How to identify a boy or man who may have XXYY Syndrome

A layman’s guidebook for people who may be in a position to help identify undiagnosed boys and men
A letter to men diagnosed with XXYY Syndrome or spouses, parents/family members of males with XXYY who do not identify with the signs and symptoms in this booklet:

The information in this booklet is based on what we know about infants, toddlers, teens and men with XXYY from families who have come forward. If you or a family member has been diagnosed with XXYY Syndrome and you have not contacted the XXYY Project, please do so—even if you do not need us.

The reasons we need to hear from you:

- Medical research on XXYY has been largely based on those identified with XXYY who have sought support. We need your participation in order to have the most accurate information about the needs, medical and other issues related to XXYY.
- We are in the process of developing a new patient registry. We need you to be part of that.
- Families of boys who are significantly impacted by the signs and symptoms of XXYY outlined in this booklet need to know that you exist. It gives them hope.
- We may have identified (or will continue to identify) medical issues related to XXYY that you need to be aware of. Research so far has already identified some.
- We would like to know about your success so that we can help families to replicate them.
- Because we want to know if this booklet reached you and how it reached you.

It has been our mission to find you since 1998!

To families of deceased individuals who had XXYY Syndrome
We are so sorry for your loss and we would like to honor your loved one. We would truly appreciate it if you would contact us as well. We are in the process of developing a patient registry that will document every medical aspect of XXYY possible. Your input into our registry on your loved one’s medical issues and cause of death would provide extremely valuable information for others. We hope you will consider contacting us.

To Contact the XXYY Project:
Through the AXYS Helpline:
Toll Free: (888) 999-9428
Outside U.S. and Canada: (303) 400-9040

E-mail: support@xxyysyndrome.org
www.xxyysyndrome.org
Facebook: facebook.com/xxyyproject
Twitter: @xxyyproject
(It is best to contact by email for the purpose of this booklet)

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This booklet may not be used for any other purpose than to provide information for potential XXYY families.
The photos in this booklet may not be reproduced by anyone for any reason.
Purpose of this booklet
Since 1998, parents of boys and men with XXYY Syndrome have been on a mission to find as many people diagnosed with XXYY Syndrome as possible throughout the world. Initially an informal group, the founding parents of what is now the XXYY Project have maintained a Web site and strong Internet presence and have connected with organizations serving people with disabilities around the world to find every diagnosed person we can find. While we have located hundreds, we know there should be thousands living today.

There are several reasons we believe we are not locating all of these families:

- Some people do not have Internet access.
- There are countries we are still not able to reach, but even in countries we do reach we are not finding the thousands that should exist.
- Language barriers limit us. We are a small organization using English as our primary language but we are still not reaching all English-speaking families.
- There may be individuals with XXYY Syndrome, parents and spouses who are not looking for a support organization either because they don’t need it or because they don’t think we exist.

But we believe these are the main reasons we are not locating them:

- These people are either not diagnosed or they are mis– or under-diagnosed with other conditions (especially Autism and ADHD), because there are many symptoms of XXYY Syndrome that either look like other conditions or often co-exist with other conditions (technically called comorbid conditions).
- There may be people living with XXYY who think they have Klinefelter syndrome (XXY).
- There may be individuals with XXYY Syndrome who do not have significant signs and symptoms outlined in this booklet. We especially need to find these individuals. If you have XXYY or if you are a parent, sibling or friend of someone who has XXYY who DOES NOT have these symptoms, please contact the XXYY Project!
- There may be individuals with XXYY Syndrome who are institutionalized whose families are no longer a part of their lives.

This booklet was created to help parents, spouses, other organizations, teachers, speech and language pathologists, occupational therapists, disability service providers, psychologists and mental health providers, babysitters, neighbors, family members, Autism organizations, learning disability organizations, ADHD organizations, and basically anyone to identify a boy or man who may have XXYY Syndrome. In so doing, we are hoping to dramatically increase the rate of diagnosis.

Receiving a full and accurate diagnosis is extremely important for boys and men with XXYY Syndrome to receive the medical attention and service supports they may need to live full lives. The more individuals we can identify, the more they can be included in medical research that can help develop therapies and understand the medical issues they have.

We ask you to review this booklet and if you think you know someone with XXYY Syndrome, suggest that they obtain genetic testing. Share this booklet with any person or organization that you think might be in a position to identify an undiagnosed boy or man. You could change someone’s life by doing so.

This booklet is not a medical paper although it does utilize information we know so far from medical research about XXYY Syndrome. It is meant to help those who may be in contact with a boy or man with XXYY to recognize the condition. This booklet should not be construed as medical advice nor predictive of the lives of any boy or man with XXYY. Until more males are diagnosed with XXYY and/or we find those without these symptoms, we do not know the full spectrum of XXYY.
To Autism, ADHD, Learning Disability, Intellectual and Developmental Disability, Mental Health Communities:

The XXYY Project is specifically reaching out to you because we have strong evidence that people with XXYY Syndrome are being served in your communities and many of them are undiagnosed. Some are diagnosed but have not found the XXYY Project. These individuals may not be receiving the benefit of interventions that could help them.

So many of the people the XXYY Project knows who have been diagnosed with XXYY Syndrome were not diagnosed until they were teens or even adults. It is extremely important that it is not assumed that someone would have recognized that they needed genetic testing. Their parents may have been satisfied with the diagnoses they do have, even though there are other symptoms that are not explained by those. Some parents may have been told that genetic testing should be done, but they decided not to pursue it. The first case of XXYY was not reported until 1960. The testing for XXYY was not available before that time and not widely used for a long time. It is safe to assume that there may be many people with XXYY who were diagnosed with intellectual and developmental disabilities in the years after 1960 who were never tested. Most of the adult cases we see are individuals who were not tested until the 80’s and 90’s and beyond. As a result, undiagnosed people with XXYY may be facing medical problems they do not know about, including some life-threatening conditions such as blood clots, heart problems, severe food allergies and more.

We need your help to reach them.

Please review this booklet thoroughly and use it as a training tool for your staff. Feel free to distribute it to families that might benefit.

The Hallmarks of XXYY:
There are many symptoms of XXYY outlined in this booklet by age group. Not all people with XXYY have all of the symptoms and sometimes they are only mildly affected. However, there are a few symptoms that do apply to a majority of those who have XXYY:

- Low muscle tone
- Speech delay
- Developmental delay
- Small testicles, delayed or stalled sexual development, low testosterone (hypogonadism)
- Taller than his family and in puberty and adulthood if he was not treated, he may be extremely tall

When added to the other symptoms such as learning disabilities or ADHD, Autism Spectrum Disorder, mental health diagnoses or intellectual disability, elbow deformities and other medical problems, a male with the above symptoms who has the body types and facial features shown in this booklet should have genetic testing. Some of his medical problems may be unexplained. For example, he may have unexplained white matter brain lesions. He may have tics, tremors and seizures. Again, when added to the above list, he needs to be tested.

This booklet contains photos of over 50 different men and boys with XXYY
Although we have used photos of the same person more than once in some cases, it is important to realize how many different people are represented.
What is XXYY Syndrome?

48, XXYY is a sex chromosome variation that affects one in every 17,000 males who are born.² XXYY Syndrome is the name attached to the cluster of symptoms that arise as a result of the 48, XXYY chromosome pattern, or an extra set of X & Y chromosomes. People of all races and ethnicities can have 48,XXYY.

48, XXYY is one of several types of sex chromosome variations, including those that are considered as variants of Klinefelter Syndrome, 47,XXY and 48,XXX, 49,XXXXY, XY/XXY and another syndrome called Jacob Syndrome or 47,XYY, all of which affect males. Similar female syndromes include Turner Syndrome (XO) and several variations with added X’s, such as Trisomy X (47,XXX). There are important differences, between boys and men with 47,XXY and those with 48,XXYY and some authors have questioned whether 48, XXYY males should be included under the umbrella of Klinefelter Syndrome.

How many people in the world should have XXYY Syndrome?

Based on the rate of incidence, this is a random sampling of countries:

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of males with XXYY Syndrome that should be living</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide</td>
<td>212,335</td>
</tr>
<tr>
<td>United States</td>
<td>9,262</td>
</tr>
<tr>
<td>Canada</td>
<td>1,026</td>
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<tr>
<td>China</td>
<td>42,219</td>
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<tr>
<td>United Kingdom</td>
<td>1,855</td>
</tr>
<tr>
<td>India</td>
<td>38,079</td>
</tr>
<tr>
<td>Germany</td>
<td>2,389</td>
</tr>
<tr>
<td>Indonesia</td>
<td>7,393</td>
</tr>
</tbody>
</table>

Although the XXYY Project does have members in the United States, many European countries, Canada and a few members in Asia and some other countries, our numbers are only in the hundreds.

How is a person diagnosed with XXYY Syndrome?

Diagnosing 48, XXYY requires a genetic test called a karyotype. The test is done by drawing blood and an analysis is done on the cells of the blood to determine the boy or man’s chromosomal make-up. In some instances, a boy can have some normal XY cells and some XXYY cells. This is called mosaicism.

Where should a person go if they think they may have XXYY Syndrome?

The first step is to visit a pediatrician, a developmental pediatrician or your primary care doctor and ask for a referral for genetic testing with a geneticist.

References

[1] The incidence of 48,XXYY syndrome was originally estimated at 1/50,000 (Sorensen et al., 1978), but a recent report found the 48,XXYY karyotype in 1/17,000 males in a newborn screening (Nielsen et al., 1991).

[2] Grannmatico et al., 1990 Males with XXYY have two X and two Y sex chromosomes, instead of one each. XXYY is sometimes considered a variant of another syndrome called Klinefelter Syndrome, or 47 XXY. There are other types of sex chromosome anomalies such as XYY, XXXY, XXXXY, and variations in girls such as XO (Turner Syndrome), XXX, XXXX. and XXXXX.
What does XXYY look like?
People ask us all the time if you can tell by looking at someone if they have XXYY Syndrome like you can with Down Syndrome. The answer is yes and no. If you have ever seen a group of boys and men with XXYY together, you do realize that they have many similarities and you can actually identify them. Parents were the first to realize that this was true. However, average people would not immediately notice their features unless they had seen a group of them before. Therefore, we present to you what XXYY looks like in boys and in teens and men, because there are differences as they get older. XXYY affects people of all races and ethnicities.

Physical features

Height
The first, most obvious physical feature of a person with XXYY Syndrome is that they are typically taller than their family. This is not as obvious when they are small but they do tend to be in the upper percentile for growth or taller and bigger than classmates. When they are teens and adults and have not been diagnosed or treated, they may be significantly taller than their family—and by that we mean they can reach 7 feet tall.
What does XXYY look like?

Physical Features (continued)

Facial Features

Boys and men with XXYY Syndrome have several facial features that can be distinct. They may not all have all of these features: wide-set eyes, large bridge of the nose, full lips, folds in the eyelids, large foreheads, prominent brow and sometimes pronounced indentations in the temples.
What does XXYY look like?

Facial features (continued)

As we have said previously, boys with XXYY often look very much alike. These photos of eight different boys and teens with XXYY show the most classic facial features and how they look similar.
What does XXY look like?

Physical features (continued)

Other

There are several other physical features associated with XXY. Not all males with XXY may have all of them: Flat feet (pes planus), curved pinky fingers (clinodactyly), breast development (gynecomastia), chest indentation (pectus excavatum, not as prominent as shown in the graphic below), deformities of the elbow (cubitus varus and radioulnar synostosis), long arms, deformity in the knee joint where it bends backwards (genu valgum).

As a result of the features of the legs and arms, you may notice that a boy or man with XXY walks or runs in an unusual way or that his arms do not lay flat against his body. His elbows may protrude unusually or his arms may appear to be turned in an usual way.
What does XXYY look like?

Physical features (continued)

**Body types**

Boys and men have distinguishable body types. They may be very thin or heavy and have little body hair until they receive testosterone replacement therapy. Again, his elbows may be very prominent.

17 year old teen with XXYY (left) with his 22 year old brother

30 year old man with XXYY with his aunt
What should we look for?
Since many, if not most boys and men are never diagnosed with XXYY, it is important that you never take for
granted that he should have already been diagnosed, especially if he is a teen or adult. XXYY impacts each
person differently, on a spectrum similar to Autism. A person may not have all of these issues. Here, we
have broken down the signs of XXYY by age groups.

Newborns & infants
A few of the newborns whose parents have contacted us have received a diagnosis at birth because their
baby had a heart condition, club foot or doctors thought the child might have a genetic condition because of
various signs they saw. Heart conditions are associated with some but not all males with XXYY. Instead, the
signs of XXYY typically begin with developmental issues and feeding problems beginning at birth into
toddler age.

Newborns and infants with XXYY may:
• have trouble latching on and sucking.
• sleep more than other babies and fall asleep often such as
while eating or playing.
• appear to be “floppy” or can’t hold themselves or their
necks up. They may fall over while sitting more than other
babies their age.
• begin having mild to severe delays in developmental
milestones like rolling over.
• have difficulty with fine or gross motor skills (for example,
may not be able to pick up a Cheerio from their high chair
tray).
• not crawl like other babies. They may scoot on their
behinds instead.
• have small and/or undescended testicles.
• have hernias.
• be allergic to milk products/formula and may have projectile
vomiting.
• gag a lot.
• have trouble holding a baby bottle.
What should we look for?

**Toddlers**

Delays in development become more obvious in toddlers with XXY. In addition to some of the signs outlined in the newborn and infant phase, there are other signs of XXY in toddlers.

**Toddlers with XXY may:**

- talk late or not at all. They may get very frustrated during attempts to communicate. They may have a “language of their own” that only those close to them understand.
- not be able to pull themselves up.
- walk late (beyond 2 years old).
- have trouble with balance. May fall often.
- potty train late and may not even potty train fully until much later.
- begin having temper tantrums which may continue beyond the “terrible twos”.
- have trouble learning to ride a tricycle.
- begin showing lack of judgment and impulsivity.
- hit, pinch and bite more than other toddlers.
- have croup-like coughs often, asthma, allergies or hospitalizations for respiratory problems.
- have trouble learning to drink from a straw or sippy cup.
- have a far-away look in his eyes as if in a fog.
- when they do walk, they may have an unusual gait and may have difficulty climbing stairs in an alternating step fashion. They may not be able to run.
- refuse to sleep in his bed. Instead, he might be found sleeping under his bed, beside his bed on the floor or in other places like closets after he has been safely tucked into bed.
- have staring spells or seizures.
- have night terrors.
- have heart problems/abnormalities
What should we look for?

**School-aged**
School-aged boys with XXY begin to show deficits in learning, socialization and self-regulation along with other signs outlined. They will also continue to have many of the issues they had when they were younger.

**School-aged boys with XXY may:**
- still have speech problems that require speech therapy.
- have learning disabilities that require special education supports. They may have low IQ and/or adaptive functioning scores on tests.
- have trouble waiting for his turn to talk in school.
- have trouble with voice regulation.
- be behind his peers in reading and math.
- continue to have temper tantrums or frustration-based outbursts.
- be extremely shy, withdrawn or introverted. (It is important to know that boys with XXY are not always shy.)
- have difficulty making friends.
- behave in socially inappropriate ways.
- fall asleep in school often even when he has an appropriate bed-time.
- tell many tall tales.
- have trouble in physical education classes or difficulty with some sports.
- have difficulty respecting other’s space.
- have extreme reactions to noise and light.
- have unusual dental problems such as missing adult teeth, large tooth pulp, more decay than other children.
- may act out in unusual ways to get the attention of other children who are not socializing with him.
- talk back to parents, teachers, authority figures.
- talk to himself out loud.
- have difficulty following multi-step directions.
- have difficulty writing and taking notes.
- have a tremor in his hand or thumb.
- have tics.
- have trouble taking tests.
- be diagnosed with ADHD.
- be diagnosed on the Autism spectrum (PDD-NOS, Asperger’s) or executive function issues.
- have sensory issues.
- have auditory processing disorder or sensory processing disorder.
- be diagnosed with asthma, food and environmental allergies.
- have difficulty with personal hygiene.
- have extreme sugar-cravings.
- bite his nails a lot.
- have scoliosis.
What should we look for?

Teen-aged
Teen-aged boys with XXYY begin showing signs of delayed puberty and their social immaturity becomes more of a barrier in their interactions. Most boys with XXYY are behind their peers in social age, meaning that they may be 16 years old but have the maturity of a 10 or 12 year old.

Teen-agers with XXYY may:
- still have speech problems but the verbal signs of speech delay have diminished or disappeared.
- have great struggles with social interactions and peer relationships. They may have few or no friends.
- have difficulty in social interactions with girls due to low social age.
- be bullied—a lot.
- still have outbursts.
- say anything that they are thinking about out loud without filtering it for appropriateness and/or cuss.
- still have difficulty with respecting other people's space.
- still have difficulty in physical education classes.
- have delayed or stalled puberty or no signs of puberty such as no body hair.
- have difficulty staying on task.
- dominate conversations without giving others a chance to speak.
- have accidents such as falling, tripping, trouble on bicycles.
- lack judgment.
- be impulsive.
- steal from others.
- not be able to stay home alone.
- continue to be sensitive to noise, light.
- continue to have food and environmental allergies and asthma.
- have difficulty with personal hygiene.
- need to be constantly prompted to do things.
- have great difficulty cleaning their rooms or conversely be overly neat.
- have increased tics and/or tremor.
- continue to have dental problems and may need braces.
What should we look for?

**Adults**

Adult males with XXYY continue to have the issues they had in the past. However, they may also begin to have new features and health problems.

**Adults with XXYY may:**

- have sleep apnea.
- be unusually thin OR unusually heavy.
- have low testosterone levels (hypogonadism).
- be exceptionally tall for their family, especially if they have not received testosterone replacement therapy.
- begin to have more pronounced facial features.
- have pronounced hand tremors.
- have diabetes.
- have severe food allergies.
- continue to have significant dental problems.
- continue to be behind in social age.
- have trouble keeping jobs.
- have trouble with interactions with coworkers.
- not have been able to attend or succeed in college.
- complain of a lot of pain in joints and back.
- have headaches.
- have thyroid problems.
- have blood clots.
- be in community programs for people with disabilities.
- still have frustration-based outbursts.
- have vision problems.
- have difficulties in relationships.
- still be interested in activities that teens are interested in doing.
- be easily influenced by bad people and make friends with the wrong crowd.
- have diabetes.
- have acid reflux.
- have digestive problems.
- have other health problems.
- have leg ulcers.
As they grow up
Below are photos of individuals as they have grown from boys to teens or men. Each line is a single individual. The photos show how boys with XXY change over time. Each line is one person as they grew.
Other diagnoses

It is important to note that in addition to the symptoms we have listed in this booklet that have been commonly seen in XXYY, there is a list of other diagnoses that have been noted in various cases. Some of these are not in medical literature (yet):

- Polydactyly
- Cleft palate/Pierre-Robin
- Palatoplasty for VPI (no cleft)
- Tourette Syndrome
- Unilateral kidney
- Various brain abnormalities
- Thrombotic Thrombocytopenic Purpura (TTP)
- Colon cancer
- Pulmonary embolism
- Pituitary adenoma
- Eosinophilic esophagitis (EoE)
- Schleroderma
- Non-Hodgkin lymphoma

We have also noticed anecdotally that our families have twins running in their families. We have many boys and men with XXYY in our group who are fraternal or identical twins.

Please refer to: A New Look at XXYY Syndrome, Tartaglia et al. 2008

In memory of:
Willie, Ryan, Joey, Buzz and Jimmy
Deepest Thanks

To individuals with XXYY and their families
The XXYY Project is deeply thankful to the individuals with XXYY and their families for being so incredibly generous in sharing your photos for this booklet. We know that if we reach even one undiagnosed boy or man with XXYY, we have truly accomplished something. The families that are part of the XXYY Project have always been very concerned with finding individuals and families and are ready to provide support to whomever finds this booklet and receives the XXYY diagnosis.

Deepest Thanks

If this booklet made you realize...

...that you may “know that guy” (or you may be that guy)
You are not alone. In spite of the fact that XXYY is rare, we are here and we have been here for many years, searching for you. We are like your long-lost family.
Bring this booklet to your doctor. Tell them to also look up this medical literature:
A New Look at XXYY Syndrome, Tartaglia et al. 2008

Ask for genetic testing.
Once you have positive XXYY genetic testing results:
Join us in our quest to get answers for every person with XXYY Syndrome.

If you got genetic testing
And the result is XXY, XYY or other...

Because XXYY looks somewhat similar to Klinefelter Syndrome (XXY) or Jacob Syndrome (XYY), some people who identify with this booklet may end up diagnosed with one of these conditions instead of XXYY. There are also other variations such as XXXY, XXXXY, XYYY and so on. If you are diagnosed with any of these, please contact AXYS. The XXYY Project is a project of AXYS:
AXYS (formerly known as KS&A)
www.genetic.org
Toll Free: (888) 999-9428
Outside U.S. and Canada: (303) 400-9040