# A guide to the investigation of children with developmental delay in East Anglia

**The guide**

These guidelines were produced by an expert group of geneticists and paediatricians in East Anglia as part of a multi-disciplinary project on learning disability undertaken by the Cambridge Genetics Knowledge Park. Further information on the project and supporting documentation is available on the CGKP website

**Definitions**

Learning disability is strictly defined as a significant impairment of cognitive and adaptive function with onset before 18 years of age. It is usually described as mild, moderate or severe. Learning disability/developmental delay is a common problem affecting 1-3% of the population.

Overview article on definition and prevalence of learning disability. Gillberg, Lancet. 2003; Sep 6;362(9386):811-21*

Click here for a descriptive summary of the epidemiology and molecular characteristics of learning disability (see sections on definition and prevalence).

**Aetiology of learning disability**

Delay may be determined by genetic or environmental factors (eg Down syndrome, Fragile X syndrome), antenatal or perinatal problems such as rubella, or prematurity (eg cerebral haemorrhage), early infancy (eg meningitis), or later in childhood (eg head injury). For many children, the cause will not be apparent. In the absence of a family history, there may still be a genetic basis to a child's developmental delay, which might have important genetic implications for future pregnancies.

Click here for a descriptive summary of the epidemiology and molecular characteristics of learning disability (see sections on aetiology).

**Assessment, investigation, diagnosis and beyond - the parent viewpoint**

Before proceeding with assessment, investigation and diagnosis take time to consider the parent viewpoint. Why is finding a precise diagnosis and cause of the learning disability important to them, and how can the whole process be undertaken in such a way that it achieves maximum benefit?

This was investigated through an online discussion forum, and through interviews and focus groups by the Project group. Key findings included:

- "Just to know" - to seek an answer to uncertainty, to provide confirmation that there is something wrong, to be reassured that they are not to blame, to have a name for their child's condition.
- To understand the future likely needs of the child, anticipate problems and hope for the best scenarios
- To understand what the condition means for the rest of the family

- To provide an end to the diagnostic quest
- To find others affected by the same condition
- To help the child find support and services

These and other benefits and potential problems of a genetic diagnosis are described in detail in the CGKP report.

Click here for parents' guide, which may be helpful in your discussion with parents.

**Why is finding a cause important? - a more clinical viewpoint**

The clinical benefits of achieving a specific diagnosis include:

**Aetiology** :

- To establish a specific cause and allay concerns about other possible causes such as events during pregnancy.
- To gain an understanding of the condition and possible prognosis:
- To guide optimal management:
- Medical evaluation: it can enhance medical evaluation by enabling the clinician to undertake a targeted evaluation (eg with monosomy 1p36 would include specific evaluation for hearing and visual impairment, palatal abnormalities, and cardiomyopathy or structural cardiac abnormalities in children).
- Surveillance: it can help target a programme of surveillance and vigilance (eg in Down Syndrome would include monitoring for cardiac disease, celiac disease and thyroid function, and vigilance for arthritis, atlantoaxial subluxation, diabetes mellitus, leukaemia, obstructive sleep apnoea and seizures).

Genetic advice Being able to define more precisely the molecular abnormality can also help to give more accurate advice about the possibility of recurrence or risk to the extended family. Thus, for example, a balanced parental translocation substantially increases the risk of an unbalanced event in the family, whereas if the abnormality is found to have arisen *de novo* and the parental karyotypes are normal, then the risks of recurrence are very low.

Support for family: knowing that a child has a rare disorder can lead to a referral to support organisations where they can meet other parents of children with the same of a similar condition. This is useful for emotional, social and practical support over the years as they care for the child.

**Assessment of developmental delay**

The following consensus documents were used as the baseline from which the East Anglian guidelines were developed:

- M. Shevell MD *et al.* Practice parameter: Evaluation of the child with global developmental delay, 2003, Special Article, pp. 367-380; Summary in PDF , Summary in html
- Curry CJ *et al.* Evaluation of Mental Retardation: Recommendations of a Consensus Conference. Am J Med Genet 1997:72:468-472

- van Karnebeek CDMD *et al.* Diagnostic investigations in individuals with mental retardation: a systematic literature review of their usefulness. European Journal of Human Genetics (2005) 13, 6−25

Following referral for concerns over developmental progress, the paediatrician undertakes a careful history including a detailed family history (FH) and examination of the child with assessment of growth (ht, wt and head circumference) and development and may involve other professionals in this process.

A variety of tools are used in clinical practice. Some of the standard ones used within the United Kingdom are:

- Griffiths Mental Development Scales
- Denver Developmental Screening Test
- Cash's Schedule of Growing Skills

The clinician will exclude the possibility of chronic illness as the cause, both clinically, and through a baseline haematology and biochemical profile. Tests may be offered to try to determine the cause. Testing will be guided by clinical features, but even in the absence of these, investigations can still be useful. Children with significant developmental delay, at whatever age, should be considered for investigation.

**Investigations that should be considered initially in all patients**

These are usually requested by the paediatrician

Chromosome analysis: this is the investigation with the highest yield for children with unexplained developmental delay

- Xu J, Chen Z. Advances in molecular cytogenetics for the evaluation of mental retardation. Am J Med Genet. 2003 Feb 15;117C(1):15-24
- Anderson G, Schroer RJ, Stevenson RE (1996) Mental retardation in South Carolina II. Causation. Proc Grenwood Genet Center 15
- FitzPatrick DR, Pearson P *et al*. A school based study of children with learning disability indicates poor levels of genetic investigation. J Med Genet 2002;39:4 e19

A chromosome analysis is a very broad investigation which can identify problems anywhere in the genome. Specific FISH tests for submicroscopic microdeletions (eg. Williams, 22q11 syndrome) can also be requested.

Papers describing the microdeletion and associated phenotype identified by FISH analysis include:

- Williams syndrome - Ewart AK, Morris CA *et al*. Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. Nat Gen 1993;5:11-16
- 22q11 deletion syndrome - Driscoll D, Salvin J *et al*. Prevalence of 22q11 microdeletions in DiGeorge and velocardiofacial syndromes: implications for genetic counselling and prenatal diagnosis.
  J Med Genet 1993;30:813-17
- Ryan AK, Goodship JA, Wilson DI *et al*. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. J Med Genet 1997;34:798-804

**Fragile X analysis:** this is the commonest cause of inherited learning disability, but remains a rare disorder. It has fairly non-specific features and is difficult to diagnose on clinical grounds so it is therefore offered to all children with developmental delay.

- Review: Crawford DC, Acuna JM, Sherman SL. FMR1 and the fragile X syndrome: human genome epidemiology review. Genet Med. 2001;3:359-71

**Creatine Kinase in boys:** some boys with Duchenne muscular dystrophy present with speech delay and delayed motor milestones &/or global delay.

- Bushby KM, Hill A *et al*. Failure of early diagnosis in symptomatic Duchenne muscular dystrophy. Lancet 1999;353(9152):557-8 *

**Thyroid function tests:** children born in the UK should have been tested for congenital hypothyroidism on the newborn blood spot screen. If this result was normal (need confirmation), unless there are clinical signs suggestive of hypothyroidism, repeat investigation is not required.

- Koch CA, Sarlis NJ (2001) The spectrum of thyroid diseases in childhood and its evolution during transition to adulthood: natural history, diagnosis, differential diagnosis and management. J Endocrin Invest 2001;24(9) : 659-75.

Amino and organic acids: inborn errors of metabolism are individually rare, but may present with non-specific features eg. developmental delay &/or failure to thrive. Plasma & urine samples should be arranged if there is developmental regression, episodic decompensation, parental consanguinity, a family history or physical examination findings consistent with a metabolic disorder eg. microcephaly, macrocephaly, hepato-splenomegaly. 'Non-specific' abnormalities are more common than true diagnoses.

The diagnostic yield of "metabolic screening" is relatively low in children presenting with developmental delay alone but should be considered in those where the initial evaluation and first line tests have failed to give an answer. These disorders may be very rare but some are amenable to treatment.

- Poplawski NK, HarrisonJR, Norton W, Wiltshire E, Fletcher JM (2002) Urine amino organic acids analysis in developmental delay or intellectual disability J Paediatr Child Health 2002; **38**(5) : 475-480
- Kumps A, Duez P, Maardens Y (2002) Metabolic, nutritional, iatrogenic and artifactual sources of urinary organic acids: a comprehensive table. Clin Chem 2003; **48**(5): 708-717
- Amino acid analysis by Shih VE and Organic acid analysis by Hoffman GF, Feyh P in Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases. Editors: Blau N, Duran M, Blaskovics ME, Gibsom KM. Second edition Springer-Verlag Berlin Heidelberg New York 2003, p11-56.

**Urine glycosaminoglycans (mucopolysaccharidoses):** in children with developmental regression, glue ear, coarse features, macrocephaly.

Urine glycosaminoglycans (GAG) quantitation provides a screening test only. False positives are common, especially in young infants. False negatives also occur, particularly in patients with Morquio Disease (MPS IV) and less often in Sanfilippo (MPS III). If there is a strong clinical suspicion of a mucopolysaccharidosis GAG typing should be undertaken.

- Muenzer J (2004) The mucopolysaccharidoses: A heterogeneous group of disorders with variable pediatric presentations. J Pediatr. 2004;144(5 Suppl): S27-534

**Ophthalmological opinion:** especiallyif there isconcern regarding vision, eye signs (eg nystagmus or neurological signs or microcephaly). In addition, examination of the eyes might reveal retinitis pigmentosa (fundus) or structural abnormalities characteristic of certain syndromes eg hypertelorism in Coffin-Lowry syndrome, Opitz G).

**Audiology assessment:** especially if there is speech delay or concern regarding hearing.

**Consider congenital infection:** in children with intrauterine growth retardation, microcephaly and eye/hearing signs. Requires comparison of maternal booking and current maternal serology. Useful for children up to ~18 months of age.

## Further investigations that may be arranged in particular clinical circumstances

**Telomeres:** where routine chromosome analysis is normal but a chromosome abnormality is suspected.

Large studies suggest a prevalence of about 6.7% in an unselected population with mental retardation.

- Knight SJL, Regan R *et al* Subtle chromosomal rearrangements in children with unexplained mental retardation. Lancet 1999;354(9191):1676-81 *
- Flint J, Knight S (2003) The use of telomere probes to investigate submicroscopic rearrangements associated with mental retardation. Curr Opin Genet Dev.2003;13:310-316
- Koolen DA, Nillesen WM, Versteeg MH, Merkx GF, Knoers NV, Kets M, Vermeer S, van Ravenswaaij CM, de Kovel CG, Brunner HG, Smeets D, de Vries BB, Sistermans EA (2004) Screening for subtelomeric rearrangements in 210 patients with unexplained mental retardation using multiplex ligation dependent probe amplification (MLPA). J Med Genet. 2004;41:892-899

**Cranial MRI scan:** MRI scanning in young children with developmental delay requires day case admission to hospital and sedation or anaesthesia. It is indicated in children with microcephaly, macrocephaly, neurological signs (eg hemiplegia, nystagmus, optic atrophy), seizures, unusual facial features (eg spacing of eyes). The diagnostic yield in normally grown children, with no relevant history or neurological signs is very low.

- van Karnebeek CDMD *et al.* Diagnostic investigations in individuals with mental retardation: a systematic literature review of their usefulness. European Journal of Human Genetics (2005) 13, 6−25

The papers listed describe quite high rates of abnormality found on MRI scanning children with LD (up to 60% in one series). However, in many cases the diagnosis would have been apparent from the history, examination or other investigations. In other cases the abnormalities found would not have necessarily caused the LD and might confuse the situation.

- Ashwal S, Russman BS, Blasco PA, Miller G, Sandler A, Shevell M, Stevenson R; Quality Standards Subcommittee of the American Academy of Neurology; Practice Committee of the Child Neurology Society. Neurology. 2004 Mar 23;62(6):851-63.
- Demaerel P, Kingsley DP, Kendall BE. Isolated neurodevelopmental delay in childhood: clinicoradiological correlation in 170 patients. Pediatr Radiol. 1993;23(1):29-33.
- Curry CJ, *et.al.* Evaluation of mental retardation: recommendations of a Consensus Conference: American College of Medical Genetics. Am J Med Genet. 1997 Nov 12;72(4):468-77.
- Poussaint TY and Barnes PD. Imaging of the developmentally delayed child. Magn Reson Imaging Clin of North America.2001;9(1):99-119.


**Congenital Myotonic Dystrophy (CMD)**

Myotonic dystrophy: in children with motor or global delay with floppiness, history of poor suck and poor feeding in infancy or weakness and fatigue in childhood or a family history of myotonic dystrophy.


- Cobo AM, Poza JJ *et al.* Contribution of molecular analyses to the estimation of the risk of congential myotonic dystrophy. J Med Genet 1995;32:105-08
- Koch MC, Grimm T *et al.* Genetic risk for children or women with myotyonic dystrophy. Am J Hum Genet 1991;48:1084-91


**Angelman/Prader-Willi Syndrome(PWS):** in children with seizures and no/very little speech (AS), infants with floppiness or young children with obesity and a history of poor feeding (PWS).

Excellent review of clinical features and genetic basis of Angelman syndrome


- Clayton-Smith J, Laan L. Angelman syndrome: a review of the clinical and genetic aspects. J Med Genet. 2003 Feb;40(2):87-95.


**Overview of clinical presentations of PWS**


- Gunay-Aygun M, Schwartz *et al.* The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. Pediatrics 2001;108:E92


Creatine Kinase in girls (muscle disorders):if significant delay in motor milestones with/without associated global delay.

Excellent compendium of muscle disorders presenting in infancy and childhood including those presenting with developmental delay.


- Dubovitz V. Chapter 12 'The Floppy infant syndrome' in Muscle Disorders in Childhood. WB Saunders 1995 pp457-72.
- Tubridy N, Fontaine B, Eymard B. Congenital myopathies and congenital muscular dystrophies. Curr Opin Neurol. 2001;14:575-82.


**Lactate (mitochondrial disorders):** there is usually multisystem involvement. Key features include; growth retardation, visual/hearing impairment, abnormal MRI findings. (Local professional opinion)

**Radiographs (X-rays):** if there are features suggestive of skeletal involvement. If delay is associated with macrocephaly and tall stature, an X-ray of the left wrist can be helpful to assess bone age.

## Specialised investigations that may be arranged in conjunction with specialist services

**MECP2 analysis (Rett syndrome):** only in girls with features consistent with Rett syndrome.

There is a good yield for patients with classical Rett syndrome

- Webb T, Latif F. Rett syndrome and the MeCP2 gene. J Med Genet 2001;38:217-23 *

  MECP2 Mutations are rarely found in children with non-syndromic mental retardation

- Poirier K *et al*. Mutations in exon 1 of MECP2B are not a common cause of X-linked mental retardation in males. Eur J Hum Genet 2005;13:523-524

**7-deyhdrocholesterol (Smith-Lemli-Opitz syndrome):** in children with microcephaly, 2,3 syndactyly, cleft palate, congenital heart defect.

- Jira PE, Waterham HR, Wanders RJA, Smeitink, Sengers RCA, Wevers RA (2003) Smith-Lemli-Opitz syndrome and the DHCR7 gene. Ann Hum Genet. 2003 May;67(Pt 3):269-80

**VLCFA's (peroxisomal disorders):** in children with hypotonia, delayed closure of the anterior fontanelle and multisystem involvement.

- Wanders RJA (2004) Metabolic and molecular basis of peroxisomal disorders: a review. Am J Med Gen, 2004; **126A(4)**: 355-375.

**Electrophoresis of transferrin isoforms (congenital disorders of glycosylation):** in children with multisystem involvement (eg lipodystrophy).

- Gr ü newald S, Mattheus G, Jaeken J (2002) Congenital Disorders of Glycosylation: A Review. Pediatr Res**, 2002;52**(5): 618-624.

**White cell enzymes (lysosomal storage disease):** in children with hepatomegaly, coarse features and/or regression.

- Wilcox WR (2004) Lysosomal Storage Disorders: The need for better pediatric recognition and comprehensive care. J Pediatr, 2004; 144(5) : S3-S14

**Acyl carnitines (fatty acid oxidation disorders):** in children with a tendency to fasting hypoglycaemia, prolonged failure to thrive, hypotonia or cardiomyopathy.

- Sim KG, Hammond J, Wilcken B (2002) Strategies for the diagnosis of mitochondrial fatty acid b - oxidation disorders. Clin Chim Acta, 2003; **323** (1-2) : 37-58.

## Indications for referral to a clinical geneticist

The following textbook gives a good general account of the roles of the genetic service and indications of referral

- Harper P. Practical genetic counselling 5th edition. Butterworth-Heinmann 1998

  Indications include:

- Abnormal chromosome analysis or other abnormal genetic test result.
- Any child with moderate/severe developmental delay of unknown cause.
- Congenital anomaly, unusual facial features or multisystem problems in addition to developmental delay.
- Unusual growth parameters eg microcephaly or macrocephaly, short or tall stature, failure to thrive or severe obesity.
- Parental consanguinity or a FH of developmental delay or learning disability.
- Bundey S, Aslam H. A five-year prospective study of the health of children in different ethnic groups, with particular reference to the effect of inbreeding. Eur J Hum Genet 1993;1:206-219
- Parents seek advice about diagnosis or recurrence risks for future pregnancy.
- Turner G, Partington M. Recurrence risks in undiagnosed mental retardation. J Med Genet 2000:37:E45 *

## Indications for referral to a paediatric neurologist

- Developmental regression
- Abnormal neurological features on examination or investigation

The paediatric neurologist may help with diagnosis where the above are present. In the absence of these they are unlikely to add information. At present all children should primarily be seen by a local paediatrician with expertise in developmental delay. If they find abnormalities, but are unable to make a diagnosis, then referral may be appropriate.

---

This guide was written by a multidisciplinary group in East Anglia: Helen Firth & Lucy Raymond (Clinical Genetics), Alasdair Parker (Paediatric Neurology), Moira Pinkney (Community Paediatrics) and Jacqui Calvin (Biochemistry). The work was part of a wider programme supported by the Cambridge Genetics Knowledge Park. For further information, copies of the document and associated reference material see *www.addenbrookes.org.uk/genetics/index.html*

---

## Instructions for accessing full text articles via Athens (marked *)

If you are part of NHS you should be able to register with Athens which allows you access to many full text publications and resources.
Step 1: Go to https://www.athens.nhs.uk/region/ Click **Start Registration Process** button
Step 2: Choose your region and area

Step 3: Select your NHS/social care organisation
Step 4: Enter your personal details and click the **Submit Details** button

Your Athens username and password will be emailed to you within 10 days.
**NB:** Most of the articles above are not accessible via Athens unless you or your library have subscription to them.

Relevant Links:

- Athens resources (e.g. OVID journals, ProQuest, BioMed Central and many more)
- NHS National Library for Health
- NHS fulltext journals

## Instructions for accessing full text articles not available via Athens:

1. Check your own your own organisation's library. Ask your librarian for help.

2. Contact the British Library. Go to http://catalogue.bl.uk/ to search for the publication you are looking for. To order articles from the British Library without an account, go to http://www.bl.uk/services/document/orddocs.html

Back to top  Back to 'Overview of our work'