Fragile X Syndrome

Health Watch Table

1. Head, eyes, ears, nose, throat

Considerations	Recommendations
Children: ▸ *Vision*: strabismus, refractive errors are common ▸ *Hearing*: recurrent otitis media is common ▸ *Nose*: sinusitis is common	▸ Undertake newborn vision and hearing screening and an auditory brainstem response (ABR) ▸ Refer for a comprehensive ophthalmologic examination by 4 years of age ▸ Visualize tympanic membranes at each visit
Adults: ▸ strabismus and refractive errors are common	▸ Undertake hearing and vision screening at each visit with particular attention to myopia and hearing loss

2. Dental

Considerations	Recommendations
Children and Adults: ▸ High arched palate and dental malocclusion are common	▸ Refer to a dentist for a semi-annual exam

3. Cardiovascular

Considerations	Recommendations
Children: ▸ Mitral valve prolapse (MVP) is less common in children (~10%) but may develop during adolescence	▸ Auscultate for murmurs or clicks at each visit. If present, do an ECG and echocardiogram; refer to cardiologist, if indicated
Adults: ▸ MVP is common (~ 80%). ▸ Aortic root dilation usually is not progressive ▸ Hypertension is common and exacerbated by anxiety	▸ Undertake an annual clinical exam. Based on findings, obtain an ECG and echocardiogram. Refer to cardiologist, as appropriate ▸ Measure BP at each visit and at least annually ▸ Treat hypertension when present

4. Sleep

Considerations	Recommendations
Children and Adults: ▸ Obstructive sleep apnea (OSA) may be due to enlarged adenoids, hypotonia or connective tissue dysplasia ▸ Sleep apnea is more common in individuals with Fragile X-associated tremor/ataxia syndrome ▸ *Children and Adults*: Sleep-onset or sleep-maintenance insomnia is common	▸ Ascertain a sleep history, examining bedtime, waketime, time needed to fall asleep and possible waking throughout the night ▸ Assess for evidence of OSA ▸ Refer to a sleep specialist, as appropriate ▸ Behavioral sleep interventions or supplemental melatonin may be helpful

5. Gastrointestinal

Considerations	Recommendations
Children: ▸ In infants, feeding problems are common with recurrent emesis associated with Gastroesophageal Reflux Disease (GERD) in ~ 30% of infants	▸ Refer for assessment of GERD. Thickened liquids and upright positioning may be sufficient to manage GERD

6. Genitourinary

Considerations	Recommendations
Children and Adults: ▸ Inguinal hernias are relatively common in males ▸ Macroorchidism generally develops in late childhood and early adolescence and persists ▸ Ureteral reflux may persist into adulthood	▸ Assess for inguinal hernia annually beginning at age 1 year ▸ Reassure patients and caregivers that macroorchidism does not require treatment ▸ Monitor for signs of urinary tract infections (UTI), screen with urinalysis. ▸ Evaluate recurring UTIs with cystourethrogram and renal ultrasound. Refer to a nephrologist. ▸ Consider and assess for a renal etiology, such as scarring, as the basis for persistent hypertension

7. Sexual function

Considerations	Recommendations
Adults: ▸ Males and females are fertile	▸ Consider discussion of recurrence risk and reproductive options as a basis for referral to a geneticist. Make such a referral even if Fragile X is only suspected so that molecular testing can be undertaken in the person concerned and relevant family members

8. Musculoskeletal (MSK)

Considerations	Recommendations
Children & Adults: ▸ Hyperextensible joints and pes planus are common. Scoliosis, clubfeet, joint dislocations (particularly congenital hip) may also occur	▸ Undertake an MSK exam at birth, then at each regularly scheduled checkup ▸ Elicit a history of possible dislocations ▸ Refer to an orthopedic surgeon as dictated by clinical findings ▸ Consider referral to a physical therapist (PT) or an occupational therapist (OT) to improve specific aspects of gross or fine motor skills if joint laxity or hypotonia interferes with function ▸ Consider referring to a physiotherapist and podiatrist for orthotics

9. Neurology

Considerations	Recommendations
Children & Adults: ▸ ~ 20% have epilepsy (may include generalized tonic-clonic seizures, staring spells, partial motor seizures, and temporal lobe seizures) ▸ Hypotonia is common, in addition to fine and gross motor delays ▸ Epilepsy occasionally persists into adulthood	▸ Ascertain a history of seizures, which usually present in early childhood ▸ Assess for atypical seizures in adulthood if suspicious findings occur or if intellectual function decreases ▸ Arrange an EEG if epilepsy is suspected from the history ▸ Refer to a neurologist as dictated by clinical findings

10. Behavioral/mental health

Considerations	Recommendations
Children: ▸ 70%-80% are hyperactive; ~ 30% have autism ▸ Autistic-like features are common and may indicate concurrent autism spectrum disorder ▸ Anxiety and mood disorders can also be present ▸ Some features of autism, tantrums and aggression as well as anxiety and mood disorders may be treated with specific pharmacological agents ▸ Sensory defensiveness is common and may trigger problem behaviors	▸ Make an early referral to a clinical psychologist for essential parental teaching of appropriate behavior modification techniques following diagnosis ▸ Hyperactivity may be managed using stimulant medications after age 5 years ▸ Refer to an intensive behavioral intervention autism treatment program if autism spectrum disorder is present ▸ Consider a referral to a psychiatrist for possible mental health disorders ▸ Refer to a speech and language therapist following diagnosis
Adults: ▸ Aggressive behavior, sensory defensiveness, attention deficit hyperactivity disorder (ADHD), mood instability, and anxiety are common in adolescence and adulthood	▸ Consider referral to a psychiatrist or psychologist to assess and manage possible mental health disorders ▸ Violent outbursts may occur, especially in males, and may respond to behavioral and/or pharmacological measures (as for children)

11. Endocrine

Considerations	Recommendations
Children: ▸ Precocious puberty may occur	▸ Include attention in clinical examination to signs of precocious puberty in females. ▸ Refer to an endocrinologist for consideration of use of a gonadotropin agonist to manage precocious puberty
Adults: ▸ Premenstrual symptoms (PMS) may be severe	▸ Ascertain history of PMS with attention to menstruation, anxiety, depression, and mood lability. Consider an selective serotonin re-uptake inhibitor (SSRI) to stabilize mood if PMS symptoms are severe enough

12. Other

Considerations	Recommendations
▸ Occasionally presents as Prader-Willi syndrome-like phenotype ▸ **Premutation Carriers:** ▸ A late onset tremor/ataxia syndrome has been reported in ~ 40% – 50% of male and ~ 8% of female Fragile X premutation carriers ▸ Premature ovarian failure by age 45 has been reported in ~ 20% – 40% of female Fragile X premutation carriers ▸ Psychiatric problems (e.g., mood and anxiety disorders) seem likely to occur in both male and female Fragile X premutation carriers 1, 2	▸ For management of obesity and hyperphagia, consider approaches recommended for persons with Prader-Willi syndrome ▸ Refer to appropriate specialists (e.g., neurologist, endocrinologist, psychiatrist) as indicated to assist in managing Prader-Willi syndrome-like symptoms ▸ If premutation is suspected but not yet identified, order Fragile X DNA testing or refer to a genetics clinic ▸ To manage depression or anxiety in premutation carriers, SSRIs, regular exercise and counseling have been helpful

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Expert Clinician Reviewers
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Modified with permission of Surrey Place Centre. This tool was reviewed and adapted for U.S. use by physicians on the Toolkit's Advisory Committee; for list, view here.

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Resources

- 8 published Fragile X syndrome health care guidelines reviewed and compared (For full list of references, see http://ddprimarycare.surreyplace.ca/wp-content/uploads/2018/03/HWT_Fragile-X.pdf) Accessed March 2025.
- Fragile X syndrome websites that may be helpful for families and caregivers
  - FRAXA Research Foundation, www.fraxa.org. Accessed March 2025.
  - The National Fragile X Foundation, www.fragilex.org. Accessed March 2025.
  - Fragile X Research Foundation of Canada, www.fragilexcanada.ca. Accessed March 2025.

References

1. Amiri K, Hagerman RJ, Hagerman PJ. Fragile X-associated tremor/ataxia syndrome: an aging face of the fragile X gene. *Arch Neurol* 2008 Jan;65(1):19-25.

2. Bourgeois JA, Coffey SM, Rivera SM, Hessl D, Gane LW, Tassone F, et al. A review of fragile X premutation disorders: expanding the psychiatric perspective. *J Clin Psychiatry* 2009 Jun;70(6):852-62.