

# **Effectiveness of posthumous molecular diagnosis from a kept baby tooth**

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In September 1991, a seven year old girl died of pneumonia after a five year history of undiagnosed neurological decline. She was the second live-born child of a couple with a healthy elder son, now in his mid-twenties and with a partner. The girl was born at term after a pregnancy complicated only by slight early bleeding. Two previous pregnancies had resulted in stillbirths due to abruptio placentae. The child thrived during her first year and there were

no parental concerns. At 16 months, however, unease emerged because she was not walking independently. Parental anxiety was further heightened by loss of previously acquired words.

At 17 months, she fell down steps, hitting her head on a cement floor but did not lose consciousness. By her second birthday functional hand use, which had developed to the stage of self-feeding and pushing toy cars, was replaced by repetitive hand movements, including relentless finger chewing and sucking. Seizures, which responded only partially to anticonvulsant therapy, started after her 3<sup>rd</sup> birthday. Between the ages of two and four years she underwent intensive neurological investigations which did not reveal a cause for her condition. Her deterioration continued and, in the absence of a diagnosis, her parents began to wonder whether they had somehow been responsible. As well as fears about the role of a vaccination a month prior to the onset of symptoms, mother harboured concerns about a possible inherited disorder, and father feelings of guilt about the circumstances of her fall.

During the child's lifetime a definite medical diagnosis was never made although Rett syndrome had been suggested by an occupational therapist visiting her school. An article about Rett syndrome in a women's magazine in 2002, (eleven years after the child's death), rekindled the mother's interest in exploring this diagnosis. By now she had become concerned about the potential genetic risk for any future grandchildren. In 2004 contact with the Australian Rett Syndrome project,<sup>1</sup> resulting from an internet search, led to the family's participation and completion of a study questionnaire. Information provided was clinically consistent with Rett Syndrome and the mother enquired about whether diagnostic confirmation could be provided by examination of DNA from a kept baby tooth or lock of hair. After discussion and explanation about the limitations of the test sensitivity (~80%) it was agreed to proceed.

The tooth was cut open laterally (figure 1), the pulp removed and digested with Proteinase K and DTT, and DNA extracted using 5% Chelex 100.<sup>2</sup> Mutation screening by bidirectional sequencing of the *MECP2* coding regions revealed a nonsense mutation (c.502C>T; p.R168X), which is a well known recurrent mutation causative of Rett syndrome.<sup>3</sup>

The result and its implications were explained to the family. Beyond feelings of relief from finally understanding the cause of their daughter's condition and subsequent death, diagnostic confirmation has helped in other ways. The sense of guilt about the child's fall at two years of age has gone, as have the longstanding fears about her vaccination as a toddler. Explanation (1) of the nature of X-linked inheritance (*MECP2* gene is on the X chromosome) and (2) that the rare male-associated *MECP2* phenotype involves neurological impairment often of neonatal onset<sup>4</sup> has allowed the couple to appreciate that their son's good health alone demonstrates that he could not have inherited the mutation responsible for his sister's illness.

Posthumous molecular genetic diagnosis using DNA from commonly treasured baby teeth is now technically simple. Although common in forensic medicine, accessing DNA posthumously from unconventional sources such as deciduous dental pulp has been seldom used in genetic counselling situations.<sup>5</sup> We proceeded with this investigation on the basis of a clear clinical rationale. As well as diagnostic confirmation, the result has also brought closure to many long-standing psychological stresses for a couple, one sign of which was the drive that eventually prompted the investigation 14 years after the death of their daughter.

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1. Colvin L, Fyfe S, Leonard S, et al. Describing the phenotype in Rett syndrome using a population database. *Arch Dis Child* 2003; 88:38-43.
  2. Walsh PS, Metzger DA, Higuchi R. Chelex 100 as a medium for simple extraction of DNA for PCR-based typing from forensic material. *Biotechniques* 1991;10:506-13.
  3. Christodoulou J, Grimm A, Maher T, Bennetts B. RettBASE: The IRSA MECP2 variation database-a new mutation database in evolution. *Hum Mutat* 2003;21:466-72.
  4. Moog U, Smeets E, Van Roozendaal K, Schoenmakers S, Herbergs J, Schoonbrood-Lenssen A, Schrandt-Stumpel C. Neurodevelopmental disorders in males related to the gene causing Rett syndrome in females (MECP2) *Eur J Paed Neurol* 2003;07:5-12.
  5. Restagno G, Ferrone M, Doriguzzi C, Palmucci L, Mongini T, Carbonara A. Carrier detection of Duchenne muscular dystrophy through analysis of DNA from deciduous teeth of a dead affected child. *Prenat Diagn* 1995;15:672-4.

Caption for Figure 1

Baby tooth-uncut and cut surfaces.

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