# The Human Developmental Biology Resource (HDBR)

A unique resource

- funded by the Wellcome Trust and Medical Research Council since 1999.
- has ethics approval to collect, store and distribute human embryonic and fetal tissue.
- distributes material to registered projects throughout the research community.
- material is used to study gene expression in relation to congenital diseases, including birth defects and inherited metabolic disorders.

Two centres

- Institute of Human Genetics, Newcastle.
- Institute of Child Health, UCL, London.

# Why establish the HDBR?

- There is a need to extend gene expression studies from animal models to human.
- Early human embryonic and fetal material is very scarce.
- A centralised resource is practically and ethically more acceptable.
- The service function is not easily provided by a collection within individual research labs.

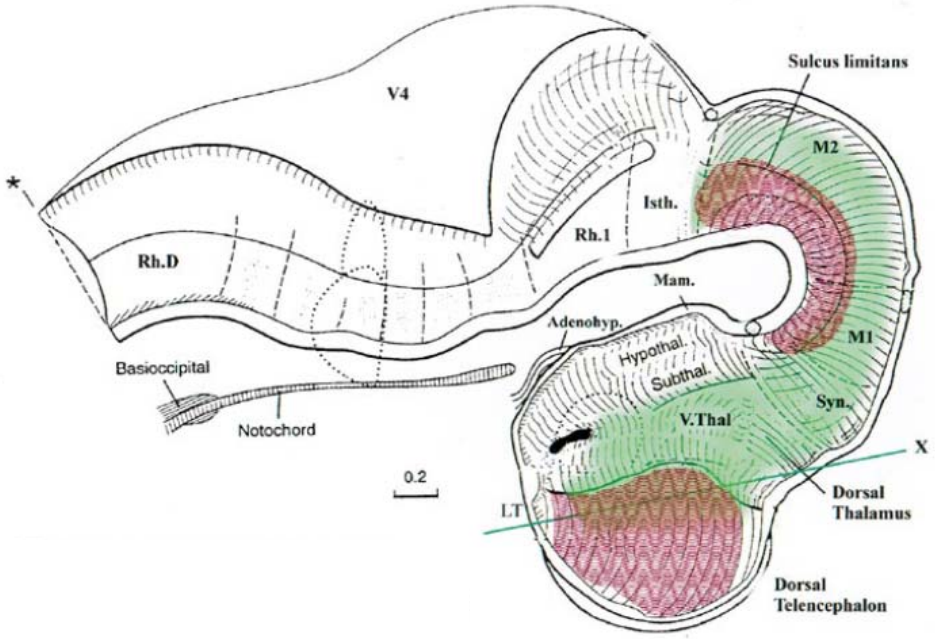
# Why use the HDBR ?

- **It is important that studies using animal models (e.g. mice) are replicated in humans, as species differences do occur.**

- Work performed by members of the HDBR has demonstrated human-mouse differences in the embryonic expression patterns of developmental control genes and disease genes.

- For example differences in Wnt7a expression have been observed between the mouse and human developing brain. Fougerousse et al. 2000. **Human Molecular Genetics.**

# Schematic representation of Wnt7a expression.




Human CS15

Mouse 12.5dpc

Human/Mouse

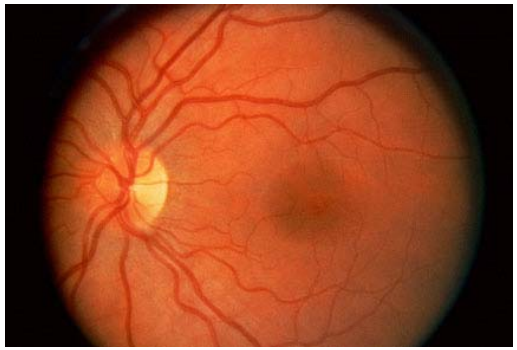
Human Wnt7a expression in the midbrain is confined to dorsolateral region and extends rostrally in the forebrain as far as the caudo-basal areas of telencephalon.

Mouse Wnt7a expression shows significant differences to human: a ventral midbrain distribution and expression in dorsal and lateral regions of the telencephalon.

# Why use the HDBR ?

- **To analyse human specific defects and syndromes.**
- Kallmann syndrome is a congential human syndrome.
- Characteristics: hypogonadotropic hypogonadism and anosmia.
- Deletions or point mutations of a gene (KAL1) located at Xp22.3 are responsible for the disease.
- KAL1, plays a key role in the migration of Gonadotropin-releasing hormone (GnRH) neurons and olfactory nerves to the hypothalamus.
- This syndrome can not be investigated in mouse models as there is no mouse KAL1 gene.

# Why use the HDBR ?



- **To analysis human specific structures.**

- The human eye differs from animal models such as the mouse.

- The human eye possess a macula which is an oval-shaped highly pigmented yellow spot at the back of the retina. Near its centre is the fovea, a small pit that contains the largest concentration of cone cells in the eye and is responsible for central, high resolution vision.

- The mouse eye does not have a macula.

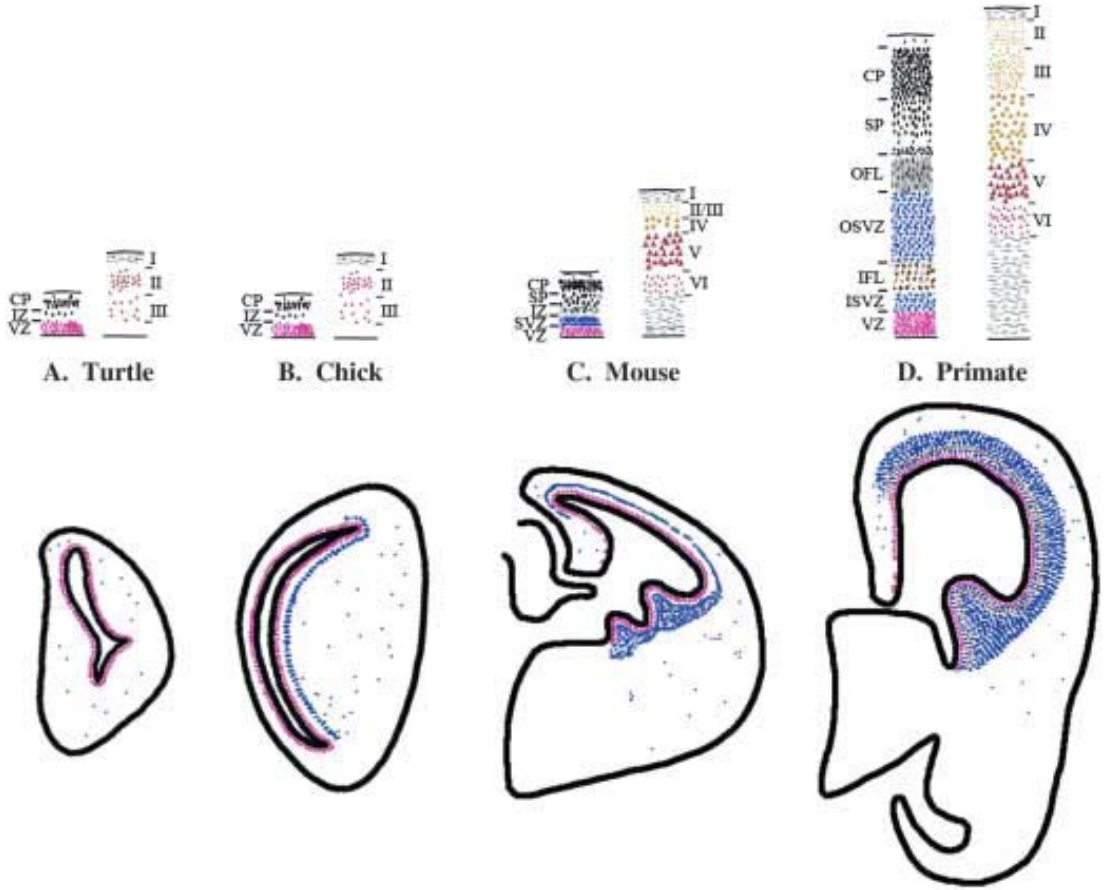
- Human eyes contain 3 types of cones, short (Blue), mid (Green) and long (Red).

- Mouse eyes contain 2 types of cones  short (Blue) and mid (Green).

# Why use the HDBR?

**To analyse the developing human brain**

Defects such as mental retardation, schizophrenia and autism are thought to have their origins in early brain development.




During evolution the brain has changed in size and shape due to an increase in the number and thickness of layers in the cortex.

# Why use the HDBR ?

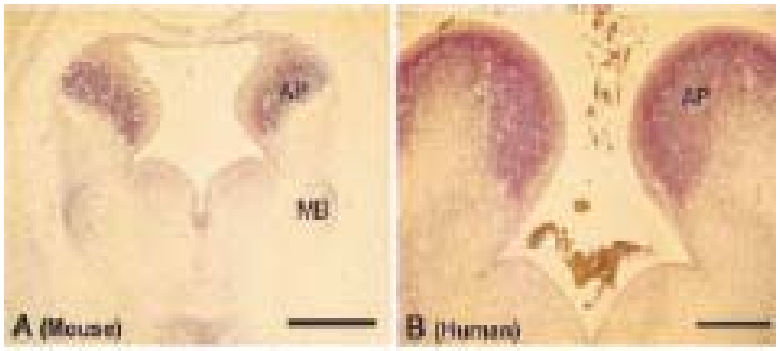
- **To analyse the development of speech and language.**

- FOXP2 was the first gene to be implicated in a speech and language disorder.

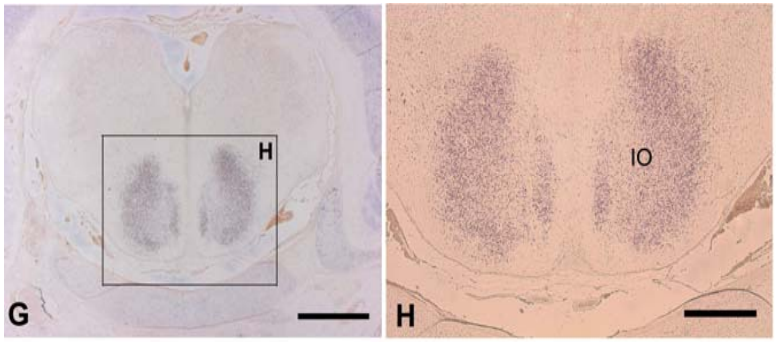
- The gene was shown to be expressed in the alar plate, cortical plate, basal ganglia, thalamus, inferior olives and cerebellum.

- The expression of FOXP2 in these areas supports its role in the development of corticostriatal and olivocerebellar circuits involved in motor control.

# Expression pattern FoxP2/FOXP2 in mouse and human embryos




Expression in the alar plate in 8 week human embryo and 13.5 dpc mouse brain




Expression in the inferior olivary nuclei in 9 week human brain

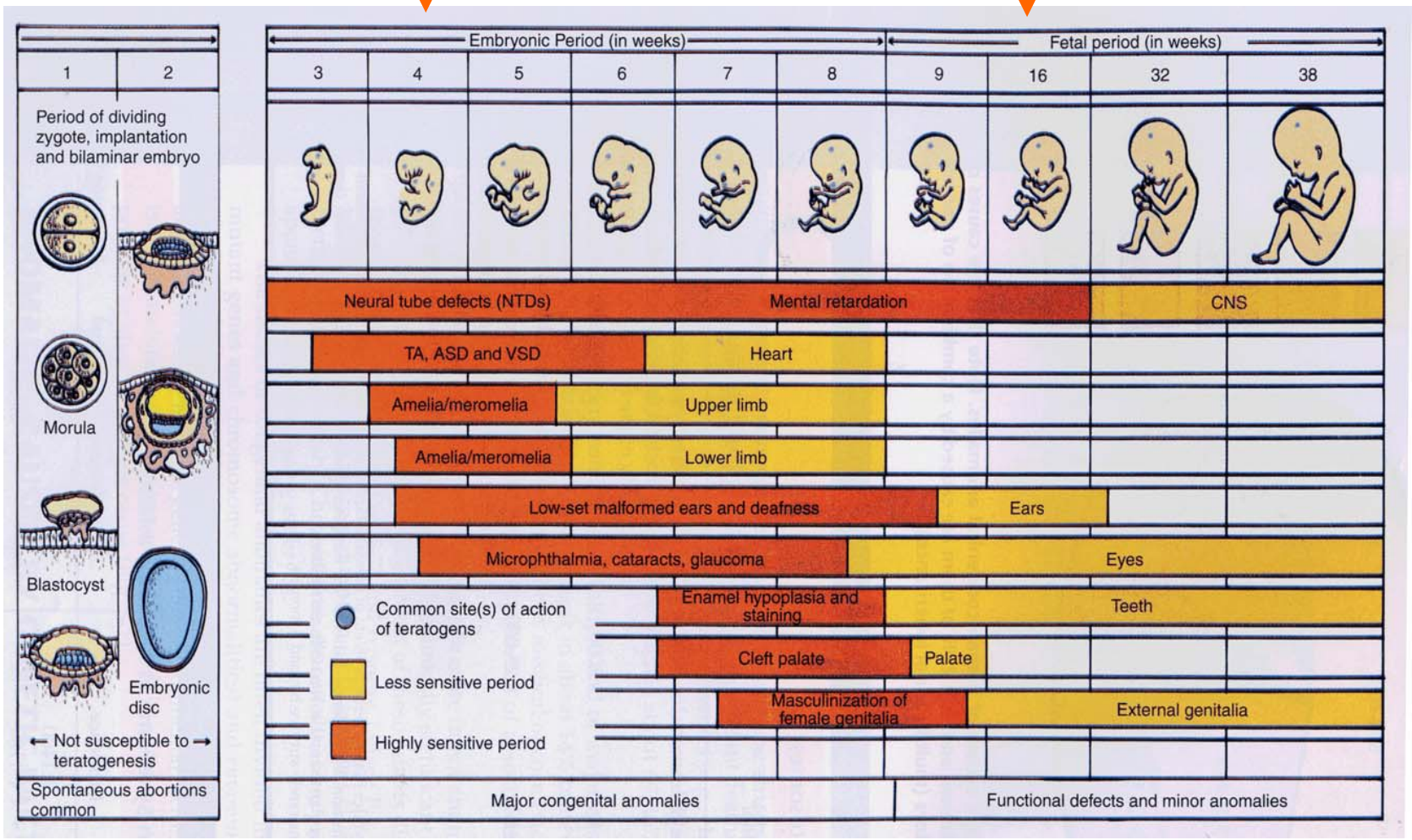
Lai et al (2003) *FOXP2* expression during brain development coincides with adult sites of pathology in a severe speech and language disorder. **Brain** 126, 2455-62

# Material provided by the HDBR

- Human embryonic and fetal material between 4 -12 weeks of gestation.
- Fresh tissue for the generation of cell lines, stem cells, DNA, mRNA or protein. mRNA prepared from HDBR tissue has been successfully used in microarray experiments.
- Frozen tissue, wax embedded or sectioned material.
- Fetal Tissue Bank archive has fetal tissue between 8 -19 weeks of gestation. Frozen, wax embedded or cryopreserved tissue for the generation of cell lines.
- HDBR material is karyotyped.
- Normal material is provided for research.
- Abnormal material can be provided on request.

# Critical periods of Human development

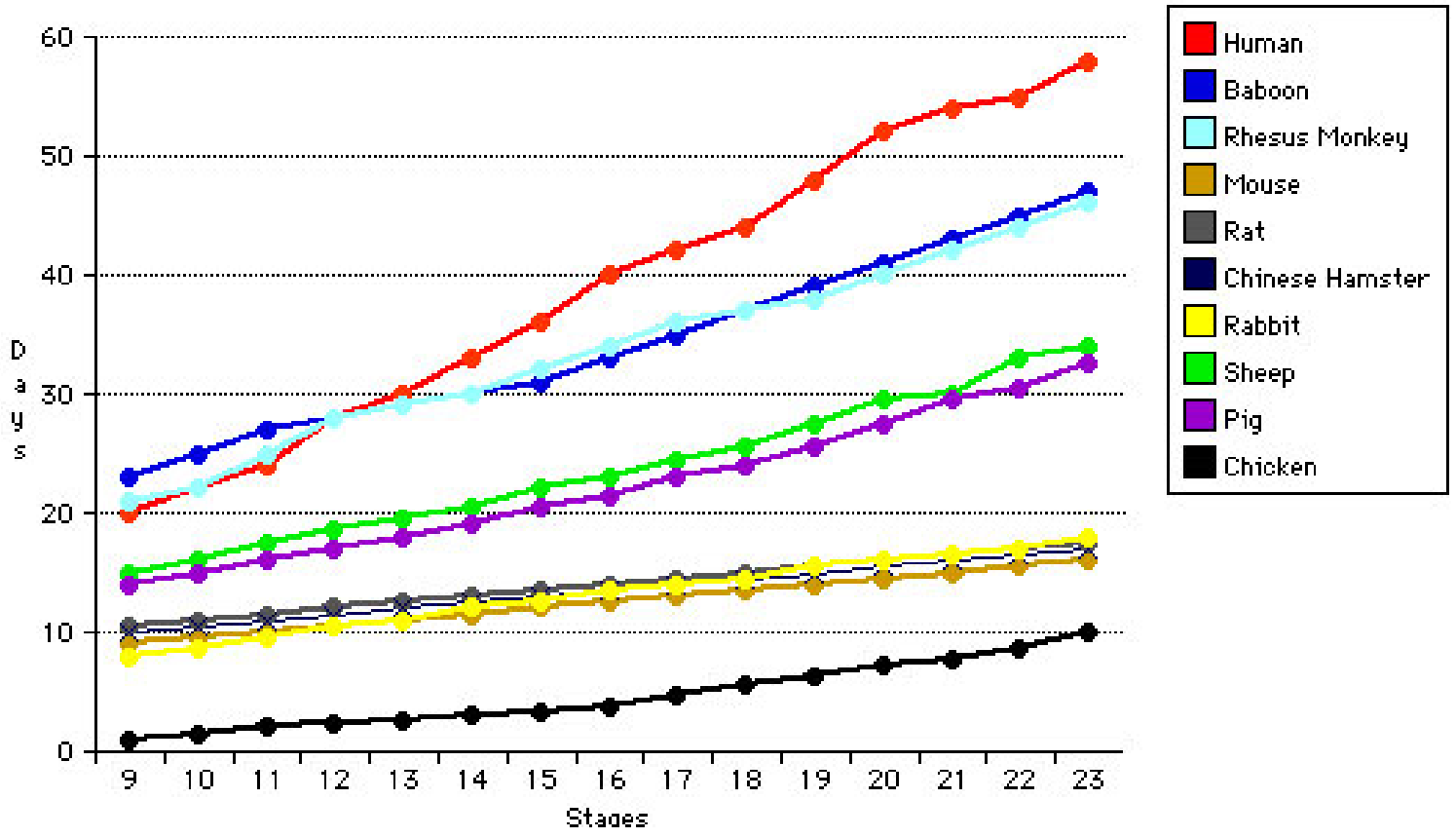
**HDBR collection 4 and 12 weeks of gestation**



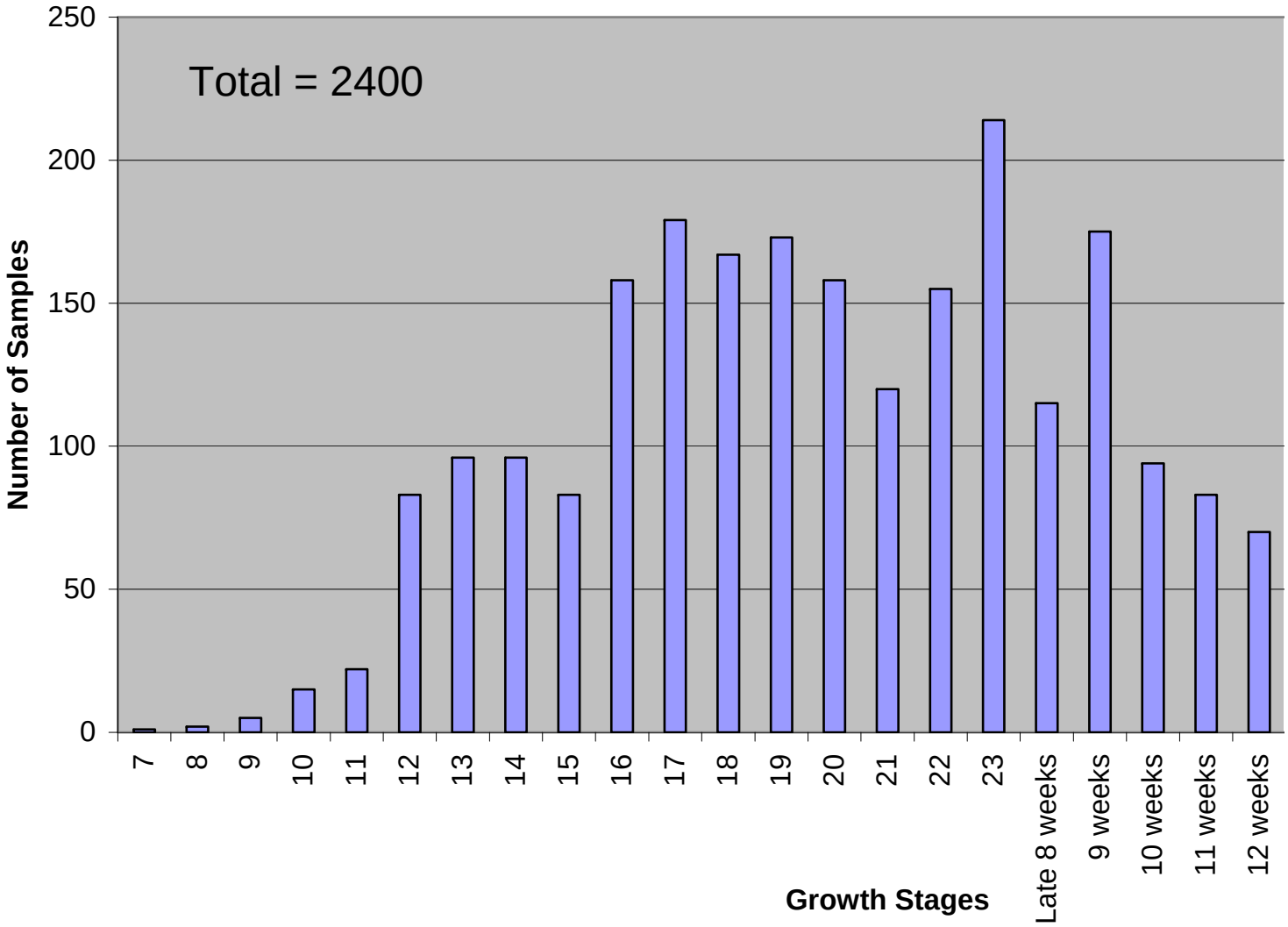
# Carnegie staging system

- Franklin Mall of the Carnegie Institute Washington started to collect and analyse human embryos in 1887.
- 7000 human embryos are stored in the collection.
- Embryos are in the first eight weeks of gestation.
- Each embryo was checked for anatomical land marks and detailed measurements were performed.
- Some of the material was sectioned.
- Carnegie stages defined as 1 to 23 cover the first eight weeks of gestation.

# Carnegie Stages



# Total number of embryos/foetuses in the HDBR collection



# Karyotypically abnormal embryos in the collection

**5%** of all embryos collected are karyotypically abnormal

- Additional chromosomes 4, 8,13, 14, 15, 16, 18, 20, 21, 22 and X.
- Additional set (69) or 2 sets of chromosomes (92).
- Chromosome transpositions
- Mosaicism

# Phenotypically abnormal embryos in the collection

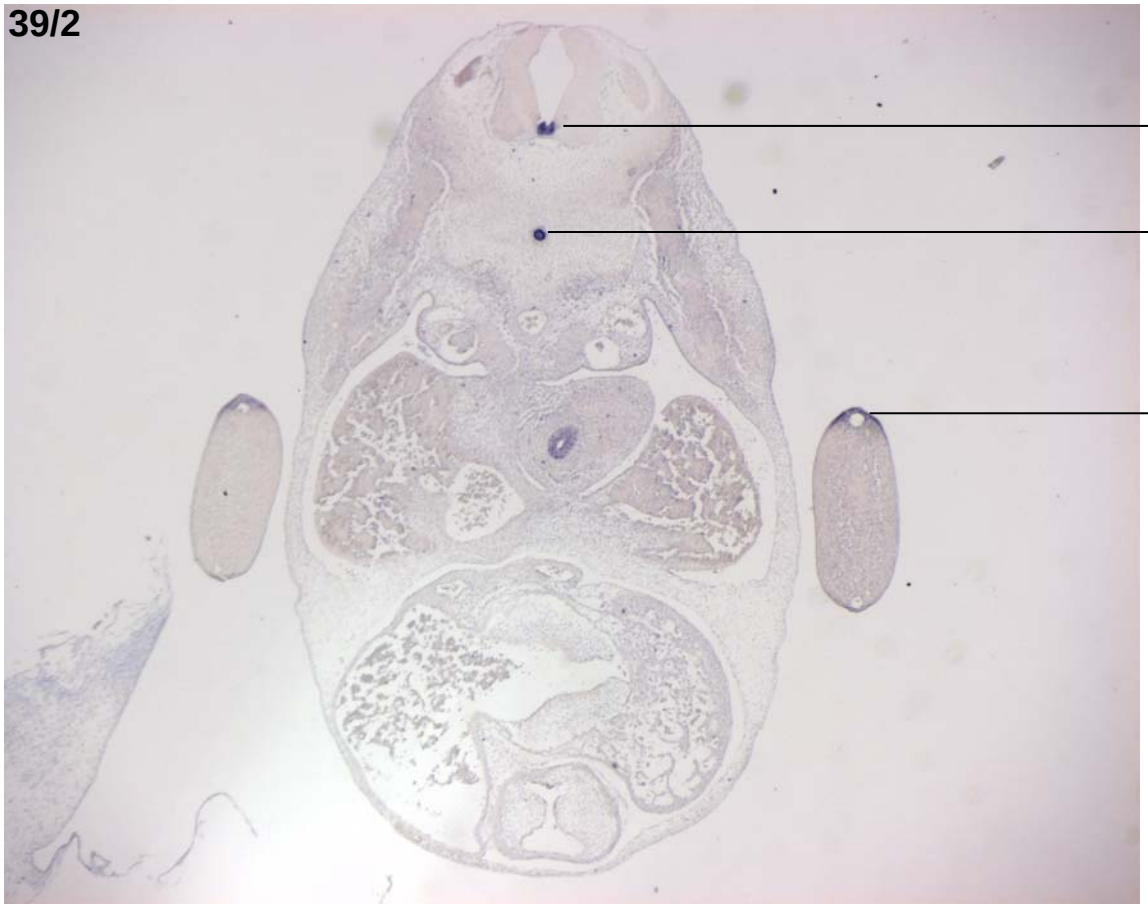
**9%** of all embryos collected have an abnormal phenotype

- Neural tube defects
- Limb/digit defects
- Cleft lip
- Eye defects
- Head abnormalities

# In House Gene Expression Service (IHGES)

- The HDBR provides a service to analyse gene expression on sectioned human material.
  - RNA *in situ* hybridisation.
  - Protein expression is analysed by immunohistochemistry.
  - The HDBR provides electronic images for publication and advice on interpretation of results.
  - Data will be deposited, in a public database.

# Quality Control
# Shh expression, E816, CS16, slide 39

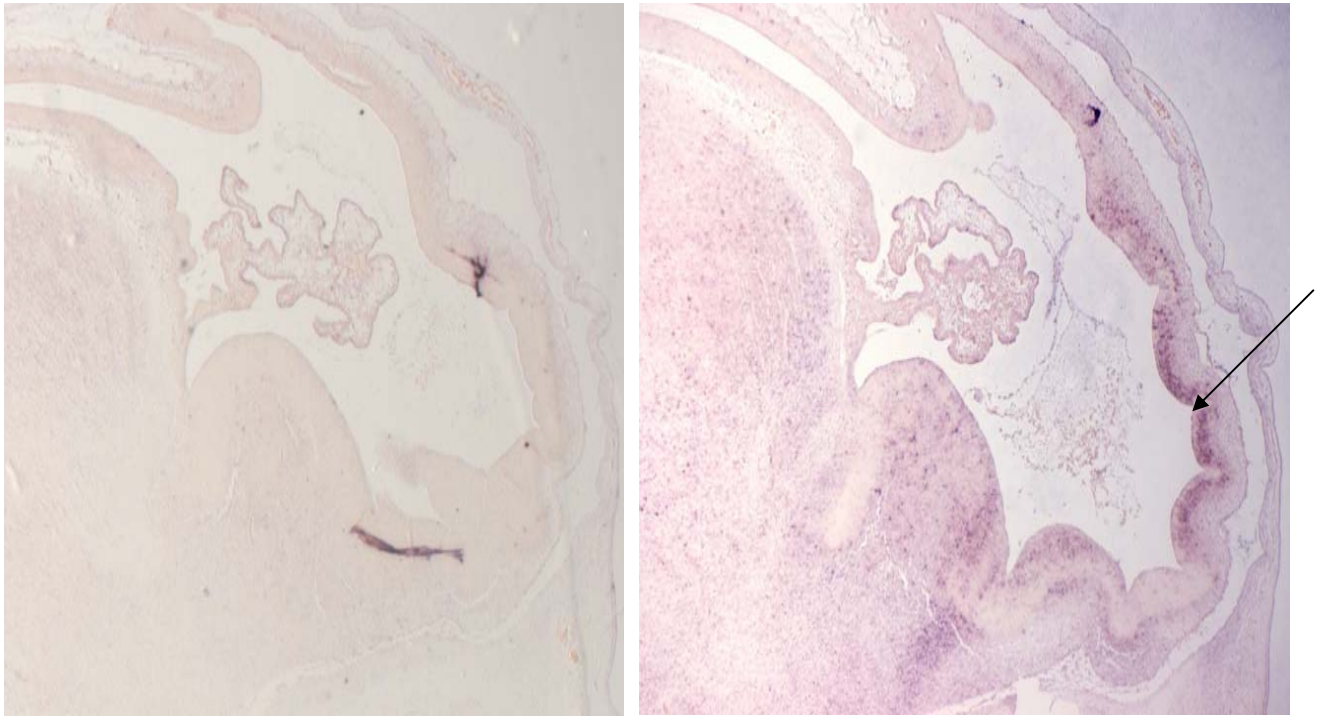


# A recent gene expression project

- Autism spectrum disorder (ASD) represents a group of childhood neurodevelopmental and neuropsychiatric disorders.
- Patients have defects in socialisation and communication.
- Repetitive or unusual behaviour with learning disability in 70%.
- Incidence 6 per 1000.
- Professor Monaco and co workers identified a novel region of genetic linkage on chromosome 16q21 that is limited to families with ASD and learning disability.
- This area contained a single gene, cadherin 8.
- They also showed deletions within cadherin 8 in two unrelated families with ASD and learning disability.

# Expression of Cadherin 8

- By *in situ* hybridisation we demonstrated that Cadherin 8 is expressed in the cortical plate of 9 week old human fetus.



sense Anti-sense

Rare familial 16q21 microdeletions under a linkage peak implicate cadherin 8 (CDH8) in susceptibility to autism and learning disability. ***J Med Genet.*** 2010 Oct 23.

# Human Developmental Biology Resource

- The HDBR is a core funded resource supported by a programme grant from the Welcome Trust and MRC.
- Tissue or sectioned material is available free of charge.
- A gene expression service using both RNA in situ hybridisation and immunohistochemistry is provided. This service is provided at a very competitive rate.
- We are seeking new projects for both the expression service and the resource.

# Further information

## Web site www.hdbr.org

**HDBR London, Institute of Child Health, UCL.**
**Director Professor A.J. Copp**
**Manager Dr D. Gerrelli**
**Hdbr@ich.ucl.ac.uk**

**HDBR Newcastle, Institute of Human Genetics, Newcastle University.**
**Director Professor S. Lindsay**
**Manager Mr S. Lisgoe**
**Hdbr@newcastle.ac.uk**

MRC Medical Research Council

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