

Data supplement

Table DS1 Schizophrenia in families of probands with intellectual disability

Study	Sample origins	Cases	Comparison	IQ range	Findings
Gustavson (1986) ⁴⁹	North Swedish isolate born 1829–1960	26 persons with intellectual disability from two large pedigrees	None	Not reported	Very high incidence of schizophrenia in families of probands with intellectual disability: 23 out of 26 persons with intellectual disability had close relatives with schizophrenia including 7 (27%) with a parent, 1 with a brother (4%), and 18 (69%) with second- to fourth-degree relatives.
Penrose (1938) ⁷	Representative sample of patients under care of Royal Eastern Counties Institution for intellectually disabled persons, Colchester	1280 patients with intellectual disability	Not applicable for this comparison	'Mental ratio' ranging from under 20 ('idiot') to over 70 ('dull')	Although the rate of schizophrenia in this sample was twice the rate of affective psychoses (3.8% (48 out of 1280) compared with 1.9% (24 out of 1280)), the rate of schizophrenia among relatives was almost half the rate of affective psychoses. Overall, there were 610 relatives with severe psychopathy: 103 relatives had schizophrenia and 199 had affective psychoses i.e. 17.1% of the relatives with severe psychopathy had schizophrenia, and 32.6% had an affective psychosis.
Greenwood (2004) ⁵⁰	L.S. Penrose's Ontario data collected mid-1800–1944	183 probands with a psychiatric hospital admission and intellectual disability	183 paired first- and second-degree relatives with a psychiatric hospital admission and schizophrenia or psychotic affective disorder	Assumed to be in the mild range	The risk of schizophrenia in the relatives of probands with intellectual disability was 1.5 times the risk of a psychotic affective disorder. Overall, there were more parent–offspring pairs (80) than sibling pairs (51), and there was no evidence of X-linked transmission of intellectual disability given that there was no excess of mother–son pairs compared with mother–daughter pairs.

Table DS2 Intellectual disability in families of probands with schizophrenia

Study	Sample origins	Cases	Comparison	IQ range	Findings
Heston (1966) ⁵¹	Oregon, USA	47 children reared in foster homes, born 1915–1945 to women with schizophrenia and confined to State psychiatric hospital	50 matched control children reared in foster homes	IQ < 70	4 out of 47 case children compared with 0 out of 50 control children ($P=0.052$) had intellectual disability; one child with intellectual disability also had schizophrenia
Modrzewska (1980) ⁵²	North Swedish isolate born 1829–1960	453 offspring of 214 individuals with schizophrenia (39 with two parents with schizophrenia and 514 with one parent with schizophrenia, combined for the intellectual disability analysis)	624 offspring of unaffected parents from the same isolate	IQ < 50	Incidence of intellectual disability (IQ < 50) was significantly higher in offspring with at least one parent with schizophrenia compared with control offspring from the same isolate with unaffected parents: 4.5% (22 out of 492) of those with one or two schizophrenia-affected parents had intellectual disability compared with 0.5% (3 out of 596) of those with schizophrenia-unaffected parents ($P<0.001$)
Alaghband-Rad (1998) ⁵³	NIMH childhood-onset schizophrenia study	18 consecutive study probands aged 10–18 met DSM-III-R criteria for schizophrenia with onset by age 12	26 full siblings	IQ < 70	Increased rate of intellectual disability in the siblings of individuals with childhood-onset schizophrenia (3 out of 26 full siblings)
NIMH, National Institute for Mental Health.					

Table DS3 Intellectual disability and/or schizophrenia in families of probands with intellectual disability and co-occurring schizophrenia					
Study	Sample origins	Cases	Comparison	IQ range	Findings
Penrose (1938) ⁷	Representative sample of patients under care of Royal Eastern Counties Institution, Colchester	204 persons with intellectual disability and co-occurring 'psychopathology' (psychosis): 72 severe (schizophrenia, affective psychoses), 132 mild ('psychoneuroses')	1076 persons with intellectual disability only	'Mental ratio' ranging from under 20 ('idiot') to over 70 ('dull')	Persons with co-occurring psychopathy and intellectual disability had more relatives with psychopathy per head compared with persons with intellectual disability alone; and those with mild 'psychopathology' (psychosis) and intellectual disability were more likely to have affected relatives than those with severe psychopathy and intellectual disability
O'Dwyer (1997) ⁵⁴	Patients with schizophrenia and intellectual disability seen by consulting psychiatrists in Yorkshire	First 50 consented patients with sufficient diagnostic and obstetric data	50 controls with intellectual disability, matched on gender, age, IQ, epilepsy. None had psychosis, but 54% (27 out of 50) had some mental illness.	ICD-10: mental retardation	In course of describing increased rates of pregnancy, delivery and neonatal complications in the persons with co-occurring schizophrenia and intellectual disability compared with controls with intellectual disability, O'Dwyer notes that there was a family history of schizophrenia in seven cases compared with two controls
Doody (1998) ⁵⁵	Persons with at least one psychiatric admission 1970–1993 in select districts in Scotland	39 persons (35 with full family history) with a discharge diagnosis of mild intellectual disability and schizophrenia or paranoid state, aged 16–65, and no Down syndrome	34 persons (31 with full family history) with schizophrenia and no premorbid cognitive impairment.	IQ 50–70	Persons with co-occurring disorders were significantly more likely to have first- or second-degree relatives with schizophrenia compared with intellectual disability controls (but not schizophrenia controls): 20 out of 35 (57%) of the co-occurring disorders group compared with 12 out of 31 (39%) schizophrenia controls (not significant) and 2 out of 23 (9%) intellectual disability controls (significant)
			28 persons (23 with full family history) with mild intellectual disability of unknown aetiology and no history of psychosis or current anti-psychotic drug use.		Persons with co-occurring disorders were also significantly more likely to have first- or second-degree relatives with intellectual disability compared with schizophrenia controls (but not intellectual disability controls): 15 out of 35 (43%) of the co-occurring disorders group compared with 2 out of 31 (7%) schizophrenia controls (significant) and 12 out of 23 (53%) intellectual disability controls (not significant).
			Controls matched on sex and age range		Multiply-affected families with intellectual disabilities and schizophrenia were significantly more common among first- and second-degree relatives of persons with co-occurring schizophrenia and intellectual disability in comparison to schizophrenia-only and intellectual disability-only controls: 9 out of 35 (26%) of the co-occurring disorders group compared with 2 out of 31 (7%) schizophrenia controls (significant) and 1 out of 23 (4.5%) intellectual disability controls (significant)

Table DS4 Positive and negative associations between specific syndromes and psychotic disorders				
Intellectual disability	Chromosomal locus ^a	Psychiatric phenotype	Positive or negative association	Selected studies (first author, year of publication)
Velocardiofacial syndrome	22q11.2 microdeletions	Schizophrenia	Positive	Bassett (1999), ⁵⁶ Murphy (1999) ⁵⁷
X-linked: any	–	Bipolar disorder Schizophrenia Childhood-onset schizophrenia Bipolar disorder/ affective psychosis	Positive Positive Positive	Papalos (1996) ⁵⁸ DeLisi (1994) ⁵⁹ Alaghband-Rad (1998), ⁵³ Kumra (1998) ⁶⁰ Gecz (1999) ⁶¹
X-linked: fragile-X syndrome	Xq27.3	Schizophrenia	Positive	Gustavson (1986) ⁴⁹
		Autism	Positive	Reviewed in Tsiouris (2004) ⁶²
Extra X chromosome: Klinefelter syndrome	XXY or mosaicism	Schizophrenia	Positive	Jablensky (1970), ⁶³ DeLisi (2005), ⁶⁴ Boks (2007) ⁶⁵
Prader–Willi syndrome	15q12 15q11-q13 maternal uniparental disomy	Affective psychosis	Positive	Boer (2002), ⁶⁶ Verhoeven (2003), ⁶⁷ Vogels (2003), ⁶⁸ Soni (2007) ⁶⁹
		Obsessive–compulsive disorder	Positive	Dyken (2001) ⁷⁰
Rubinstein–Taybi syndrome	22q13 16p13.3	Affective disorders with psychotic features	Positive	Levitas (1998) ⁷¹
Down syndrome	21q22.3 1q43 Xp11.23	Alzheimer disease	Positive	Malamud (1964), ⁷² Rovelet-Lecrux (2006) ⁷³
		Depressive disorders	Positive	Sovner (1985), ⁷⁴ Collacott (1992), ⁷⁵ Määttä (2006) ⁷⁶ – but not Mantry (2008) ⁷⁷
		Psychosis	Negative	Sovner (1985), ⁷⁴ Collacott (1992), ⁷⁵ Mantry (2008) ⁷⁷ – but not Rollin (1946) ⁷⁸
Dandy–Walker variant	3q24	Schizophrenia co-occurring with obsessive–compulsive symptoms	Positive	Papazisis (2007) ⁷⁹
a. Source of chromosomal locus (except Klinefelter): Online Mendelian Inheritance in Man (OMIM TM), Johns Hopkins University, www.ncbi.nlm.nih.gov/omim/				

Additional references

- 49 Gustavson KH, Modrzewska K, Wetterberg L. Mental retardation in a North Swedish isolate. *Clin Genet* 1986; **30**: 374–80.
- 50 Greenwood C, Husted J, Bomba M, Hodgkinson K, Bassett A. Elevated rates of schizophrenia in a familial sample with mental illness and intellectual disability. *J Intellect Disabil Res* 2004; **48**: 531–9.
- 51 Heston L. Psychiatric disorders in foster home reared children of schizophrenic mothers. *Br J Psychiatry* 1966; **112**: 819–25.
- 52 Modrzewska K. The offspring of schizophrenic parents in a North Swedish isolate. *Clin Genet* 1980; **17**: 191–201.
- 53 Alaghband-Rad J, Kumra S, Lenane MC, Jacobsen LK, Brown AS, Susser E, et al. Early-onset schizophrenia: mental retardation in siblings. *J Am Acad Child Adolesc Psychiatry* 1998; **37**: 137–8.
- 54 O'Dwyer J. Schizophrenia in people with intellectual disability: the role of pregnancy and birth complications. *J Intellect Disabil Res* 1997; **41**: 238–51.
- 55 Doody GA, Johnstone EC, Sanderson TL, Owens DG, Muir WJ. 'Pffropfschizophrenie' revisited. Schizophrenia in people with mild learning disability. *Br J Psychiatry* 1998; **173**: 145–53.
- 56 Bassett AS, Chow EW. 22q11 deletion syndrome: a genetic subtype of schizophrenia. *Biol Psychiatry* 1999; **46**: 882–91.
- 57 Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with Velo-Cardio-Facial Syndrome. *Arch Gen Psychiatry* 1999; **56**: 940–5.
- 58 Papolos DF, Faedda GL, Veit S, Goldberg R, Morrow B, Kucherlapati R, et al. Bipolar spectrum disorders in patients diagnosed with velo-cardio-facial syndrome: does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? *Am J Psychiatry* 1996; **153**: 1541–7.
- 59 DeLisi L, Friedrich U, Wahlstrom J, Boccio-Smith A, Forsman A, Eklund K, et al. Schizophrenia and chromosome anomalies. *Schizophr Bull* 1994; **20**: 495–505.
- 60 Kumra S, Wiggs E, Krasnewich D, Meck J, Smith AC, Bedwell J, et al. An association between sex chromosome abnormalities and childhood psychosis. *J Am Acad Child Adolesc Psychiatry* 1998; **37**: 292–6.
- 61 Gécz J, Barnett S, Liu J, Hollway G, Donnelly A, Eyre H, et al. Characterization of the human glutamate receptor subunit 3 gene (GRIA3), a candidate for bipolar disorder and nonspecific X-Linked mental retardation. *Genomics* 1999; **62**: 356–68.
- 62 Tsiouris JA, Brown WT. Neuropsychiatric symptoms of Fragile X syndrome: pathophysiology and pharmacotherapy. *CNS Drugs* 2004; **18**: 687–703.
- 63 Jablensky A, Janota I, Shepherd M. Neuropsychiatric illness and neuropathological findings in a case of Klinefelter's syndrome. *Psychol Med* 1970; **1**: 18–39.
- 64 DeLisi L, Maurizio A, Svetina C, Ardekani B, Szulc K, Nierenberg J, et al. Klinefelter's syndrome (XXY) as a genetic model for psychotic disorders. *Am J Med Genet B Neuropsychiatr Genet* 2005; **135B**: 15–23.
- 65 Boks MPM, de Vette MHT, Sommer IE, van Rijn S, Giltay JC, Swaab H, et al. Psychiatric morbidity and X-chromosomal origin in a Klinefelter sample. *Schizophr Res* 2007; **93**: 399–402.
- 66 Boer H, Holland A, Whittington J, Butler J, Webb T, Clarke D. Psychotic illness in people with Prader Willi syndrome due to chromosome 15 maternal uniparental disomy. *Lancet* 2002; **359**: 135–6.
- 67 Verhoeven WMA, Tuinier S, Curfs LMG. Prader-Willi syndrome: the psychopathological phenotype in uniparental disomy. *J Med Genet* 2003; **40**: e112.
- 68 Vogels A, Matthijs G, Legius E, Devriendt K, Fryns JP. Chromosome 15 maternal uniparental disomy and psychosis in Prader-Willi syndrome. *J Med Genet* 2003; **40**: 72–3.
- 69 Soni S, Whittington J, Holland AJ, Webb T, Maina E, Boer H, et al. The course and outcome of psychiatric illness in people with Prader-Willi syndrome: implications for management and treatment. *J Intellect Disabil Res* 2007; **51**: 32–42.
- 70 Dykens E, Hodapp R. Research in mental retardation: Towards an etiologic approach. *J Child Psychol Psychiatry* 2001; **42**: 49–71.
- 71 Levitas AS, Reid CS. Rubinstein-Taybi syndrome and psychiatric disorders. *J Intellect Disabil Res* 1998; **42**: 284–92.
- 72 Malamud N. Neuropathology of organic brain syndromes associated with ageing. In *Ageing and the Brain* (3rd edn) (ed. CM Gaits): 63–87. Plenum, 1964.
- 73 Rovelet-Lecrux A, Hannequin D, Raux G, Le Meur N, Laquerrière A, Vital A, et al. APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. *Nat Genet* 2006; **38**: 24–6.
- 74 Sovner R, Hurley AD, Labrie R. Is mania incompatible with Down's syndrome? *Br J Psychiatry* 1985; **146**: 319–20.
- 75 Collacott RA, Cooper SA, McGrother C. Differential rates of psychiatric disorders in adults with Down's syndrome compared with other mentally handicapped adults. *Br J Psychiatry* 1992; **161**: 671–4.
- 76 Määttä T, Tervo-Määttä T, Taanila A, Kaski M, Iivanainen M. Mental health, behaviour and intellectual abilities of people with Down syndrome. *Down Syndrome Research and Practice* 2006; **11**: 37–43.
- 77 Mantry D, Cooper SA, Smiley E, Morrison J, Allan L, Williamson A, et al. The prevalence and incidence of mental ill-health in adults with Down syndrome. *J Intellect Disabil Res* 2008; **52**: 141–55.
- 78 Rollin HR. Personality in mongolism with special reference to catatonic psychosis. *Am J Ment Defic* 1946; **51**: 219–37.
- 79 Papazisis G, Mastrogianni A, Karastergiou A. Early-onset schizophrenia and obsessive-compulsive disorder in a young man with Dandy-Walker variant. *Schizophr Res* 2007; **93**: 403–5.