Genetic issues in cerebral palsy: the Bradford experience

Dublin
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Genetic issues in cerebral palsy: the Bradford experience

- Background to our experience of genetic conditions
- Cerebral palsy in Bradford (1997 report)
- Review of genetic factors in cerebral palsy

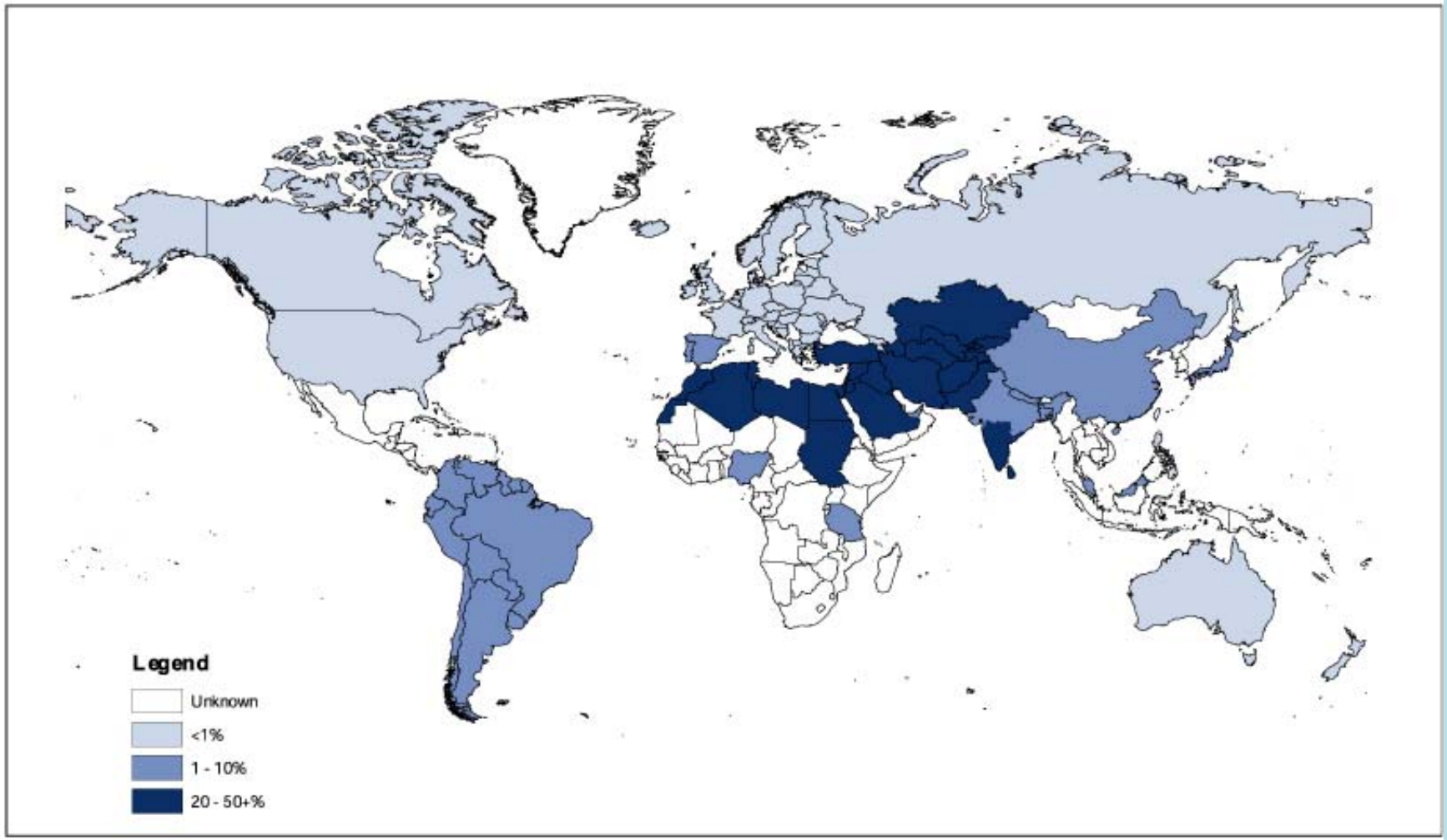
Bradford

- Population c360,000
- Children (up to 18) c106,000
- Annual births 5,000-6,000
- Pakistani origin births >45%
- Consanguinity in Pakistanis 70-80%

Cousins and clans

- Consanguinity: marriage within the family, occasional in western societies (but more popular in royal families)
- Endogamy: marriage within the community, popular in certain groups (e.g. Amish, Irish Travellers) and used to be very common with limited travel options
- Both very common globally

The global distribution of consanguineous marriage



Cousins and Clans

- Marriage within a restricted population, (family, village, island, clan or small faith group) increases risk that both partners may share autosomal recessive genes.
- This will increase risk of children having AR conditions.
- However most children of consanguineous parents will not have AR conditions.

Individual family or community

- For first cousin parents there will be an extra 2 in 100 chance of a disabled child

- For a city with 2,000 births each year to first cousin parents this will mean an extra 40 children with disabilities
- Plus further increase from previous family marriages/endogamy

Down’s syndrome

- Maternal age 20 1 in 1724
- Maternal age 35 1 in 365
- Maternal age 40 1 in 109

Hook and Chambers 1977

Impact in Bradford

- Neurodegenerative conditions
- Microcephaly
- Deafness
- Neuromuscular conditions
- Rare genetic conditions

- 149 AR conditions across paediatrics

Conditions seen this/last week

- Aicardi-Goutières syndrome
- Juvenile Sandhoff disease
- Micro syndrome
- Spinal Muscular Atrophy type I
- Hyperekplexia
- Joubert syndrome
- Galloway Mowat syndrome

Neurodegenerative conditions

- Progressive Intellectual and Neurological Deterioration (BPSU study)
- 902 UK children
- 72 in Bradford (inc Airedale)
- 27 different conditions identified in larger local study, mostly autosomal recessive

Devereux G, 2004 Arch Dis Child (Updated information in BPSU Quarterly Bulletin October 2006)

Positives

- Clinical series - juvenile Sandhoff disease
- Genes for Aicardi-Goutières syndrome
- Trials of potential treatments
- Lottery funding for community paediatric palliative care (but under threat)

Microcephaly

- 44 children
- 35 congenital, 9 postnatal
- Congenital:

Pakistani	27
Caucasian	7
Bangladeshi	1

Corry P, 2002 Community Genet.

Positives

- Geneticists have identified 6 gene loci for Primary Microcephaly
- Better understanding of what these genes do, and how the human brain grows

- Channel 4. “What makes us human”? In August 2006.

Roberts E, 2002 (J Med Genet)

The value of local research

Who was this man?
Why was work done with children in Bradford Child Development Centre important in understanding him?

Homo floresiensis (Hobbit)

- Theories of brain evolution arose from microcephaly genes identified in Bradford Child Development Centre

Woods C G 1998-2006

Picture: Nat Geographic

Deafness

- Prevalence in Bradford (1995)
  - Asian children 4.69 / 1,000
    - Genetic cause 2.41 / 1,000
    - Unknown cause 1.52 / 1,000
  - Non-Asian 1.38 / 1,000
    - Genetic cause 0.36 / 1,000
    - Unknown cause 0.54 / 1,000

Parry G, 1996 Univ of Manchester MSc thesis

Positives

- Early work on connexin gene
- One of first sites for universal neonatal screening
- Elizabeth Foundation centre for North of England

Campbell D A, 1997 J Med Genet

What does all this have to do with Cerebral Palsy?

Cerebral Palsy

"A persistent, but not unchanging, disorder of movement and posture due to non-progressive disorder of the immature brain".

Brett E M

In Paediatric Neurology 1983

Causes of cerebral palsy

- Media – poor care in labour room?
- Reality – only 10-15% due to problems during labour and many not preventable
- Prenatal, perinatal and postnatal
- Genetic causes – thought to be about 2%
- Increased awareness of factors in first and second trimesters, some of them genetic

Cerebral Palsy in Bradford

- Births in Bradford 1985-1987
- Using Yorkshire Cerebral Palsy register, birth records, CDC notes and clinical examination by 1 researcher
- 75 children reported to register, but 3 could not be traced, 2 refused consent and in 2 the diagnosis was changed.
- 68 children in study

Ethnicity for children with C P

- Asian children
- Cerebral palsy 29 children

  Prevalence 5.48 / 1,000

- Non-Asian children
- Cerebral palsy 39 children

  Prevalence 3.18 / 1,000

Sinha G, 1997. Dev Med Child Neuro

Table I. Prevalence of cerebral palsy in Northwest Europe.

	Birthyear	Prevalence per 1000 lifebirths	Birthweight specific per 1000 lifebirths			
			<1000	1000–1499	1500–2499	>2500
Northeast England	1964–1968	1.68		59.7	6.55	1.19
	1969–1973	1.39		22.9	6.40	0.96
	1974–1978	1.71		27.6	8.90	1.20
	1979–1983	2.00		76.6	8.22	1.26
	1984–1988	2.27		75.9	9.65	1.31
	1989–1993	2.45		80.0	11.80	1.26
Scotland, England	1984–1989	2.10	78.1	65.7	10.20	1.10
Northern Ireland	1981–1993	2.24				
Norway	1977–1981	1.91		88.9		
	1982–1986	1.98		28.8		
	1987–1991	2.05				
Denmark	1979–1986	2.80				
	1987–1990	2.40				
Sweden	1979–1982	2.17				
	1990–1993	2.20				
	1991–1994	2.12				
The Netherlands	1977–1979	0.77				
	1980–1982	1.00				
	1983–1985	1.84				
	1986–1988	2.44				

Asian children with C P

29 children

6 had sibling with same type of C P

1 had cousin with same type of C P

1 had aunt with same type of C P

1 had sibling with “motor impairment” but not available for examination

Cautions

- Unsophisticated ethnic data, but 26 out of 29 Asian children were Pakistani
- Data on consanguinity was vague. For Bradford Pakistanis thought to be 75-80%
- More knowledge now about endogamy (marriage within biraderi / clan)
- What about social factors, maternal health, language, access to maternity care?

Criticism

- It was suggested that we were wrong to concentrate on genetic factors
- What about poor obstetric care for Asian mothers?

- Apgar scores for my patients with C P were actually higher for Asian children

Turkey

- 117 children with cerebral palsy
- 352 case controls
- C P: 41 children (35%) consanguineous

  odds ratio 3.2 (CI 1.8-5.5)

  19 children (16%) with CP relative

Tüzün E H, Eker L

Presentation at EMCPDM Congress, Istanbul, April 2002

Turkey (2)

- We could not determine the aetiological factor in 49%....
- The increased frequency of consanguinity …strong association with a positive family history, suggest the role of genetic factors in the pathogenesis of CP in this environment.

– Serdaroglu A et al DMCN 2006

Saudi Arabia

- 103 children with cerebral palsy
- 103 controls
- Major risk factors: consanguinity, history of cerebral palsy in sibling
- Consanguinity odds ratio 2.31
- Affected sibling odds ratio 14.52

Al-Rajeh S, et al. 1991. DMCN

West Sweden (1)

- Recent mathematical analysis of prenatal and perinatal risk factors was applied to 681 children with cerebral palsy born in 1959-1970.
- Estimates that 40% of ***etiologically undiagnosed*** cerebral palsy is genetically caused.

West Sweden (2)

Estimates for genetic causes

- Premature spastic diplegia 32%
- Mature spastic diplegia 45%
- Mature hemiplegia 60%
- Pure ataxia virtually all

Costeff H, 2004

Hagberg B, Hagberg G, Olow I, 1975

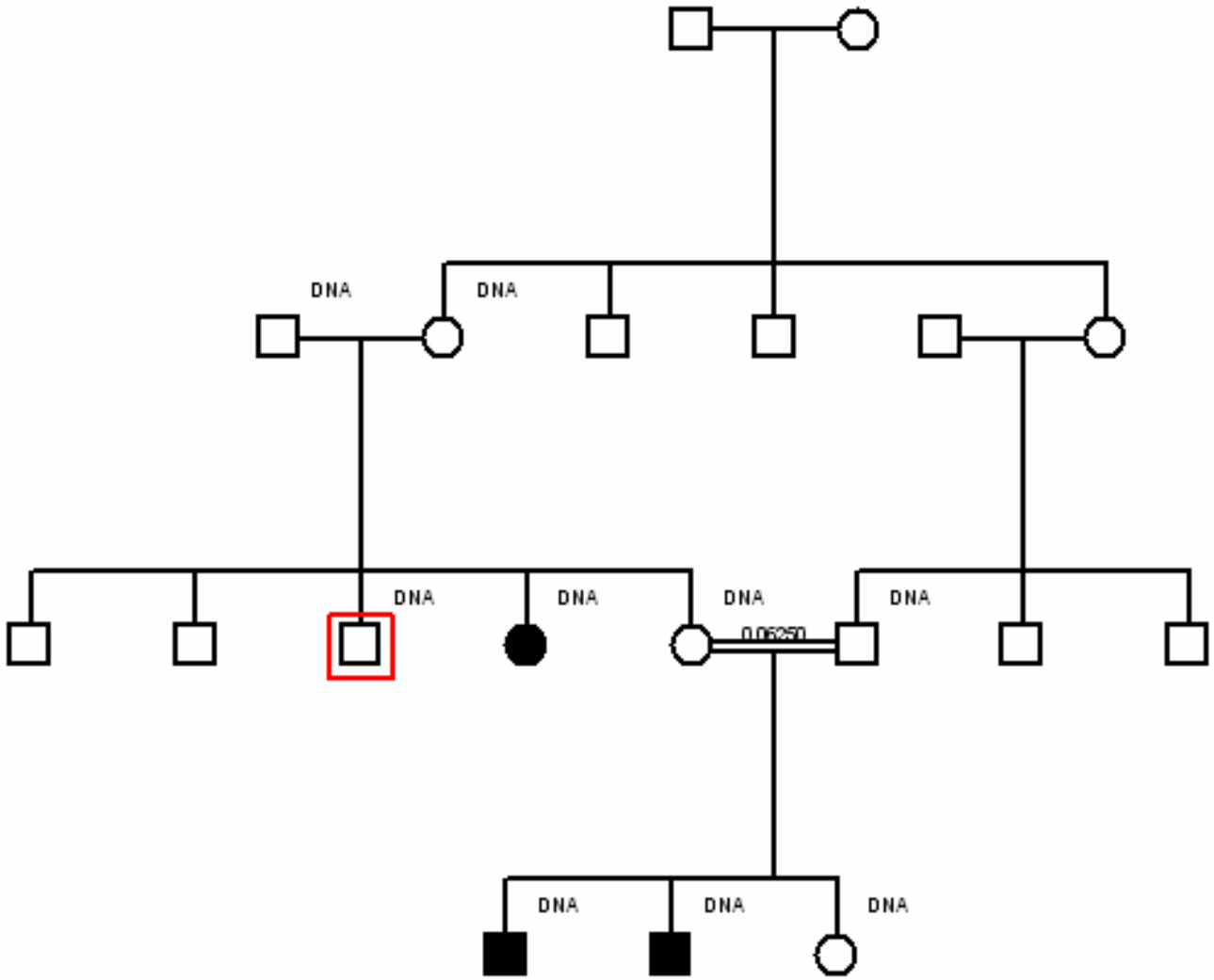
Sweden (again)

- Parents of one affected (CP) child have a **4.8 fold** risk of having a second affected child.
- c.f. **2 fold** sibling risk with most childhood cancers.

Hemminki K et al, 2007.

Familial Hemiplegia in Bradford.

- 2 brothers and aunt
- Brother, sister and father's half-brother (grandfather had first stroke at 32)
- 2 sisters and male cousin
- 1 other family: brother has hemiplegia, sister 1 has microcephaly and sister 2 has unilateral cerebral atrophy (without CP)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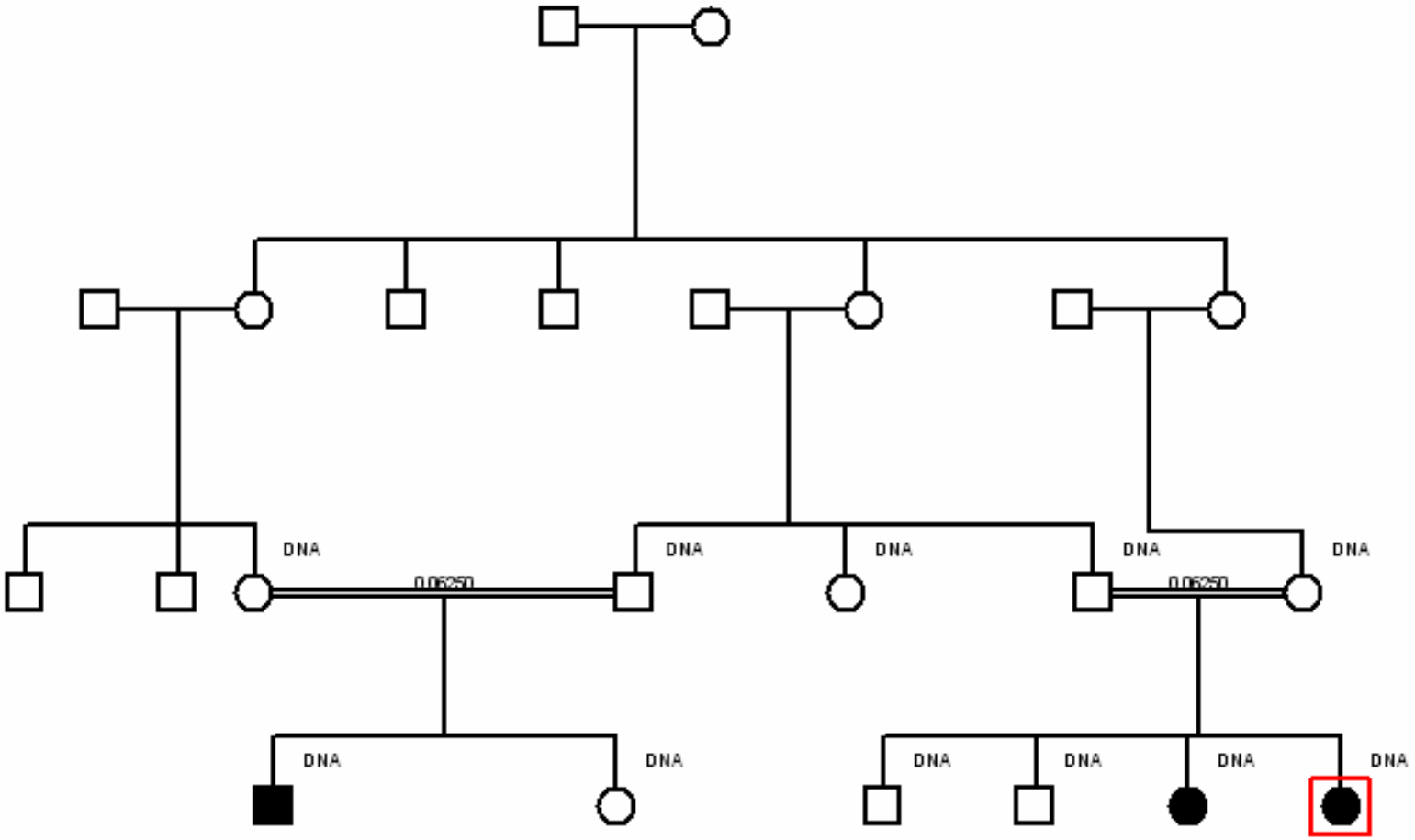
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Genetic causes for CP?

- Autozygosity mapping is easiest in consanguineous families where there are several affected individuals

Genetic causes for CP?

- Gene locus for ataxic cerebral palsy in Bradford Pakistani family mapped to chromosome 9p12-q12.

McHale D P, 2000 Eur J Human Genet

Genetic causes for CP?

- Gene locus for symmetrical spastic cerebral palsy in 3 UK families mapped to chromosome 2q24-q25.

McHale D P, 1999 Am J Hum Genet

Other recent work

- ANKRD15 gene at 9p24.3 (familial CP in Israel)
- Col4a1- familial porencephaly (Rotterdam)
- Cytokine polymorphisms (Australia)

Possible Mechanisms

- Neuronal Migration Disorders
- Thrombophilia (Leiden V, Protein C)
- Foetal inflammatory responses
- Non-progressive Metabolic?

Is cerebral palsy the right diagnosis?

- Caution:
  - Neurodegenerative disorders
  - Metabolic conditions

Gupta R Appleton R E, 2001 Arch Dis Child

Conclusions

- Familial Cerebral Palsy is rare.
- Familial Cerebral Palsy is significantly increased in consanguinity/endogamy.
- Genetic factors are probably more important than previously thought.
- Understanding of the genetic factors may help understanding of the causal mechanisms.

Genetic Studies of CP

- Collaboration with UK CP registers
- Familial cases
  - More than one affected in families
  - Sibs/cousins etc
- Particular interest in Consanguineous Families
- Please contact us if you would like to collaborate!!

- Criteria
- Diagnosis of CP with:
  - Gestation > 32 weeks
  - B.Wt > 2500 gms
  - Singelton pregnancies
  - Apgars >8 at 1,5,10
  - No history of:
    - Intrauterine infection
    - Major APH
    - PVL
    - Maternal ill-health
    - Significant maternal medication

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