Genetic Counseling and Family Support for Sex Chromosome Aneuploidies

Consensus-based recommendations from the

AXYS Clinic & Research Consortium

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Introduction

The National Society of Genetic Counselors (NSGC) defines genetic counseling as the process of "helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease."

According to the NSGC, this process includes:

- Interpreting family and medical histories to assess the chance of occurrence or recurrence of a disorder
- Educating families about inheritance
- Providing information on testing, management, prevention, resources, research, and counseling to promote informed choices and adaptation to the risk or condition

In the US, genetic counselors are usually master's level medical professionals who have a background in both clinical genetics and psychosocial counseling. These professionals are trained to assess and assist families coping with a genetic disorder.

Genetic counselors provide a range of support including:

- Translating complex medical and genetic information
- Helping families with the emotional and psychosocial issues that come with a new diagnosis
- Helping families share information with extended family members
- Making referrals to medical and mental health specialists to ensure comprehensive care

Genetic counselors typically work as part of health care teams, and can work in a variety of settings. Many genetic counselors partner with medical geneticists, perinatologists, obstetricians, oncologists, and other clinical specialists. Others work in clinical laboratories and research settings. They may also work independently in private practice.

Genetic counseling for sex chromosome aneuploidies (SCAs), also called X&Y variations, is particularly complex. This is because of several aspects unique to SCAs:

- Commonly unexpected results of prenatal screening
- The highly variable presentation associated with the conditions and uncertain prognosis
- Infertility in males with additional X chromosomes
- The process of disclosure of the diagnosis to the individual and others

Because of this complexity, we recommend that only knowledgeable and experienced board-certified genetic counselors and other qualified health professionals with similar training and experience provide genetic counseling for SCA conditions.

Section 1 of 5: Elements of initial genetic counseling

Genetic counseling sessions typically include getting a detailed multigenerational family history (called a "pedigree").

SCAs are not typically inherited conditions and most commonly occur due to a nondisjunction event during meiosis in either formation of the egg or sperm. However, a 3-generational pedigree can help identify family histories of various multifactorial traits that can potentially impact medical, developmental, and psychological outcomes in children with an SCA. In addition, parental perspectives of variable features of SCAs can be influenced by personal and family histories. These histories help to inform the counseling session and allow the counselor to provide appropriate support and information.

A detailed family history should include any individual of any gender with a history of any of the following issues.

Issues to record in family history for SCA genetic counseling			
Chronic illness or other physical conditions	**Mental health issues**	**Neurologic/ neurodevelopmental issues**	**Fertility-related issues**
Allergies (seasonal or food) Asthma Birth defects Breast Cancer Blood clots resulting in DVTs or early strokes Diabetes, high cholesterol, high blood pressure or	Anxiety Depression Psychiatric or mental health issues	ADHD or other attention-related problems Autism spectrum disorder Behavioral problems Developmental delays or history of childhood therapies (such as speech, OT, PT, or feeding, etc.)	Infertility, assisted reproduction, or adoption Multiple spontaneous miscarriages (SAB)

metabolic syndrome Gastrological problems (such as reflux, constipation, or eosinophilic esophagitis)		Intellectual disabilities or learning disabilities, including reading disabilities (such as dyslexia) Special education services Neurological problems (such as tremors, tics, or seizures)	

Discussion of prognostic implications and the phenotypic spectrum

Initial genetic counseling for SCAs should address 2 main areas:

1. Information about the associated physical, medical, developmental, and psychological features of the SCA condition
2. Anticipatory guidance on appropriate evaluations and plausible interventions for any identified problems

The high variability among SCAs and within individual karyotypes confounds the ability of a genetic counselor to provide precise prognostic information, especially in the context of a prenatal or early childhood diagnosis. However, counselors can provide information from various publications and insights.

To begin, counselors should inform families of the importance of the child's entire genetic composition and interactions with dynamic environmental variables, both of which may influence individual outcomes. Previous reports of prospective studies demonstrated that children who are prenatally diagnosed may have improved developmental outcomes, possibly attributed to proactive anticipatory guidance. However, these results may be biased toward children from higher socioeconomic backgrounds.

In addition, counselors should caution parents about inaccurate and biased information accessible through the Internet and outdated medical literature. Furthermore, parents and children may benefit from connection with other families through various support groups. However, counselors should make families aware that these groups can also present with intrinsic biases.

Discussion of potentially available interventions

Genetic counselors provide anticipatory guidance on appropriate evaluations and possible interventions for any identified problems—both at the initial visit and throughout ongoing consultation.

Children who are diagnosed in-utero or during early childhood may benefit from standardized evaluations of development as well as assessments for possible associated medical or psychological problems. Those whose initial diagnosis occurs during adolescence or adulthood may benefit from targeted medical evaluations for potential associated medical problems as well as consideration for psychological assessments based on the individual's history and any presenting concerns.

Counselors should also consider the following, as indicated:

- Further discussions regarding fertility and associated referrals
- Transition planning from adolescence to emerging adulthood
- Emotional impact of the new diagnosis and disclosure to others
- Appropriate management of previously identified problems in the context of the new diagnosis

Addressing inaccurate information

Unfortunately, some families may have received previous counseling that inaccurately depicted the diagnosis, prognosis, or both. This is largely due to a highly variable phenotype and previously published studies with significant ascertainment bias, as well as a lack of current understanding of SCAs.

Because of this, genetic counselors should ask the family about their understanding of the diagnosis and prognosis at the time of the initial evaluation. Counselors should be prepared to address previous misconceptions of the diagnosis, including associations with advanced maternal age and universal statements of cognitive impairment or intellectual disability as well as the inability to live independently, parent their own child, or achieve a higher education or a career. These blanket statements inaccurately depict the highly variable presentation and outcomes of children with SCAs. This can lead to choices that don't fully support important interventions for the child's medical management, developmental and academic outcomes, and self-esteem.

Section 2 of 5: Prevalence of SCA conditions

Consecutive newborn screening studies conducted in the 1960s and 1970s at 7 sites around the world identified over 300 newborns with SCAs. The results of these studies, as well as subsequent international studies, support SCAs being one of the most common chromosomal conditions, occurring in approximately 1/400 births (collectively).
The approximate prevalence of the most common conditions within the group of SCAs includes:

- 45,X (1,2500)
- 47,XXY (1/650)
- 47,XXX (1/1000)
- 47,XYY (1/1000)
- 48,XXYY (1/18,000)
- 48,XXXY (1/20,000)
- 48,XXXX (1/50,000)
- 49,XXXXY (1/80,000)

Most individuals with SCAs remain undiagnosed throughout their lifetime. Experts attribute this largely to the highly variable symptoms, absence of distinctive physical features, and potentially lack of awareness and accurate education among medical professionals. The more rare SCA conditions, such as 48,XXXX or 49,XXXXY, may be more likely to be diagnosed due to significant clinical phenotypes and higher rates of medical and developmental problems in these conditions.

A subset of individuals may not have SCAs in all of their cells and have SCA mosaicism. The prognosis and clinical management of patients with sex chromosome mosaicism may differ from non-mosaic individuals. Therefore, they should be counseled on a case-by-case basis, especially in consideration of fertility potential, external genitalia, and/or the presence of a 45,X cell line.

Previous studies estimate that approximately 10% of 47,XXX and 47,XYY cases, and 35% of 47,XXY cases, are ascertained within the lifetime of the individual. However, advances in prenatal screening technologies with the onset of cell-free fetal DNA screening (also known as noninvasive prenatal screening, NIPS) has likely increased both the awareness of SCAs and also the identification of SCAs among newborns.

Section 3 of 5: Testing for SCAs

Cytogenetic analysis

The diagnosis of SCAs requires cytogenetic analysis. This testing is most commonly done by either routine karyotype or chromosomal microarray (aCGH). Either of these tests can be performed on prenatal samples taken by chorionic villus sampling (CVS) or amniocentesis, cord blood at the time of delivery, or on peripheral blood after delivery. Some labs may also offer testing by saliva sample or skin biopsy, which can be helpful especially if a different tissue type (something other than peripheral blood) is needed for further evaluation. In addition, SCAs may be unsuspectingly discovered during evaluation for other conditions, and confirmatory testing by routine karyotype should be considered.

Possible presenting symptoms of SCAs as indications for chromosome testing

In post-pubertal males only

- Infertility
- Small testes
- Testosterone deficiency

In individuals of all genders and ages

- Diagnosis of autism spectrum disorder
- Growth pattern reflecting significant short or tall stature compared to family members
- Global developmental delays
- History of seizures

Cluster of multiple symptoms, which may include:

- ADHD
- Anxiety
- Dyspraxia/apraxia
- Dyslexia
- History of cryptorchidism
- Hypotonia
- Learning disabilities
- Tics or tremors
- Unexplained tall or short stature

Noninvasive prenatal screening

Noninvasive prenatal screening (NIPS) may also detect an increased chance of the fetus having an SCA. NIPS for SCAs is a maternal blood test relying on the presence of cell-free DNA from the placenta circulating in the maternal blood. NIPS is a screening test. It does not confirm a diagnosis, but rather identifies an increased risk for the condition in the fetus. Because of this, there is an associated false positive/negative rate.

NIPS is less informative in the context of maternal obesity and twin pregnancies. While the detection rate of chromosomal aneuploidies by NIPS is very high, particularly in comparison to conventional first or second trimester screening methods, the Positive Predictive Value (PPV, defined as a positive result being a true positive diagnosis) may be lower due to various confounding technical and biological factors. Notably, PPV for NIPS has been reported to range drastically from 9 to 40% for chromosome X-related abnormalities. As such, the American College of Medical Genetics and Genomics and the American College of Obstetrics and Gynecology recommend confirmatory diagnostic (prenatal or postnatal) testing for any positive NIPS result, including SCAs.

Karyotype or Fluorescent in-Situ Hybridization testing

SCA diagnostic testing by routine karyotype or Fluorescent in-Situ Hybridization (FISH) testing can also detect the presence of mosaicism, in which 2 or more populations of cells with different karyotypes are identified in one individual. Mosaicism can be identified when testing a single tissue type, such as peripheral blood, or in comparing karyotypes from different tissue types, such as peripheral blood versus skin biopsy.

Under certain circumstances, FISH testing on 50 to 500 cells may be recommended following routine karyotype testing to evaluate for low-level mosaicism. Individuals with mosaic SCA may exhibit milder or more severe symptoms, dependent upon if the additional karyotype(s) is considered normal or abnormal.

One of the more common forms of SCA mosaicism can occur in females identified to have 2 different cell types: 47,XXX in combination with 45,X. This specific mosaicism warrants additional medical evaluations. This is because the 45,X cell line (also known as Turner syndrome) can contribute to additional medical problems and necessitate long-term, targeted medical follow-up. Genetic evaluations for mosaicism commonly report on the count and/or percentages of different cell types identified and may require additional testing on different tissues such as urine, skin biopsy, or buccal epithelial cells.

SCA conditions are not typically inherited and recurrence risks for the parents are often quoted to be <1% or the associated risk for aneuploidy due to advanced maternal age at the time of delivery, whichever is greater. Exceptions to this include individuals identified to carry a chromosome translocation involving the X or Y chromosome, or if a parent is affected themselves with an SCA. Both of these circumstances warrant additional genetic counseling.

Section 4 of 5: Diagnosis disclosure

Disclosing an SCA diagnosis to the child with the SCA

Families who receive a diagnosis of an SCA during pregnancy or early childhood are often faced with questions about if, when, and how to disclose the diagnosis to the child, other family members, educators, or others participating in the child's care.

Factors commonly considered in facing disclosure to the child often include the following:

- Type of SCA
- The degree to which the SCA has impacted the child
- The child's emotional and cognitive abilities to process the diagnosis

Parental concerns surrounding disclosure commonly balance these 3 ethical concerns:

- Autonomy (the child's right to know)
- Beneficence (the benefits to the child knowing the diagnosis)
- Maleficence (the desire to do no harm to the child from knowing the diagnosis)

Research and publications support a thoughtful disclosure process to the child that focuses on the following:

- Recognize that each child is different in how they comprehend, communicate, and cope.
- Take an early and gradual approach to discussions over time.
- Provide emotional support in discussing the diagnosis, often incorporating individual strengths in context.
- Be honest, open, and calm during discussions.
- Use simple and direct language to avoid any confusion, and check to make sure the child understands.
- Encourage the child to ask questions, both during discussions and at any time.
- Engage a healthcare professional in the disclosure process or discussion, especially when parents don't feel confident in their understanding of the diagnosis.

Disclosing an SCA diagnosis to others outside the immediate family

When it comes to disclosing the diagnosis to others, parents may express the following concerns:

- Potential stigma
- Others seeking inaccurate online information

- Indirect disclosure of future infertility
- Preservation of the child's privacy
- Need for parental support

When discussing disclosure, counselors should take into account familial and cultural beliefs as well as the child's diagnosis, age, and identified symptoms.

Developmental and academic needs may be addressed independent of disclosure. However, if the child is experiencing developmental, academic, or behavioral problems and parents have been unable to access interventions appropriately, it may be beneficial to inform the school or therapists of the diagnosis. This can help support teams better direct assessments and effective interventions, as well as reframe the perception of the child given the context of the underlying genetic contribution to presenting problems.

The child's health care providers should know the diagnosis given the potential impact for the child's medical management. Due to the wide spectrum of medical, developmental and psychological features associated with SCA conditions, as well as advancements with ongoing research, we recommend including the SCA diagnosis in the child's medical record and discussing the diagnosis with the child's primary care and specialty providers to insure the most appropriate care for the child.

Go to the AXYS website (www.genetic.org) for more information and resources.

Section 5 of 5: Family support resources

An SCA diagnosis can be very difficult for families at first. Questions such as the following often arise:

- "Why me? Why our family?"
- "What do we do now?"
- "How could this affect the child's future?"
- "Who can we talk to about this?"

Families need resources to help answer these questions. Genetic counselors and other qualified health professionals can be a good source of information about the child's diagnosis and prognosis as well as screening recommendations, and treatment options. They can also help provide psychosocial support to families during this challenging time. Families should not hesitate to contact the clinician or counselor who first gave them the diagnosis.

Below are resources that may help families connect to support they need from professionals and other families.

Important note: Some families or individuals may have a very difficult time accepting the diagnosis and its potential implications. Receiving the diagnosis of an SCA can present as a traumatic event and often leads to feelings of grief, distress and guilt. It is important to remember that everyone has a unique history and learns about the diagnosis differently. However, it is also important to monitor for signs of depression, anxiety, or severe grief reactions. Individual or family counseling may be very helpful for some families coping with the diagnosis of an SCA.

The National Society of Genetic Counselors (NSGC) website
www.AboutGeneticCounselors.com

Families can get helpful resources and search for certified genetic counselors in their area.

The AXYS website's list of AXYS Clinical and Research Consortium clinics

genetic.org/clinics/
Families can connect with dedicated clinics that specialize in children and adults with SCAs. The medical and psychological professionals at these clinics can provide more information about the conditions, treatments, and research opportunities.

Given the highly variable clinical presentation of SCAs, families often desire guidance and assistance in providing accurate information to community-based care providers. A genetic counselor or other qualified health professional can help families identify

appropriate resources, provide letters and understandable information, and facilitate referrals.

The AXYS website's national professional directory of community-based SCA experts
genetic.org/professional-directory/

Families can search for community-based professionals who have experience and knowledge in SCAs. This directory helps families share information about professionals with whom they have worked and found knowledgeable and experienced in treating their child.

The AXYS website's national network of support groups
genetic.org/im-parent-affected-child/support-groups/

Parents of children with SCAs often find it helpful to talk to other parents of children with the condition, especially when the children are or similar age. Parents may be linked together through their clinicians, or through support groups and organizations. The AXYS national network of support groups) is a network of parent/family groups, sponsored by AXYS, that provide support to families across the country. They also help raise awareness of SCAs through education efforts, fundraising and advocacy.

Families may also be able to connect with others through social networking sites such as Facebook (http://www.facebook.com/) and Twitter (http://twitter.com/).

More information about early intervention

genetic.org/clinics/

The risks for developmental, behavioral, and learning issues associated with SCAs are often a significant concern for parents of young children. Early intervention programs can be helpful resources for parents as they learn how to help their child achieve early developmental milestones. Once the child is in school, therapists can help parents understand their child's language, learning, or other developmental difficulties.

The AXYS Clinical & Research Consortium (ACRC) has developed additional consensus statements addressing many of these topics. These statements provide expert consensus for the evaluation and treatment of issues common to SCAs.

More information about special education

The Wrightslaw website (www.wrightslaw.com) provides information about special education law and advocacy for children with educational needs. Topics include advocacy, ADHD, behavior and discipline, evaluations and more. The AXYS website (www.genetic.org) also has educational resources, including recorded webinars to better understand special education and individualized educational plans (IEP).

More information about research

Many families are interested in knowing what research opportunities are available or what is being done to help individuals or families affected by SCAs. Research is an important part of the sex chromosome variation world, and information about current research studies can be found on AXYS (https://genetic.org/about/research/opportunities-for-families/). Information about clinical trials for SCAs can also be found at ClinicalTrials.gov (www.clinicaltrials.gov).

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Note: *This guideline was authored by Susan Howell, MS. CGC, and Katie Grand, MS, LCGC, and has been approved by and represents the current consensus of the members of the AXYS Clinical & Research Consortium.*

The AXYS Clinical & Research Consortium was founded in 2015 and exists to:

- **Make life easier for those seeking evaluation and treatment.**
- **Bring consistency to treatment that is consensus and/or evidence-based.**
- **Advance the overall X&Y variation field through coordinated efforts including research.**
- **Bring clinical excellence to the field of X&Y variations.**

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Please contact AXYS for more information. (www.genetic.org)