HUMAN GENETIC EXPERT OPINION

Sample Case | Pediatric Expert Opinion

Fragile X Syndrome (FXS) | Psychomotor developmental delay, behavioral abnormalities, and cognitive impairment in a case with a molecularly confirmed FMR1 full mutation

Case Number	Ref.: [Court / Insurance Provider] - [Sample Case]
Client	Social Court / Health Insurance / Child Welfare Office / Pension Insurance [Sample Case]
Expert	Prof. Dr. med. Christian T. Thiel, MBA
Qualifications	Board-certified specialist in human genetics; University Hospital Erlangen; 30 years of clinical and scientific experience; expert witness for courts and insurance carriers
Date	March 28, 2026
Subject	Max M. [fictitious], born May 12, 2019 (6 years old), male (case study)
Diagnosis (ICD-11)	LD90.0 Fragile X syndrome | F70 Mild intellectual disability | F84.0 Early childhood autism (suspected)
Key question	Is there a genetically confirmed cause for the child's psychomotor developmental delay? What is the causal relationship between the molecular genetic diagnosis and the clinical impairments? What are the implications for eligibility for support, care, and pension benefits?

Declaration pursuant to § 407a ZPO

The undersigned declares that he has prepared this expert opinion impartially and to the best of his knowledge and belief. He affirms that he has no personal or financial relationship with the parties to the proceedings that could compromise his impartiality. This expert opinion is based exclusively on the documents submitted, his own examination, and the current state of medical science. The assessment is conducted in accordance with the principles of evidence-based medicine as well as the guidelines of the German Society of Human Genetics (GfHG) and the American College of Medical Genetics and Genomics (ACMG).

1. Assignment and Scope

The undersigned expert was commissioned to prepare a human genetic expert opinion regarding the clinical presentation of a six-year-old boy. The patient was diagnosed with psychomotor developmental delay, cognitive impairment, and behavioral abnormalities. Fragile X syndrome (FXS) was confirmed molecularly through the detection of a complete FMR1 mutation.

Specifically, the following questions are to be addressed:

1. Is there a genetically confirmed cause for the patient's psychomotor developmental delay?
2. What is the causal relationship between the molecular genetic diagnosis (FMR1 full mutation) and the clinically documented impairments (cognitive developmental delay, speech developmental delay, behavioral abnormalities, social interaction disorder)?
3. How should the prognosis regarding cognitive development, school readiness, and long-term independence be assessed?
4. From a human genetic perspective, what medical, therapeutic, and supportive measures are indicated?
5. What are the implications of the confirmed diagnosis under social security and pension law?

2. Examination materials and methodology

2.1 Submitted documents

– Molecular genetic report: FMR1 repeat analysis via PCR and Southern blot (Date: [Laboratory, Date]); Findings: CGG repeat expansion > 200 repeats (full mutation), methylated
– Pediatric developmental reports (pediatricians, neuropediatrics) from 2021–2026
– Developmental assessments: Bayley Scales of Infant and Toddler Development (Bayley-4), Vineland Adaptive Behavior Scales (VABS-3)
– Speech therapy reports and occupational therapy documentation
– Child and adolescent psychiatric consultation report with suspected autism spectrum disorder (ADOS-2, ADI-R)
– School support reports (special educational needs, application for a special school for intellectual development)
– Family history questionnaire (completed by the mother)

2.2 Personal examination

On [Date], Max M. was personally examined by the undersigned, together with his mother, at the Institute of Human Genetics, University Hospital Erlangen. The examination included: clinical-genetic examination, including findings on dysmorphology; assessment of developmental status through direct interaction; detailed medical history with the mother; and evaluation of the available molecular genetic findings.

2.3 Methodological Basis for the Evaluation of Findings

The evaluation of the FMR1 full mutation is performed in accordance with the current ACMG/AMP guidelines and the recommendations of the European Society of Human Genetics (ESHG). The clinical classification is based on the criteria of the WHO (ICD-11), the guidelines of the German Society for Child and Adolescent Psychiatry (DGKJP), and the care guidelines of the National Fragile X Foundation (NFXF). Statements regarding causality follow the Bradford Hill criteria.

3. Medical history

3.1 Pregnancy and Birth History

The pregnancy proceeded normally without known noxious factors or complications. Birth at 39+2 weeks of gestation, spontaneous, uneventful. Birth weight 3,420 g, length 51 cm, head circumference 34.5 cm. APGAR 9/10/10. Neonatal period without complications.

3.2 Developmental history

The mother reports that the first abnormalities were noticed at 12–15 months of age: The boy exhibited delayed motor development (did not walk independently until 20 months), a marked speech delay (first single words not until 24 months, no two-word sentences until age 3), as well as behavioral abnormalities (increased irritability, hand-biting, avoidance of eye contact, limited social skills).

The first pediatric-neuropediatric consultation took place at 2.5 years of age. Extensive diagnostic testing was initiated at age 3; the molecular genetic diagnosis of Fragile X syndrome was made at 3.5 years of age.

3.3 Current situation (at the time of examination, age 6 years)

- Language: Dysgrammatical sentence structure, limited vocabulary, occasional echolalia; Verbal comprehension better than verbal production
- Motor skills: Able to walk independently; fine motor and graphomotor skills significantly below age level (pencil grip and scissor grip not yet possible)
- Cognition: Developmental level corresponds approximately to that of a 3.5- to 4-year-old child (Bayley-4: Full Scale IQ 58)
- Behavior: increased impulsivity, signs of sensory overload, stereotypies (hand-wringing), sensory hypersensitivity (noise, touch)
- Social interaction: limited eye contact, preference for familiar people, Fear of strangers
- Self-care: not fully independent (dressing, personal hygiene with assistance)

4. Family history

The family history is of central importance for the human genetic evaluation of Fragile X syndrome, as FXS follows an X-linked inheritance pattern with a premutation-to-full-mutation dynamic.

- Mother (38 years old): Carrier of an FMR1 premutation (CGG repeat 75, results available). Clinically without relevant cognitive impairments; known to have a mild anxiety disorder. No FXTAS (Fragile X-associated Tremor/Ataxia Syndrome) – still too young for typical manifestation.
- Maternal uncle (mother's brother, 44 years old): learning disability, special education; never tested for molecular genetics—clinically highly suspected of having FXS.

- Maternal grandmother (70 years old): Carrier of an FMR1 premutation (not confirmed by molecular genetic testing, clinically suspected); shows early signs of FXPOI (Fragile X-associated Primary Ovarian Insufficiency) but was not affected.
- Father: clinically unremarkable, not a carrier of the FMR1 premutation (normal FMR1 result).
- Patient's sister (4 years old): clinically unremarkable to date; molecular genetic testing pending, has been recommended.

The mode of inheritance is consistent with known X-linked dominant inheritance with variable expressivity. Transmission occurred via the premutated mother, who expanded the full mutation during meiosis.

5. Clinical findings

5.1 General findings

Friendly boy with age-appropriate nutritional and general condition. Height 114 cm (25th percentile), weight 20.5 kg (25th percentile), head circumference 52 cm (75th percentile—relative macrocephaly). Limited willingness to cooperate; requires a longer adjustment period; repeatedly seeks contact with the mother.

5.2 Dysmorphological findings

- Facial features: elongated face, high forehead, prominent ears (protruding on both sides), slightly high-arched palate
- Skin and connective tissue: Hyperextensibility of the finger joints, soft skin
- Genitals: Bilateral macroorchism (not yet fully clinically apparent due to age; typical of the post-pubertal clinical picture)
- No other dysmorphic features; no clinically evident heart defect

The clinical findings correspond to the typical but variable phenotype of Fragile X syndrome in male children. Facial dysmorphism (long face, prominent ears) is characteristic but not pathognomonic; it becomes particularly pronounced in adulthood.

5.3 Neurological and developmental findings

- Muscle tone: mild central hypotonia
- Reflex status: age-appropriate, symmetrical
- Coordination: age-appropriate limitations; gait unremarkable
- Developmental level: gross motor skills approx. 3.5–4 years (overall developmental quotient 58 on the Bayley-4)
- Language: echolalia, dysgrammatism, limited vocabulary for a 6-year-old
- Behavior: Stereotypies (hand flapping), sensory overload observed

6. Molecular genetic findings

6.1 Laboratory findings

Molecular genetic findings - FMR1 repeat analysis

Gene: FMR1 (Fragile X Mental Retardation 1, Xq27.3)
Method: PCR-based repeat length analysis and Southern blot (methylation analysis)
Result: CGG repeat count > 200 (full mutation) Methylation status: fully methylated (FMR1 gene silenced) **Classification: Pathogenic - Fragile X syndrome (FXS) confirmed** Reference: NM_002024.6 (FMR1) | OMIM #300624

6.2 Molecular Basis and Pathomechanism

Fragile X syndrome results from a dynamic mutation in the FMR1 gene on the X chromosome (Xq27.3). Normally, the FMR1 gene contains a CGG trinucleotide repeat ranging from 5 to 44 repeats. A gray zone (intermediate) exists between 45 and 54 repeats, a premutation between 55 and 200 repeats, and a full mutation at >200 repeats. [1,2]

In the case of a full mutation—as in the present case—hypermethylation of the CpG island in the promoter region of the FMR1 gene occurs. This leads to transcriptional silencing of the gene and thus to the complete absence of the FMR1 protein (FMRP). FMRP is an RNA-binding protein that is essential for the regulation of protein synthesis at synapses. [1,3,4] Its absence leads to immature, dysfunctional synaptic plasticity, which manifests clinically as intellectual impairment, behavioral disorders, and delayed speech development.

The mother's premutation (55–200 CGG repeats) expands to a full mutation upon transmission to the son—a well-known and well-characterized mechanism (anticipation via maternal transmission). [1,2] The risk of expansion from premutation to full mutation increases with the mother's repeat length.

6.3 Classification of Findings

The detected FMR1 full mutation (CGG > 200, fully methylated) explains the clinical findings in their entirety without any remaining diagnostic doubt. This is a pathogenic finding with complete gene-phenotype concordance. The diagnosis should be stated as confirmed—not as suspected.

7. Assessment and human genetic classification

7.1 Gene-phenotype correlation

The clinical presentation of the present case corresponds to the characteristic phenotype of Fragile X syndrome in male patients with a full mutation:

– Intellectual disability: In > 99% of affected males, intellectual disability is present; the mean developmental quotient ranges from 35 to 50 (mild to

moderate intellectual disability). [3,5] The present finding (Development Quotient of 58 on the Bayley-4 at age 6) is fully consistent with this spectrum.

- Language development delay: Characteristic and one of the early signs; delayed onset of speech, echolalia, and repetitive speech are typical. [3,5]
- Behavioral characteristics: ADHD-like symptoms (impulsivity, distractibility), anxiety disorders, sensory processing disorders, and autism spectrum disorder (ASD) are common in FXS (ASD in approximately 30–50% of affected males). [3,6]
- Dysmorphic features: Facial appearance (long face, prominent ears) is characteristic; macroorchism becomes relevant post-puberty. [1,2]

The combination of confirmed FMR1 full mutation and the present clinical findings results in complete gene-phenotype congruence. There is no alternative explanation for the clinical impairments, and none needs to be seriously considered.

7.2 Differential Diagnosis from Other Causes of Developmental Delay

In every child with psychomotor developmental delay, the following should be considered in the differential diagnosis: chromosomal aneuploidies (trisomy 21, etc.), monogenic causes of intellectual disability, metabolic disorders, perinatal brain damage, environmental toxins (fetal alcohol syndrome, etc.), and autism spectrum disorders as a primary diagnosis.

In the present case, this differential diagnosis is concluded by the molecular genetic findings. **The FMR1 full mutation is a monocausal explanation sufficient for all documented clinical impairments.** Additional genetic findings are not to be expected and should not be sought, unless a clinical feature clearly lies outside the FXS spectrum.

8. Causality Assessment

8.1 Causal relationship: FMR1 full mutation and clinical impairment

The causal relationship between the documented FMR1 full-length fusion and the clinical presentation has been established with a high degree of certainty. Justification according to the Bradford Hill criteria:

- Strength of association: FMR1 full mutation in affected males is associated with intellectual disability in nearly 100% of cases; this association is the strongest known monogenic cause of hereditary intellectual disability in males. [1-3]
- Consistency: Reproduced in thousands of cases worldwide over more than 30 years; international scientific consensus. [1-6]
- Specificity: The present phenotype (developmental delay + behavioral abnormalities + facial dysmorphism + positive family history) corresponds highly specifically to the FXS profile.
- Temporality: The genetic cause is congenital and necessarily precedes any clinical manifestation.
- Biological plausibility: The pathomechanism (FMRP deficiency due to methylation-silencing) is fully elucidated at the molecular level and directly explains the clinical manifestations. [1,3,4]
- Analogy: Comparable phenotypes with identical genotypes have been described extensively and prospectively validated.

8.2 Prognosis

Fragile X syndrome is a lifelong, chronic condition. There is currently no causal treatment (as of 2026). **Intellectual impairment is permanent and irreversible.** The degree of disability remains essentially stable; with targeted intervention, specific functions can be improved, but normalization of the developmental profile cannot be achieved.

Clinical studies show that intensive early intervention measures (speech therapy, occupational therapy, early intervention, behavioral therapy interventions) can positively influence the course of development without, however, eliminating the underlying impairment. [5,6,9] Regarding school readiness: The majority of affected males require a special education school with a focus on intellectual development or, at a minimum, intensive special education support. Higher educational qualifications within a mainstream school system are not to be expected.

The long-term prognosis is as follows: Independence in adult life is severely limited. The majority of affected men require lifelong support with daily activities; vocational integration is only possible in a sheltered setting. A life without care is generally not possible for men with FXS and a full mutation. [5,7]

9. Conclusion / Expert Assessment

Summary of the expert findings

1. Confirmed diagnosis: The patient has Fragile X syndrome (FXS; OMIM #300624; ICD-11 LD90.0), caused by a full mutation in the FMR1 gene (CGG repeat > 200, fully methylated). The diagnosis is confirmed by molecular genetics. A formulation as a suspicion is not medically or scientifically justified.
2. Causal Relationship: The causal relationship between the FMR1 full mutation and all clinically documented impairments (psychomotor developmental delay, speech developmental delay, cognitive impairment, behavioral abnormalities, sensory processing disorder) is established with a probability bordering on certainty. An alternative cause is ruled out.
3. Severity: The present FMR1 full mutation in a male patient results in mild to moderate intellectual impairment (typical IQ range 35–55). The current developmental quotient of 58 on the Bayley-4 is consistent with this spectrum.
4. Permanence and prognosis: The intellectual disability is permanent, irreversible, and will persist throughout the individual's lifetime. There is no causal treatment available. The need for support (special education, therapy, and nursing care) will persist throughout the individual's lifetime.
5. Social welfare implications: The confirmed diagnosis establishes eligibility for integration assistance (SGB IX), special education support, nursing care services (SGB XI), and, if applicable, a severe disability certificate (GdB of at least 50, likely 80–100 due to the cognitive impairment and behavioral issues). An assessment of the requirements for the H designation (helplessness) is recommended.

The above expert findings are rendered to the best of my knowledge and belief, impartially and conscientiously, in accordance with § 407a ZPO. The undersigned certifies that he has no relationship of dependency with the parties and no financial interest in the outcome of the proceedings.

9a. Therapeutic and Supportive Measures

Speech Therapy / Speech-Language Pathology

- Intensive speech therapy (at least twice weekly) with a focus on language comprehension, vocabulary building, and communication. Augmentative and alternative communication (AAC) should be considered

Occupational therapy

- Sensory integration therapy (stimulus processing), fine motor skills, daily living skills

Early Intervention / Special Education

- Intensification of early intervention; application for a special education school for intellectual development or intensive inclusion support in a mainstream school
- Structured, low-stimulus learning environment (important: children with FXS are sensitive to sensory overload)

Child and Adolescent Psychiatry

- Diagnosis and, if necessary, treatment of a comorbid autism spectrum disorder (fully evaluate ADOS-2, ADI-R)
- In cases of pronounced ADHD symptoms: evaluation of medication (methylphenidate is possible for FXS, but must be assessed on an individual basis) [6,9]
- Behavioral therapy / ABA elements to promote social skills and reduce problem behaviors

Genetic family counseling

- Human genetic counseling for all first-degree relatives of the mother (premutation carrier status)
- Molecular genetic testing of the patient's sister strongly recommended (possible premutation carrier status—relevant for FXPOI risk and future family planning)
- Informing the mother about her own FXTAS risk (from age 50) and FXPOI

Interdisciplinary Coordination

- Regular pediatric and neuropediatric follow-up
- Coordination between school, therapists, social services, and human genetics

9b. Medical and Social-Legal Classification

Confirmed Fragile X syndrome with proven FMR1 full mutation and documented clinical findings establishes the following social-legal entitlements and measures:

- Law on Persons with Severe Disabilities (SGB IX): The degree of disability (GdB) is to be assessed at a minimum of GdB 80, and likely GdB 100, based on cognitive impairment (IQ range 35–55), behavioral abnormalities, and limited daily living skills. Recommendation: Submit an application to the Benefits Office.
- Mark H (Helplessness): Due to the need for assistance with daily activities (personal hygiene, dressing, supervision), an assessment for Mark H is indicated.
- Long-term care benefits (SGB XI): Care level 3 or 4 is likely based on the need for care and supervision; an assessment by the Medical Service is recommended.
- Rehabilitation Assistance (SGB IX, Part 2): Entitlement to services for participation in education (special education support, school accompaniment) and services for social participation.
- Early Intervention: Entitlement to interdisciplinary early intervention under the Early Intervention Ordinance (FrühV) exists and should be applied for or continued.

From a medical perspective, the diagnosis is fully and permanently established. A repeat genetic evaluation to verify the underlying diagnosis is not necessary. Follow-up evaluations may focus on the functional developmental level and the need for support.

10. References

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Erlangen, March 28, 2026

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