

# Developmental Delay

A resident asks...

Why would a primary care doctor want to know about the genetics of developmental delay?

**Key Points:**

- Genetic causes may account for 5%-25% of children with developmental delay, including some children with normal physical exam or minimal physical findings.
- Although a specific diagnosis rarely leads to curative treatment, it can inform the family about a child's prognosis and enable the child to receive needed services.
- In some cases, a genetic diagnosis of developmental delay informs the family about risk to other family members.

## Learning Objectives for the Developmental Delay Module

Participants will be able to:

1. Understand the role of genetics in work-up of a child with developmental delay.
2. Review fragile X syndrome.
3. Review velocardiofacial syndrome.

## **CASE # 1**

This case demonstrates the evaluation and work-up of a child with developmental delay who is ultimately found to have Fragile X syndrome.

### **Presentation:**

A continuity clinic resident presents Chad, a two-year-old child who has come for well child care. Chad's last well child visit was at 15 months of age. At that time the history and physical were normal, but Chad had no expressive language development. A decision was made to wait and watch his development in this arena. Subsequently, Chad has been seen for three episodes of otitis media. The current history indicates that Chad still has no expressive language development. He appears to hear normally and will follow simple commands. His gross and fine motor development appear normal for age. Socially, the child is described as very shy. Parents note that he is not friendly with other children or adults and consistently avoids eye contact. He is frequently irritable and is physically quite active at home.

**PMH:** Chad was the 3.5 kg product of a normal pregnancy and delivery. Mother does not relate a history of prenatal illness, medications, alcohol use or substance abuse. Chad's APGAR scores were 8 at one minute and 9 at five minutes and his neonatal course was notable only for a peak bilirubin of 17 on day 4 of life. Subsequently he has been healthy with the exception of 6 episodes of otitis media to date. Chad's newborn screen results for PKU, sickle cell anemia, and hypothyroidism were normal.

### **Additional history obtained with directed questioning:**

**FH:** Chad has a healthy 4-year-old female sibling, Kara. Kara also is shy but has been doing well in a day care environment. Kara began to speak at about 15 months of age. Chad's mother, Monica, is 26 years old and in good general health. She has a history of depression and an anxiety disorder but is currently not in therapy or receiving medication. Monica was the youngest of three children, with an older brother and a sister. Her brother had a history of being "slow" in school. He was killed in an auto accident when Monica was an adolescent. Her sister left home at 16 years of age and has had only intermittent contact with Monica over the years.

She is healthy, married, but has no children to Monica's knowledge. Monica's parents are in reasonable health for their age; at age 66, her father has hypertension and degenerative joint disease and at age 60, her mother has diet-controlled diabetes. Chad's father, Jack, is healthy. Monica is pregnant at 12 weeks gestation.

**SH:** The family is of modest means. Monica works in environmental services at a downtown office building. She struggled in school, attaining only a 10<sup>th</sup> grade education. Jack works as a backhoe operator in a local construction company. He also struggled in school but completed his high school degree. Monica and Jack are happily married and there is no history of alcohol or substance abuse or domestic violence. The family's health insurance is covered by Medicaid, although Jack will soon be eligible for coverage through his employer. Monica and Jack are practicing Catholics.

**PE:** Chad is at the 20<sup>th</sup> percentile in weight, 30<sup>th</sup> percentile in height and 95<sup>th</sup> percentile in head size – these measures are consistent with previous points on the growth chart. He is withdrawn in the mother's lap and resistant to physical exam. Consistent with previous exams, he is morphologically normal. The only notable finding is serous otitis media bilaterally. In addition, he has a long face and prominent ears; he looks like his mother in this regard. His skin findings are normal, without café-au-lait spots, shagreen patches or hypopigmented spots.

**Questions for Discussion:**

1. What diagnostic considerations should be considered with this presentation?
2. Was the right decision made at 15 months?
3. How can physical exam contribute to evaluation of the patient?
4. How would a pedigree or genogram help to evaluate the family?
5. What work-up (if any) would you recommend that the resident pursue?
6. What is the value of a specific diagnosis for the family?

## Case # 1 – Discussion

### 1. *What diagnostic considerations should be considered with this presentation?*

Developmental delay is a common problem encountered in pediatrics practice, and a genetic etiology is an important consideration. Genetic causes are currently estimated to account for 5%-25% of children with developmental delay, and include both rare and relatively common disorders (Curry et al. 1997). This is a rough estimate because most studies have been done in clinical or institutional settings where selection biases may occur, and older studies may have missed genetic causes that are now identifiable. Some associated physical findings and co-morbidities may increase the likelihood of a genetic cause of developmental delay – e.g. congenital malformations, hearing impairment (see the **Congenital Hearing Loss** module in this manual), growth retardation. However, some genetic causes, including chromosomal microdeletions, may be associated with a normal examination or mildly abnormal physical findings that are difficult to differentiate from the normal range. Genetic studies that may help in the evaluation of a child with developmental delay include chromosomal studies to evaluate conditions such as trisomies and chromosomal deletions, specific diagnostic tests such as those for Fragile X, and evaluation for metabolic disorders. Because there are many potential genetic tests to consider in this setting, some of them costly, follow up over time, with a stepwise approach to diagnosis, is appropriate when history and physical exam findings are normal or non-specific. When testing is considered, a genetic approach may help to direct testing to those conditions most likely to be present.

In this case, persistent developmental delay has been observed and it is appropriate to proceed to additional work-up. There is little in the presenting history to narrow the differential. The prenatal and birth history help to rule out prenatal and perinatal causes, such as teratogenic agents, prematurity, significant birth asphyxia, congenital infections, and exposure to toxins (tobacco, alcohol, or other medications or substances that may be abused during pregnancy). The general categories to be considered include idiopathic or familial mental retardation without a specific defined cause, environmental causes (such as family stress, domestic violence, child

abuse or neglect), chromosomal disorders, metabolic disorders, and single gene disorders, including X-linked developmental delay, which is an important consideration in affected males. Other possibilities include Pervasive Developmental Delay (and Asperger's Syndrome, which involves impaired social interaction, often with repetitive and stereotypical patterns of behavior in a child with a normal IQ; see <http://www.udel.edu/bkirby/asperger/> for more information), mild congenital or acquired hearing loss, and history of illness associated with an increased risk of mental retardation, such as episodes of dehydration/acidosis; failure to thrive; or chronic illnesses such as congenital heart disease. Occasionally, a child brought up in a non-English speaking family, might be shy and not interact fully with English speaking professionals. Thus a good professional interpreter is necessary. In addition to these non-genetic possibilities, a genetic etiology should be considered in a child with developmental delay where the pregnancy and perinatal history offer no indicators of the cause.

In considering causes of developmental delay, additional history is often crucial. Past medical history may provide important indicators of cause – e.g. morbidities associated with specific syndromes. A family history of learning problems, psychiatric disorders, autism or mental retardation increases the likelihood of an inherited cause (see question 4 below). Social history may help to identify environmental causes of learning difficulties or may point to behavioral problems that contribute to making a diagnosis.

2. *Was the right decision made at 15 months?*

In retrospect, indicators for additional work-up were present at 15 months, including language delay and a family history of learning difficulties. The timing for pursuing additional work-up is always a matter of judgment, but some physicians would have considered additional work-up at the earlier visit.

3. *How can physical exam contribute to the evaluation of the patient?*

Physical exam findings are an important clue to further work-up. All children with developmental delay should have a complete examination, to identify physical anomalies that may indicate a specific syndrome or increase the index of suspicion for a chromosomal disorder. When physical anomalies are present, consultation with a dysmorphologist may help to define the possibilities and best testing options. A dysmorphologist can help to determine whether subtle physical findings are worthy of work-up, and may provide useful advice about specific syndromes to consider, based on a constellation of physical findings. Any facial, skeletal or limb asymmetry is usually associated with a genetic etiology. Genetic problems are also more common when there is a discrepancy in the anthropomorphic measurements over time. In this case Chad's height and weight were generally in the 20-30<sup>th</sup> %tile, while his head circumference was in the 95<sup>th</sup> %tile. Congenital hearing loss in combination with development delay may also suggest specific syndromes (see **Congenital Hearing Loss** module). Skin findings may be important, as indicators of conditions such as neurofibromatosis Type 1 or tuberous sclerosis.

4. *How would a pedigree or genogram help to evaluate the family?*

A pedigree provides a visual summary of the family structure; if relevant health problems are noted, the pedigree allows a quick assessment for patterns suggestive of inherited disease. When considering developmental delay, a family history of a psychiatric problem, learning disabilities and/or mental retardation in more than one family member is suggestive of a genetic cause. In this case, the family history of learning problems in the child's maternal uncle raises the question of X-linked mental retardation, an important cause of developmental delay in males, and in particular the diagnosis of **Fragile X syndrome**. Approximately 40% of X-linked mental retardation is due to Fragile X syndrome. The mother's learning difficulties would also be compatible with this possibility, because about half of Fragile X carriers have learning problems.

This pedigree information points to the importance of assessing Chad for physical findings compatible with a known X-linked disorder, such as Fragile X syndrome. At the child's current

age of age 21 months, the physical characteristics of Fragile X may not be apparent, but would include large head, long face, prominent forehead, large ears, prominent jaw. After puberty, large testes are observed.

A genogram includes information about social as well as biological relationships (McGoldrick et al. 1999). Considering Chad's family, it is worth noting that both his parents had learning problems and that his mother has a history of anxiety and depression. These factors could contribute to a poor learning environment at home; Chad's mother's anxiety and depression could have produced emotional or social problems that contributed to Chad's developmental delay.

5. *What work-up (if any) would you recommend that the resident pursue?*

Taking family history, developmental history and physical exam into account, Fragile X is a possibility, and should be tested for (see **GeneClinics** <http://www.geneclinics.org> and **GeneTests** <http://www.genetests.org> for details of testing).

6. *What is the value of a specific diagnosis for the family?*

A specific diagnosis has several potential benefits. In this case, a diagnosis of Fragile X provides an explanation for the child's developmental delay, and provides the family with prognostic information. Answering the "why" is often a value in and of itself when a child has developmental delay. In addition, services that may be of benefit to the child, for both cognitive and social needs, may be easier to obtain with a specific diagnosis. The diagnosis also provides information about other family members who may be at risk for this condition, including future children, and thus leads to consideration of additional genetic testing in the family.

The developmental delay seen in Fragile X syndrome is typically moderate rather than severe. Often the phenotype includes behavioral problems such hyperactivity, poor eye contact and withdrawn social behavior, perseverative speech, and at the extreme, autism. The prevalence of

Fragile X has been estimated to be about 1 in 5000; among unselected males with developmental delay the condition is estimated to be present in 3-6%.

The molecular genetics of fragile X are complex (see **GeneClinics** summary; McIntosh et al. 2000). The phenotype of developmental delay is determined primarily by the number of CGG trinucleotide repeats in the gene: a “full” mutation is said to be present when >230 repeats are present, and is associated with developmental delay in 100% of males and approximately 50% of females. The normal number of CGG repeats is <55; when an intermediate number are present (55-230), a “premutation” is said to be present. People carrying a premutation generally have normal intellect (rare cases of mild impairment have been reported). However, when a premutation is transmitted by the mother, it may expand to a full mutation (see **GeneClinics** in the **Reference** section of this manual for table summarizing the empiric risk for an affected child when a mother carries a premutation). Additional molecular genetic complexity derives from modifying factors: aberrant gene methylation and CGG repeats. Rarely, reversions may occur (reduction in the number of CGG repeats with gene transmission from parent to child). In addition, about 1% of patients with Fragile X syndrome have a different molecular defect in the gene. These complexities underscore the importance of detailed counseling and careful consideration of testing options when testing is undertaken.

The diagnosis of Fragile X has important implications for the family, and may well correct previous misapprehensions about the significance of the condition. For instance, it is not uncommon for children with Fragile X syndrome to display symptoms that may lead to a misdiagnosis of idiopathic autism or another disorder having substantially different implications. In this case, it is the likely explanation of the mother’s learning difficulties and those of her deceased brother. The recurrence risk is high for this family. Although testing will be needed to confirm the mother’s status, her son’s status suggests that she carries the full Fragile X mutation. Prenatal diagnosis and termination of affected pregnancies are options in this situation, but may not be of interest to the family. Supportive counseling over time may help the parents to take in all the implications of the Fragile X diagnosis. These include both reproductive issues and the question of sharing the diagnosis and its implications with other family members.

## CASE # 2

This case illustrates the slow unfolding of the diagnosis of **22q11deletion syndrome**. The diagnosis was not made on the initial genetics evaluation, but was ultimately made at age 32.

Cathy was born in 1968 with a cleft palate and a single umbilical artery. She was diagnosed with cerebral palsy, with no known birth trauma. The mother subsequently had a normal pregnancy, Cathy's younger sister Brenda, and then a miscarriage of a fetus with a cleft palate. The family was offered genetic consultation but initially did not pursue it because they planned no more pregnancies. At age 4, Cathy, who had always been somewhat "slow," had difficulty adjusting to a day care environment, and presented for further evaluation. Standardized testing indicated that cognitive development was mildly to moderately delayed, motor development was mildly delayed, and language development was significantly delayed.

Her medical history at the time of her evaluation at age 4 was otherwise unremarkable. Physical exam revealed evidence of cleft lip and palate repair but no other craniofacial abnormalities. Growth had been consistently at the 30%, with normal head circumference. She had no abnormal skin findings. She had a mild gait abnormality consistent with the diagnosis of CP. Work-up included a chromosomal study and metabolic studies, both of which were normal. The family was counseled that no specific genetic etiology could be found. She was considered to have CP and mild to moderate MR of unknown, presumably multifactorial etiology.

Cathy continued to have learning difficulties but did well with them and completed high school. Her big problems began as a young adult when she developed a picture of intermittent psychosis, thought to be temporal lobe epilepsy. She has had at least 2 grand mal seizures as well. A psychiatrist followed her for years and tried virtually every seizure and antipsychotic medicine with intermittent relief at best but steady deterioration. A neurologist followed her as well. She developed fairly severe sleep apnea but was unable to tolerate any treatment including O2. Although these medical problems were of increasing concern, no further etiological investigation was pursued for many years, because the complete evaluation done at age 4 had revealed nothing

specific. She progressed to the point that she was hospitalized in a psychiatric locked ward, so preoccupied with frightening voices that she was unable to be managed short of an involuntary hospitalization.

When she was 32, her mother got in touch to report that her sister Brenda had talked to a neurologist in Boston who advised re-evaluation. He noted that clinical understanding of developmental problems and their associated complications had progressed considerably since Cathy's initial evaluation at age 4; perhaps a second look might be worthwhile. This conversation triggered an interest in additional work-up. The family did not expect that there would be a treatment but were still seeking an explanation for their daughter's difficulties. Brenda, who was married and thinking of having children, also wondered if Cathy's problems implied any risk for her children. As their family physician, they have brought their questions to you and are asking for your recommendation. What will you say to the family?

**Question for Discussion:**

1. How can genetic evaluation be helpful at this point?

## CASE # 2 – Discussion

### 1. *How can genetic evaluation be helpful at this point?*

As in all areas of medicine, there has been an increasing ability to find specific causes for developmental delay. Given advancing technology, it is especially important for the primary care physician to think “genetic causes” if there is no clear-cut etiology in a child with developmental delay. The genetic hypothesis is particularly important when there is more than one malformation or deformation or when there is a positive family history. The psychiatric and cognitive/developmental history are an important part of the family history as well. In this case there is a clear indication for exploration of the genetic possibilities.

Recognition of new syndromes and technological improvements in testing—in particular, improved cytogenetic techniques—have led to an increasing ability to define specific genetic causes for problems like Cathy’s. Thus, a negative work-up 25 years ago does not preclude a genetic cause to Cathy’s problems. The value of a genetic diagnosis in Cathy’s case would be three-fold: (1) it would provide an explanation; (2) it might provide valuable prognostic or therapeutic information; and (3) it would inform the family about the potential for other family members to be affected, in particular, about any risk to Brenda’s children.

The approach to work-up is the same as it would be in an initial evaluation: medical history, full physical exam looking for any dysmorphic features other than the known cleft lip and palate; growth measurements; developmental history, family history, social history. Testing considerations would include chromosomal studies and biochemical testing.

In Cathy’s case, repeat chromosomal studies revealed a 22q11 deletion (**22q11 deletion syndrome**). This abnormality, due to a small deletion on chromosome 22, would not have been detected in the chromosomal studies done 28 years ago, and illustrates the power of new, more precise testing techniques. The increased sensitivity of the test also has led to a recognition of the wide phenotypic variability of this syndrome. It is now known to encompass the phenotypes

previously described as diGeorge syndrome and velocardiofacial syndrome. As these associations imply, the phenotypic manifestations are variable (see **GeneClinics** summary in the **Reference** section of this manual). The most common manifestations are cardiac abnormalities, palatal abnormalities, learning disabilities and characteristic facial features. Of these, Cathy had only two: palatal abnormalities and learning disabilities. Her CP and psychiatric problems are assumed to be part of the syndrome, but the frequency with which these complications occur is not yet known. Molecular diagnosis, in this case the documentation of a specific small chromosomal deletion, thus can lead to a re-evaluation of the epidemiology and definition of a syndrome. It is likely that many patients are yet to be identified, who, like Cathy, have somewhat atypical features of the syndrome as currently described.

In addition to providing an explanation for Cathy's problems, this diagnosis led to testing of both parents, to ensure that neither was a deletion carrier (this occurs in about 6% of cases). Both were chromosomally normal, indicating that Cathy carried a de novo mutation. However, the history of miscarriage of a fetus with cleft lip and palate raised the possibility of gonadal mosaicism (i.e. the possibility that the de novo chromosomal deletion in fact occurred in gonadal tissue of one of the parents, and thus could be passed on to subsequent children). For this reason, Brenda was also tested, and was found to be without the deletion. For the family, the most reassuring aspect of Cathy's diagnosis is the knowledge that there was nothing else they should have or could have done to ameliorate Cathy's problems. This knowledge brought a relief that was unexpectedly great; Cathy's parents had not previously realized how much they had worried about possible oversights in Cathy's care.

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