences of parents and individuals who received an SCA diagnosis. Additionally, our recruitment mechanism excluded participants who terminated pregnancies in response to a diagnosis. Results of this study suggest that parents overwhelmingly desire the presentation of SCAs in a more optimistic context. It is also essential to provide patients and medical providers with the resources and education necessary to support families on diagnosis. Standardization and clinical integration of patient education materials of SCAs may facilitate the work of providers and improve the experience of families. Attention should be paid to designing procedures for the return of diagnoses to provide concrete direction for the next steps of care. Both parents and

affected individuals largely preferred to receive a diagnosis as early as possible as it facilitates timely access to early interventions, opportunities to consider fertility preservation, and parental preparation. It is critical that improvements be made in how the diagnosis of an SCA is delivered to ensure parents and individuals receive the support and comprehensive care necessary to adapt to and thrive with an X or Y variation.

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Author Contributions

Study Conception and Design: MA, JE, SP; Data acquisition: CJ, JE; Data analysis: CN, KAR, JE; Drafted the manuscript: CJ, CN, KAR, MA; Manuscript revision: CJ, CN, KAR, JE, SP, MA; Final approval of manuscript: CJ, CN, KAR, JE, SP, MA.

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Supplemental Material

Supplemental material for this article is available online.

References

1. Pieters JJ, Kooper AJ, van Kessel AG, Braat DD, Smits AP. Incidental prenatal diagnosis of sex chromosome aneuploidies: health, behavior, and fertility. *ISRN Obstet Gynecol*. 2011;2011:807106.
2. Abramsky L, Chapple J. 47,XXY (Klinefelter syndrome) and 47,XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. *Prenat Diagn*. 1997;17:363-368.
3. Bondy CA. New issues in the diagnosis and management of Turner syndrome. *Rev Endocr Metab Disord*. 2005; 6:269-280.
4. Lalatta F, Tint GS. Counseling parents before prenatal diagnosis: do we need to say more about the sex chromosome aneuploidies. *Am J Med Genet A*. 2013;161A:2873-2879.

5. Pieters JJ, Kooper AJ, Eggink AJ, et al. Parents' perspectives on the unforeseen finding of a fetal sex chromosomal aneuploidy. *Prenat Diagn.* 2011;31:286-292.
6. Bardsley MZ, Kowal K, Levy C, et al. 47,XYX syndrome: clinical phenotype and timing of ascertainment. *J Pediatr.* 2013;163:1085-1094.
7. Boada R, Janusz J, Hutaff-Lee C, Tartaglia N. The cognitive phenotype in Klinefelter syndrome: a review of the literature including genetic and hormonal factors. *Dev Disabil Res Rev.* 2009;15:284-294.
8. Cordeiro L, Tartaglia N, Roeltgen D, Ross J. Social deficits in male children and adolescents with sex chromosome aneuploidy: a comparison of XXY, XYY, and XXYY syndromes. *Res Dev Disabil.* 2012;33:1254-1263.
9. Hong DS, Reiss AL. Cognitive and neurological aspects of sex chromosome aneuploidies. *Lancet Neurol.* 2014;13:306-318.
10. Leggett V, Jacobs P, Nation K, Scerif G, Bishop DV. Neurocognitive outcomes of individuals with a sex chromosome trisomy: XXX, XYY, or XXY: a systematic review. *Dev Med Child Neurol.* 2010;52:119-129.
11. Otter M, Schrandner-Stumpel CT, Curfs LM. Triple X syndrome: a review of the literature. *Eur J Hum Genet.* 2010;18:265-271.
12. Tartaglia N, Davis S, Hench A, et al. A new look at XXYY syndrome: medical and psychological features. *Am J Med Genet A.* 2008;146A:1509-1522.
13. Bojesen A, Gravholt CH. Klinefelter syndrome in clinical practice. *Nat Clin Pract Urol.* 2007;4:192-204.
14. Bondy CA; Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab.* 2007;92:10-25.
15. Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. *J Clin Endocrinol Metab.* 2003;88:622-626.
16. Bianchi DW, Parsa S, Bhatt S, et al. Fetal sex chromosome testing by maternal plasma DNA sequencing: clinical laboratory experience and biology. *Obstet Gynecol.* 2015;125:375-382.
17. Mazloom AR, Džakula Ž, Oeth P, et al. Noninvasive prenatal detection of sex chromosomal aneuploidies by sequencing circulating cell-free DNA from maternal plasma. *Prenat Diagn.* 2013;33:591-597.
18. Nicolaides KH, Musci TJ, Struble CA, Syngelaki A, Gil MM. Assessment of fetal sex chromosome aneuploidy using directed cell-free DNA analysis. *Fetal Diagn Ther.* 2014;35:1-6.
19. Linden MG, Bender BG. Fifty-one prenatally diagnosed children and adolescents with sex chromosome abnormalities. *Am J Med Genet.* 2002;110:11-18.
20. Linden MG, Bender BG, Robinson A. Genetic counseling for sex chromosome abnormalities. *Am J Med Genet.* 2002;110:3-10.
21. Mennuti MT, Chandrasekaran S, Khalek N, Dugoff L. Cell-free DNA screening and sex chromosome aneuploidies. *Prenat Diagn.* 2015;35:980-985.
22. Abramsky L, Hall S, Levitan J, Marteau TM. What parents are told after prenatal diagnosis of a sex chromosome abnormality: interview and questionnaire study. *BMJ.* 2001;322:463-466.
23. Hall S, Marteau TM, Limbert C, et al. Counselling following the prenatal diagnosis of Klinefelter syndrome: comparisons between geneticists and obstetricians in five European countries. *Community Genet.* 2001;4:233-238.
24. Marteau TM, Nippert I, Hall S, et al; Decision-making After Diagnosis of Fetal Abnormality (DADA) Study Group. Outcomes of pregnancies diagnosed with Klinefelter syndrome: the possible influence of health professionals. *Prenat Diagn.* 2002;22:562-566.
25. Sagi M, Meiner V, Reshef N, Dagan J, Zlotogora J. Prenatal diagnosis of sex chromosome aneuploidy: possible reasons for high rates of pregnancy termination. *Prenat Diagn.* 2001;21:461-465.
26. Shaw SW, Chueh HY, Chang SD, Cheng PJ, Hsieh TT, Soong YK. Parental decisions regarding prenatally detected fetal sex chromosomal abnormality and the impact of genetic counselling: an analysis of 57 cases in Taiwan. *Aust N Z J Obstet Gynaecol.* 2008;48:155-159.
27. Radicioni AF, De Marco E, Gianfrilli D, et al. Strategies and advantages of early diagnosis in Klinefelter's syndrome. *Mol Hum Reprod.* 2010;16:434-440.
28. Visootsak J, Ayari N, Howell S, Lazarus J, Tartaglia N. Timing of diagnosis of 47,XXY and 48,XXYY: a survey of parent experiences. *Am J Med Genet A.* 2013;161A:268-272.