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Title:

The incidence, prevalence and clinical features of MECP2 duplication syndrome in Australian children

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Abstract

Aim: The aim of this study was to assess the incidence and prevalence of *MECP2* duplication syndrome in Australian children, and further define its phenotype.

Methods: The Australian Paediatric Surveillance Unit was used to identify children with *MECP2* duplication syndrome between June 2014 and November 2017. Reporting clinicians were invited to complete a questionnaire. Clinician data (n=20) was supplemented with information from the International Rett Syndrome Phenotype Database and from caregivers (n=7). Birth prevalence and diagnostic incidence were calculated.

Results: The birth prevalence of *MECP2* duplication syndrome in Australia was 0.65/100,000 for all live births and 1/100,000 for males. Diagnostic incidence was 0.07/100,000 person years overall and 0.12/100,000 person years for males. The median age at diagnosis was 23.5 months (range 0 months-13 years). A history of pneumonia was documented in three quarters of the clinical cases of whom half had more than nine episodes. Cardiovascular abnormalities were reported in three. A clinical vignette is presented for one child who died with severe idiopathic pulmonary hypertension. The majority (13/15) of males had inherited the duplication from their mothers and two had an unbalanced translocation.

Conclusion: *MECP2* duplication syndrome is a rare but important diagnosis in children because of the burden of respiratory illness and recurrence risk. Pulmonary hypertension is a rare life threatening complication. Array comparative genomic hybridization testing is recommended for children with undiagnosed intellectual disability or global developmental delay. Early cardiac assessment and ongoing monitoring is recommended in *MECP2* duplication syndrome.

Key words

Developmental, Genetics, *MECP2* duplication, Population Based, Intellectual disability

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What is already known on this topic

1. MECP2 duplication syndrome has been postulated to account for 1.1% of males with X-linked intellectual disability.
2. Common features include severe intellectual impairment, infantile hypotonia progressing over time to lower limb spasticity, dysmorphic facial features, recurrent respiratory infections, constipation and seizures.
3. Pulmonary hypertension is an emerging cause of early death in males with MECP2 duplication.

What this paper adds

1. The first documentation of incidence and prevalence of MECP2 duplication syndrome.
2. Further exploration of the phenotype of MECP2 duplication syndrome.
3. A clinical vignette of a child with MECP2 duplication syndrome who died from pulmonary hypertension.

Introduction

Methyl CpG binding protein 2 (MeCP2) is a global repressor of transcription, encoded by the *MECP2* gene on the X chromosome, Xq28.^{1,2} Dysregulation of epigenetic mechanisms underlie two disorders involving *MECP2*, Rett syndrome and *MECP2* duplication syndrome.³ Rett syndrome is caused by loss-of-function mutations or deletions in the *MECP2* gene, while duplications of the same gene result in MeCP2 overexpression.²⁻⁴ Early studies of *MECP2* duplication syndrome reported phenotypes of severe intellectual disability, infantile hypotonia, poor speech development, recurrent infections, epilepsy and progressive spasticity.⁴⁻⁷ Over time, other features have been recognised including regression of motor skills, behavioural symptoms and multiple comorbidities.^{8,9} Lower respiratory tract infections such as bronchiolitis and pneumonia are prevalent and associated with serious illness.^{8,10} Pulmonary hypertension resulted in early death in two cases.¹⁰

While most females appear to be either asymptomatic carriers, or display psychiatric symptoms such as anxiety and depression, phenotypes similar to males have also been reported.^{8,9,11,12}¹⁰ The majority of males with *MECP2* duplication syndrome inherit the duplication from their mother, however *de novo* cases have been reported.⁶ A female carrier will transmit the duplication to 50% of her sons who will all be affected whilst 50% of her daughters will carry the duplication.¹³ Males with an additional copy of the *MECP2* gene may also have additional copies of adjacent genes such as *IRAK1*, *FLNA* and *GDI1* which may result in a more severe phenotype with important implications for immunological,

gastrointestinal and other neurological functioning.¹⁴⁻¹⁶ Some females may be asymptomatic due to skewed X-inactivation that preferentially inactivates the rearranged chromosome.^{17, 18} Additionally, triplication of the *MECP2* locus has been reported to cause a more severe phenotype.¹⁹

Although one study reported the presence of a *MECP2* duplication in 3/283 (1.1%) of males with X-linked intellectual disability who had normal karyotype and fragile X studies, there have been no published population-based studies assessing the incidence and prevalence of *MECP2* duplication syndrome.¹⁴ Using these aforementioned data¹⁴ and data on the prevalence of X-linked intellectual disability,^{20, 21} we estimated an Australian male birth prevalence of *MECP2* duplication syndrome of 1.6/100,000 live births.

Using clinical information provided by doctors reporting to the Australian Paediatric Surveillance Unit (APSU),²² this study has assessed the incidence and prevalence of *MECP2* duplication syndrome in Australia, and further defined its clinical features.

Materials and methods

Data sources

The APSU, established in 1993, facilitates national surveillance of rare conditions through monthly reporting by approximately 1400 to 1500 paediatricians (personal communication) across Australia. We identified children with *MECP2* Duplication syndrome using the APSU (Figure 1) for the period between June, 2014 and November, 2017.²² Reporting clinicians were invited to complete a questionnaire on their patient's development and clinical characteristics (including dysmorphic features, comorbidities, medical history and features that occur in Rett syndrome) as well as family history. Clinicians were also asked to provide genetic reports when possible.

The individual patient questionnaires were supplemented, where available, with information held in the International Rett Syndrome Phenotype Database (InterRett). Established in 2002,

InterRett contains genotypic and phenotypic information provided by clinicians and caregivers on individuals with Rett syndrome and associated disorders including *MECP2* duplication syndrome.^{8, 23} The information used from InterRett was provided by caregivers of affected children, as in a previous study.⁸ Ethics approval was obtained from the University of Western Australia Human Research Ethics Committee while the family of the child described in the clinical vignette provided consent for publication.

Data analysis

Birth prevalence and incidence of diagnosis were estimated using methods employed in previous research.^{24, 25}

When calculating birth prevalence, the numerator consisted of Australian children (or males) born in a particular year from July 1, 2002 to June 30, 2016 and diagnosed with *MECP2* duplication syndrome between July 1, 2005 and June 30, 2017. The denominator was the number of live births (or male births) in Australia for the year.

When calculating diagnostic incidence, the numerator was all Australian children (or males) born since July 1, 2002 and diagnosed in a particular year from July 1, 2005 to June 30, 2017. The denominator was the number of individuals (or males) at risk of diagnosis in the same year. For example, in 2005 the denominator was all Australian children under 3 years of age on June 30, 2005, while in 2015 the denominator was all children under 13 years of age on June 30, 2015.

The Australian Bureau of Statistics' Estimated Resident Population (ERP), calculated on June 30 each year, was the source of population data for the incidence and prevalence calculations.²⁶ Our oldest paediatric case was born in July 2002, and *MECP2* Duplication syndrome was first described as a cause of severe intellectual disability in 2005.⁴ One case reported by clinicians was an adult patient (aged 22 years) and was excluded from calculations of birth prevalence, diagnostic incidence, and age of diagnosis and ascertainment.

The age of diagnosis was obtained from either InterRett or follow-up contact with reporting clinicians. If this was unattainable, an age was estimated from sources including the date of genetic testing, age of ascertainment, or contact with families.

Developmental milestones were only reported in those who were at an age where they would be expected to learn that skill.²⁷ For example use of words for communication was only examined from the age of nine months onwards.²⁸ The minimum age at which a patient could be diagnosed with autism was defined as two years.

Descriptive statistics were reported as median and range values or proportions where appropriate. Statistical analysis was performed using STATA software (version 13).²⁹

Results

As of census date (November 6, 2017), questionnaire data was available for 20 individuals (16 males, 4 females), including two male sibling pairs. Through InterRett questionnaire data, seven additional males were identified for inclusion in the incidence/prevalence calculations. Of those, two were an additional male sibling pair, and one was the brother of a questionnaire participant. Among the total 27 individuals, four (two of whom were ascertained by clinicians and two through InterRett), died prior to the census date.

Prevalence/Incidence

The median age of diagnosis of *MECP2* duplication syndrome was 23.5 months (IQR 12.3-77.5 months, range: 0 months-13 years). The overall (n=26) birth prevalence from 2002-2016 (Figure 2) was calculated as 0.65/100,000 live births, while the birth prevalence for males (n=22) was 1.06/100,000 live male births. The diagnostic incidence from 2005-2017 for children born from 2002-2017 (n=24), seen in Figure 3, was calculated as 0.07/100,000 person years, while the male (n=20) diagnostic incidence was 0.12/100,000 person years.

Clinical cases

Cases were ascertained from paediatricians at a median age of 8.3 years (range: 0.4-13.8 years). Developmental delay was the most common early presentation, present in 17/20, and hypotonia was reported in 15/20 (Table 1). One female with a *de novo* duplication presented with mild pulmonary stenosis and a duplex left kidney. A male with an unbalanced X:22 translocation also had a vascular ring.

Inheritance data was available for 17/20 cases. Thirteen males inherited the duplication from their mother, and two females had *de novo* duplications. Two males had unbalanced translocations, arising from balanced X:14 and X:22 translocations in their respective mothers.

Dysmorphic features

Dysmorphic features were described in 14/16 males and 2/4 females (total 16/20). The commonly reported features included depressed nasal bridge (n=5), plagiocephaly (n=3), prominent ears (n=3) and tapered fingers (n=3). Both females with dysmorphic features had macrocephaly and one male had microcephaly. Five of 16 males had cryptorchidism, and four of those also had micropenis (Table 1).

Development and behaviour

Severe intellectual impairment or global developmental delay was present in all males and three of the four females. In the children aged nine months or older, 4/15 males and 3/4 females (total 7/19, range 3.9-10.4 years) could speak words (two in sentences, one in phrases and the remainder only single words) at the time of ascertainment.

Over 90% (11/12 males and 3/3 females) acquired independent sitting, with just over three quarters of males and all females learning to crawl (Table 3). At ascertainment, over half of males and two of three females could walk independently, with the majority having an ataxic gait. One of those eight males later lost the ability to walk while all females maintained the ability. In just over 40% (7/15 males and 1/4 females) clinicians reported some regression in

gross motor skills. Tone was decreased in over 60% (10/15 males and 2/4 females; aged between 4 months to 12 years) but was increased in 15% (3/15 males and 0/4 females; 9 to 22 years) and considered normal in just over 20% (2/15 males and 2/4 females; 7 to 14 years) of the patients.

For those aged two years and over, just under half of the males and 3/3 females (total 8/15) had a diagnosis of autism. Repetitive behaviours were the most common symptom of autism observed, reported in three quarters of patients (Table 1). Interestingly, bruxism, night time laughter and choreiform movements were also fairly common in those diagnosed with autism each affecting 3/8 individuals. Sleep disturbance was the most common behavioural feature and was reported in 14/16.

Medical history

Seizures were reported in 11 of the 20 cases (Table 1), with a median age of onset of 5.8 years (range 8 months–10 years) and eight of these were on anticonvulsant medication. Constipation was reported for half and difficulty swallowing in just over a half with two individuals required gastrostomy feeding.

A history of ear or respiratory infections was reported in 18/20, with pneumonia being the most common infection and reported in three quarters (Table 2). Of those with a history of pneumonia, just over half had nine or more episodes in their lifetime, with the youngest being six years old. Two patients were treated with prophylactic antibiotics.

Two cases died during the course of the study, aged 25 years and 11 months, with the causes of death being sepsis and pulmonary hypertension, respectively. The child who died suddenly from pulmonary hypertension was diagnosed with *MECP2* duplication syndrome at four months of age. (Box 1). He presented with hypotonia and feeding difficulties. During infancy he suffered with pneumonia, bronchiolitis and otitis media. Upon hospitalisation at 11 months and seven days, he was diagnosed with right ventricular hypertrophy secondary to pulmonary hypertension. Shortly after admission, the child had a cardiac arrest which resulted in hypoxic

ischaemic brain injury. Extracorporeal membrane oxygenation was withdrawn and he died shortly afterwards.

Discussion

Since first being reported in 2005,⁴ progress has been made in further describing the characteristics of *MECP2* duplication syndrome, with two large studies being published in the past three years.^{8, 10} This study further explores the phenotype of *MECP2* duplication syndrome, and is the first to estimate its incidence and prevalence using population-based methods.

We found the male birth prevalence to be approximately 1/100,000 which is lower than previously extrapolated.^{20, 21} Conversely, with a total birth prevalence of 0.65/100,000, the representation of females to males was higher than the 1:7 ratio demonstrated in our previous study.⁸ Birth prevalence shows an average downward trend over time, however with the median age of diagnosis being almost two years of age, we expect the values of later years of our observation period to be underestimated. The three peaks in diagnostic incidence correspond to three sets of brothers being diagnosed within months of each other. Given the small population identified in this study, and high recurrence risk, the effect of these clustered diagnoses would be comparatively large. Although the median age of diagnosis was ~24 months, the interquartile range was 12.3-77.5 months such that one quarter of the children would be over six and a half years at diagnosis. The oldest individuals to be diagnosed were a child of 13 years and an adult of 22 years clearly demonstrating that this disorder is not being diagnosed in a timely manner in Australia and also suggesting that we have underestimated the true prevalence.

There was a high burden of respiratory illness, with over a third having more than nine episodes of pneumonia. This pattern of recurrent respiratory infections is consistent with the findings of our previous study⁸ and the recent French case series.¹⁰ Since IgA/IgG₂ deficiency has been shown to be associated with increased susceptibility to infections in *MECP2* duplication syndrome possibly related to a duplication of the *IRAK1* gene, a potential

treatment option in addition to supportive measures and antibiotic prophylaxis is immunoglobulin supplementation,³⁰ as described in a recent case study.³¹ Additionally, physical therapy can assist in the maintenance of respiratory health³² although the roles of gastrostomy^{33, 34} and immunoglobulin therapy³¹ remain uncertain.

Three individuals had cardiovascular abnormalities, with one dying suddenly from pulmonary hypertension during infancy. Pulmonary hypertension was also present in three of the 59 cases in the French case series and was the cause of death in two.¹⁰ We support their recommendation for baseline cardiac assessment at time of *MECP2* Duplication syndrome diagnosis and regularly thereafter.¹⁰

Poor functional abilities and intellectual disability were common in the individuals in our study, as has been found previously.¹⁰ Hypotonia was also common, in keeping with the findings from the French case series.¹⁰ Scoliosis however was reported less frequently than in that study¹⁰ but this would be consistent with ours being a younger population. Given the respiratory and other morbidities which can be exacerbated by scoliosis, regular monitoring by an orthopaedic specialist, as recommended for Rett syndrome, should be an important component of overall clinical management.³⁵ We were somewhat surprised to find that choreiform movements were reported in seven patients, but this is consistent with previous and recent literature.^{9, 36} More than half of those older than two years were diagnosed with autism in keeping with previous reports and manifested as repetitive behaviours, poor eye contact, anxiety, compulsive behaviours and hand stereotypies.^{9, 37} We also identified similarities in behavioural features between our cohort and females with Rett syndrome, including sleep disturbances, bruxism, night laughing and screaming spells.³⁸⁻⁴⁰

Dysmorphic features have been reported frequently in the literature,^{4, 8, 10-12, 15, 41} and were described in 16 of our 20 cases. While dysmorphic facial features including depressed nasal bridge, and prominent ears were the most recognised, the proportions were less than that described in the French case series which had the advantage of clinical photographs.¹⁰ Cryptorchidism was found in a similar proportion of males (5/16) to that in the French case series¹⁰ but we found a higher proportion of micropenis. Reliance on recall by clinicians,

many of whom were not clinical geneticists with expertise in dysmorphology, is likely to account for these differences.

We identified females who expressed the clinical phenotype, consistent with the findings of our previous study⁸ and other literature.^{18, 42-46} Two of four females with genetic data had *de novo* duplications, described in the literature as being associated with a severe phenotype.^{18, 45, 46} Most males in our study inherited the duplication from their mother and the remaining 2/15 had an unbalanced translocation.

A key strength of this study is the use of the APSU, with 92% of Australian paediatricians and paediatric sub-specialists participating in surveillance.²² We recognise that lack of reporting could have a major influence on prevalence estimates, given the rarity of the disorder. However, we have attempted to minimise this through the additional use of InterRett family-reported data. We also contacted some clinicians who were initially unable to complete all aspects of the questionnaire to minimise missing data.

In conclusion, we have defined the incidence and prevalence of *MECP2* duplication syndrome in Australian children and have expanded the description of the clinical phenotype. Respiratory illness has a high burden on these children, and we suggest early and aggressive supportive treatments. Moreover, early cardiac screening is important to identify pulmonary hypertension, given that it has been reported in association with sudden death. There remains an urgent need for the development of an international database with a longitudinal component to further inform the natural history of this disorder.^{8, 23}

With the high familial inheritance it is critical that the diagnosis of *MECP2* duplication syndrome be made in a timelier manner than has been occurring to date in Australia. We endorse the need for early chromosomal microarray testing for those with global developmental delay, especially in the presence of dysmorphic features and developmental and behavioural abnormalities.

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Table 1. Clinical features of males and females with *MECP2* Duplication syndrome.

	Males and females (total= <i>n</i>)	Total proportion (%)	Males (total= <i>n</i>)	Females (total= <i>n</i>)
Clinical presentation				
Developmental delay	17 (20)	85	15 (16)	2 (4)
Hypotonia	15 (20)	75	14 (16)	1 (4)
Feeding problems	9 (20)	45	8 (16)	1 (4)
Breathing problems	6 (20)	30	6 (16)	0 (4)
Dysmorphic features	5 (20)	25	4 (16)	1 (4)
Stereotypic movements	2 (20)	10	2 (16)	0 (4)
Dysmorphic features				
Face	11 (20)	55	10 (16)	1/4
Head	8 (20)	40	6 (16)	2/4
Genitals	5 (20)	25	5 (16)	0/4
Hands	5 (20)	25	4 (16)	1/4
Feet	5 (20)	25	4 (16)	1/4
Other	4 (20)	20	2 (16)	2/4
Symptoms of autism reported in those with an autism diagnosis				
Autism diagnosis	8 (20)	40	5 (16)	3 (4)
Repetitive behaviours	6 (8)	75	4 (5)	2 (3)
Difficulty using eye gaze	5 (8)	63	3 (5)	2 (3)

Anxiety	4 (8)	50	1 (5)	3 (3)
Difficulty adjusting to change	4 (8)	50	3 (5)	1 (3)
Hand stereotypies	4 (8)	50	3 (5)	1 (3)
Compulsive behaviours	3 (8)	38	1 (5)	2 (3)
Gaze avoidance	3 (8)	38	2 (5)	1 (3)
Other behavioural features				
Sleep disturbances	14 (16)	88	12 (14)	2 (2)
Bruxism	9 (15)	60	9 (14)	0 (1)
Night laughing	7 (14)	50	7 (13)	0 (1)
Choreiform movements	7 (15)	47	6 (13)	1 (2)
Uncontrolled screaming spells	5 (15)	33	5 (13)	0 (2)
Medical symptoms and comorbidities				
Seizures	11 (20)	55	10 (16)	1 (4)
Difficulty swallowing	11 (20)	55	10 (16)	1 (4)
Constipation	10 (20)	50	10 (16)	0 (4)
Sleep apnoea	8 (20)	40	7 (16)	1 (4)
Gastro-oesophageal reflux	5 (20)	25	5 (16)	0 (4)
Abdominal bloating	4 (20)	20	4 (16)	0 (4)
Scoliosis	3 (20)	15	3 (16)	0 (4)

Shallow breathing	1 (20)	5	1 (16)	0 (4)
Breathlessness	1 (20)	5	1 (16)	0 (4)
Apnoea whilst awake	1 (20)	5	1 (16)	0 (4)

Table 2. Ear and respiratory issues.

	Number, total $n = 20$ (proportion, %)	Number with over nine episodes (proportion in number affected, %)
Pneumonia	15 (75)	8 (53)
Other respiratory infection	12 (60)	5 (42)
Otitis media	10 (50)	3 (30)
Bronchiolitis	7 (35)	1 (14)
Asthma	3 (15)	1 (33)

Table 3. Gross motor function.

	Males (total= <i>n</i>)	Females (total= <i>n</i>)	Males and females (total= <i>n</i>)	Median age, range (months)
Gross motor skills				
Acquisition of independent sitting	11 (12)	3 (3)	14 (15)	18, 9-48
Acquisition of crawling	10 (13)	3 (3)	13 (16)	25, 10-80
Acquisition of independent walking	8 (14)	2 (3)	10 (17)	48, 18-96
Walking with ataxic gait	6 (8)	1 (2)	7 (10)	125, 27-166
Lost ability to walk	1 (8)	0	1 (10)	156
Regression of gross motor skills	7 (15)	1 (4)	8 (19)	86, 24-120

Figure 1. Method of data collection for Phase 1. Adapted from He et al.²²

Figure 2. The birth prevalence of *MECP2* Duplication syndrome in Australia, from 2002 to 2016, smoothed over 2 years. \square , total birth prevalence; \square , male birth prevalence.

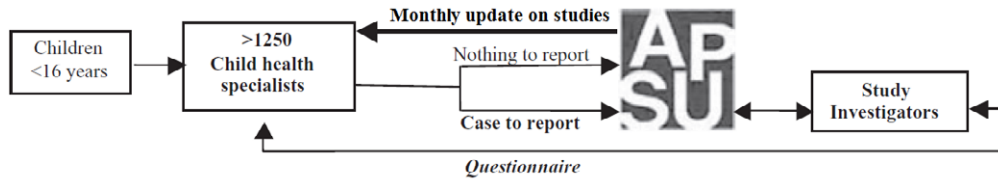
Figure 3. The rate of *MECP2* Duplication syndrome diagnosis in Australia between 2005 and 2017 for people born between 2002 and 2017, smoothed over 2 years. \square , total diagnostic incidence; \square , male diagnostic incidence.

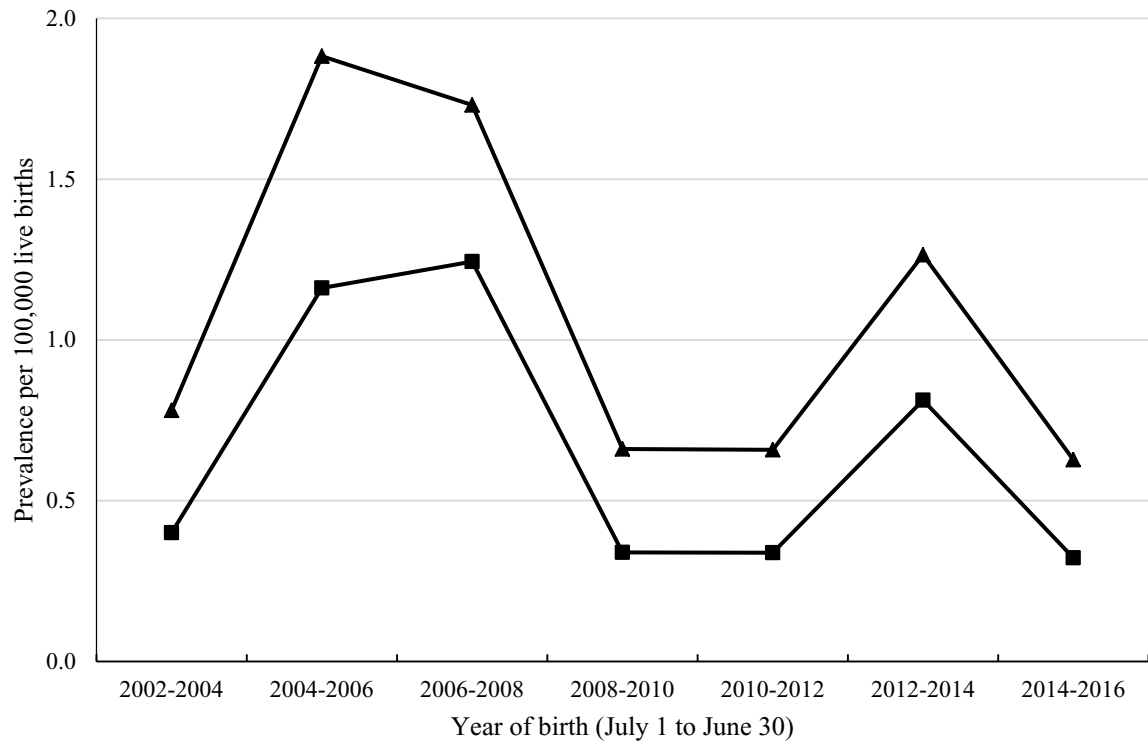
Box 1. Clinical vignette of child with *MECP2* duplication syndrome who died from severe idiopathic pulmonary hypertension at age 11 months.

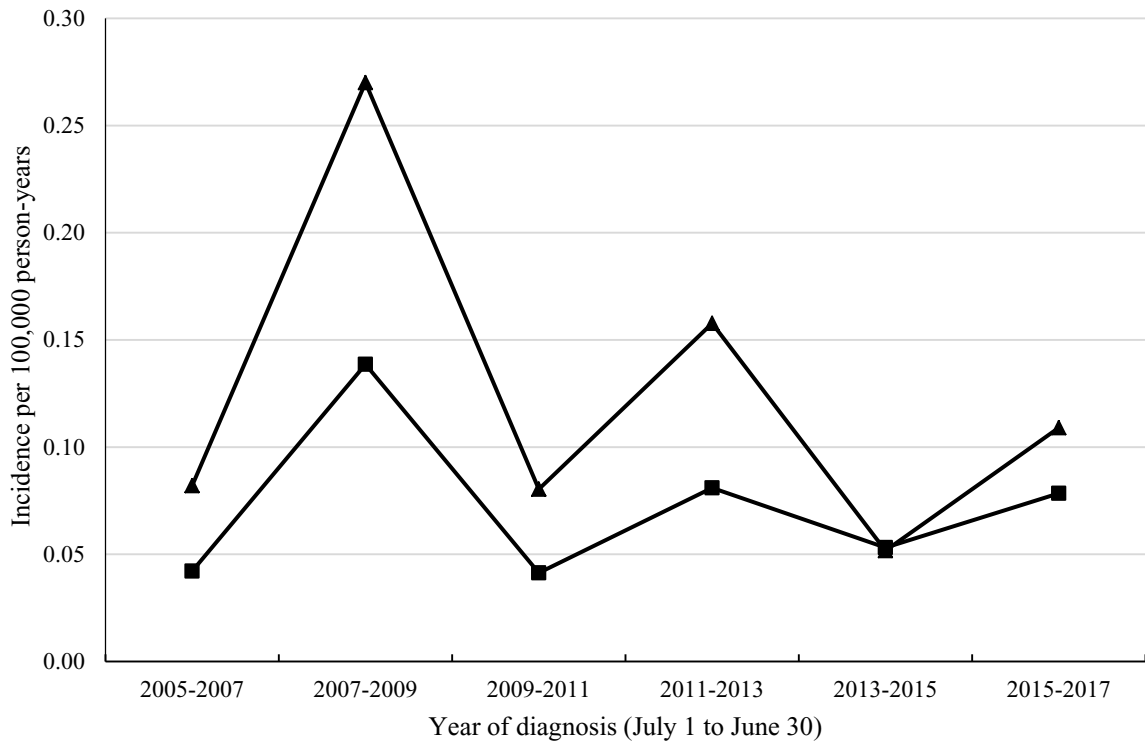
At diagnosis, the child was a 4 month old male presenting with hypotonia, and feeding difficulties. He was noted to have cryptorchidism and micropenis. The child experienced several episodes of pneumonia, bronchiolitis, otitis media and other respiratory infections. He did not develop seizures. This child's duplication was due to an unbalanced translocation between the q arm of the X chromosome and the p arm of chromosome 14. His mother carried a balanced translocation.

The child presented to an Emergency Department aged 11 months and 7 days with irritability, lethargy and generalised oedema. An echocardiogram demonstrated right ventricular hypertrophy secondary to pulmonary hypertension. CT pulmonary angiography confirmed pulmonary hypertension with no evidence of pulmonary emboli. Soon after presentation, the child had a cardiac arrest, required resuscitation and was managed with extracorporeal membrane oxygenation (ECMO). A brain CT scan showed severe hypoxic ischaemic brain injury to his brain. Clinicians and parents together made the decision to withdraw ECMO and the child died.

At autopsy, the child's combined lung weight was under the 5th percentile for age, the heart weight was over the 75th percentile, with significant enlargement of the right atrium and ventricle. The cause of death was determined to be severe idiopathic pulmonary hypertension, leading to cardiorespiratory arrest and hypoxic ischaemic cerebral insult.







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Conflicts of Interest

There were no conflicts of interest in the writing of this paper.