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The imprinted gene and parent-of-origin effect database now includes parental origin of *de novo* mutations

Rivka L. Glaser*, Joshua P. Ramsay[1] and Ian M. Morison[2]

Department of Biology, Massachusetts College of Liberal Arts, North Adams, MA 01247, USA, [1]Department of Microbiology, University of Otago, PO Box 56, Dunedin, New Zealand and [2]Department of Biochemistry, University of Otago, PO Box 56, Dunedin, New Zealand

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ABSTRACT

The imprinted gene and parent-of-origin effect database (www.otago.ac.nz/IGC) consists of two sections. One section catalogues the current literature on imprinted genes in humans and animals. The second, and new, section catalogues current reports of parental origin of *de novo* mutations in humans alone. The addition of a catalogue of *de novo* mutations that show a parent-of-origin effect expands the scope of the database and provides a useful tool for examining parental origin trends for different types of spontaneous mutations. This new section includes >1700 mutations, found in 59 different disorders. The 85 imprinted genes are described in 152 entries from several mammalian species. In addition, >300 other entries describe a range of reported parent-of-origin effects in animals.

INTRODUCTION

'Parent-of-origin effects' is a broad term that encompasses two distinct phenomena—parent-of-origin effects on transcription, and parent-of-origin effects on mutation rates. A parent-of-origin effect on transcription, or genomic imprinting, results from epigenetic modification of the genome which, in turn, results in unequal transcription of parental alleles. For these imprinted genes, expression of the alleles is dependent upon the sex of the parent from which they were inherited (1). A parent-of-origin effect on mutation rate, however, refers to the preferential occurrence of some spontaneous mutations in either the father's or the mother's germ line. The mechanisms by which these spontaneous mutations arise depend upon the parental germ line in which the mutation occurred. For example, base substitutions, arising from errors during replication, tend to be paternal in origin, owing to the greater number of cell divisions in spermatogenesis as compared with oogenesis (2). Chromosomal abnormalities, however, tend to be maternal in origin. Oocytes are arrested in prophase of meiosis I until sexual maturity, when one oocyte per month is selected to resume the cell cycle. It is thought that the longer the oocytes are arrested in meiosis, the greater the chance for a nondisjunction event to occur (3). Advanced parental age seems to influence the development of some, but not all, of these mutations (also referred to as the paternal or maternal age effect) (2).

THE DATABASE

In 1998, the catalogue of imprinted genes and parent-of-origin effects was first published (4). This catalogue served as the basis for the development of a more comprehensive, searchable, online database, made publicly available in 1999. The original database included 41 imprinted genes, and other parent-of-origin effects, including some records on the parental origin of spontaneous mutations (5).

We have added recently a comprehensive section on spontaneous mutations that show a bias with respect to their parental origin. This new part of the database can be searched according to mutation type, disorder, chromosomal location, gene name and inheritance pattern. Each entry in the database is hyperlinked to the relevant reference in PubMed. Outcomes of the search are presented in a tabular format with the following information: disorder, inheritance pattern, incidence of disorder, gene name, chromosomal location, evidence of a paternal or maternal age effect, mutation type and any recurrent mutations associated with a parent-of-origin effect, number of paternal mutations, number of maternal mutations and PubMed reference (e.g. Table 1). In the case of base substitutions, data are separated according to the type of base substitution (missense mutation, nonsense mutation or

*To whom correspondence should be addressed. Tel: +1 413 662 5548; Email: rglaser@mcla.edu
Correspondence may also be addressed to Ian M. Morison. Tel: +64 3 479 5391; Fax +64 3 479 7738; Email: ian.morison@otago.ac.nz

Table 1. Example of report for parental origin of *de novo* mutations showing base substitutions within a CpG dinucleotide

Disorder	Inheritance	Incidence	Gene	Chromosomes	Paternal age effect	Maternal age effect	Recurrent mutations	Mutation type	TS/TV	No. of pat. cases	No. of mat. cases	Reference
Apert	AD	1/160 000	FGFR2	10q26	Y	N	S252W (C→G) P253R (C→G)	P(MS)–CpG	TV	57	0	Moloney,D.M. *et al.* (1996) (6)
Achondroplasia	AD	1/10 000	FGFR3	4p16.3	Y	N	G380R (G→A) G380R (G→C)	P(MS)–CpG	TS, TV	40	0	Wilkin DJ (1998) (7)
Hutchinson–Gilford Progeria syndrome	AD		LMNA	1q21.2	Y	N	G608G (C→T)	P(MS)–CpG	TS	4	0	Eriksson M *et al.* (2003) (8)
Hutchinson–Gilford Progeria syndrome	AD		LMNA	1q21.2	Y	N	G608G (C→T)	P(MS)–CpG	TS	3	0	D'Apice MR *et al.* (2004) (9)
Muenke syndrome	AD	1/30 000	FGFR3	4p16.3	Y		c749C→G	P(MS)–CpG	TV	10	0	Rannan-Eliya SV *et al.* (2004) (10)
von Hippel-Lindau	AD	1/36 000	VHL	3p25–p26	N			P(MS)–CpG	TS	2	0	Richards FM *et al.* (1995) (11)
Rett syndrome	XD	1/10 000–1/15 000 females	MECP2	Xq28			R294X	P(MS)–CpG	TV	0	1	Girard M *et al.* (2001) (12)
Rett syndrome	XD	1/10,000-1/15,000 females	MECP2	Xq28			R294X	P(NS)–CpG	TS	4	0	Girard M *et al.* (2001) (12)
Rett syndrome	XD	1/10 000–1/15 000 females	MECP2	Xq28			R168X (C→T) R270X (C→T)	P(NS)–CpG	TS	2	1	Amir RE *et al.* (2000) (13)
Rett syndrome	XD	1/10 000–1/15 000 females	MECP2	Xq28	N			P(MS)–CpG	TS	7	1	Trappe R *et al.* (2001) (14)
Rett syndrome	XD	1/10 000–1/15 000 females	MECP2	Xq28	N		c502C→T c880C→T R270X(C→T)	P(NS)–CpG	TS	13	0	Trappe R *et al.* (2001) (14)
Hemophilia B	XR	1/30 000	FIX	Xq27.1–27.2	Y	Y		P–CpG	TS	6	3	Ketterling RP *et al.* (1999) (15)
Hemophilia B	XR	1/30 000	FIX	Xq27.1–27.2				P–CpG	TS	8	12	Green PM *et al.* (1999) (16)

AD, autosomal dominant; XD, X-linked dominant; XR, X-linked recessive; P, point mutation; MS, missense mutation; NS, nonsense mutation; CpG, mutation in a CpG dinucleotide; TS, transition mutation; TV, transversion mutation.

splice site mutation), whether the mutation is a transition or transversion mutation, and whether the base substitution falls within a CpG dinucleotide. For deletions and insertions, the distinction is made between large deletions and insertions (>20 bp) and small deletions and insertions (<20 bp). This size distinction is made based upon the possibility of different mechanisms contributing to these different types of mutations, and therefore potentially different parental origins (2). In general, large deletions do not appear to have a parent-of-origin effect, whereas small deletions tend to be more paternal in origin.

Currently, >1700 mutations with a parent-of-origin effect are catalogued in this database. These mutations are found in 59 different disorders. Large deletions comprise the largest category in this database, with ~900 mutations catalogued. Base substitutions form the second largest category in the database, with ~400 mutations.

The other major section of the database includes known imprinted genes and observations of other putatively imprinted genes. Of the 464 database entries, 152 entries describe 85 unique imprinted genes in humans, mice, cattle, sheep, pigs, rats and marsupials, as well as 14 genes for which the evidence of imprinting is conflicting or provisional. The imprinted genes have been described recently in a review publication (17). The phenotypic consequences of human and mouse uniparental disomies are described in 31 entries. An additional 186 entries report parent-of-origin effects in the transmission or linkage of simple and complex genetic conditions including human diseases and animal quantitative traits.

DATABASE ACCESS AND USAGE

The imprinted gene and parent-of-origin effect database is housed at the University of Otago in Dunedin, New Zealand and can be accessed at www.otago.ac.nz/IGC. The database is maintained by the corresponding authors who welcome submissions and comments and is updated as new literature is published. Submissions to the imprinted gene database should be directed to I.M.M. and submissions to the parental origin of *de novo* mutations database should be directed to R.L.G. Users of the database are asked to cite this article in their publication.

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REFERENCES

1. Reik,W. and Walter,J. (2001) Genomic imprinting: parental influence on the genome. *Nature Rev. Genet.*, **2**, 21–32.
2. Glaser,R.L. and Jabs,E.W. (2004) Dear Old Dad. *Sci. Aging Knowledge Environ.*, **2004**, re1. Review.
3. Crow,J.F. (2000) The origins, patterns and implications of human spontaneous mutation. *Nature Rev. Genet.*, **1**, 40–47.
4. Morison,I.M. and Reeve,A.E. (1998) A catalogue of imprinted genes and parent-of-origin effects in humans and animals. *Hum. Mol. Genet.*, **7**, 1599–1609.
5. Morison,I.M., Paton,C.J. and Cleverly,S.D. (2001) The imprinted gene and parent-of-origin effect database. *Nucleic Acids Res.*, **29**, 275–276.
6. Moloney,D.M., Slaney,S.F., Oldridge,M. *et al.* (1996) Exclusive paternal origin of new mutations in Apert syndrome. *Nat. Genet.*, **13**, 48–53.
7. Wilkin,D.J., Szabo,J.K., Cameron,R. *et al.* (1998) Mutations in fibroblast growth-factor receptor 3 in sporadic cases of achondroplasia occur exclusively on the paternally derived chromosome. *Am. J. Hum. Genet.*, **63**, 711–716.
8. Eriksson,M., Brown,W.T., Gordon,L.B. *et al.* (2003) Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature*, **423**, 293–298.
9. D'Apice,M.R., Tenconi,R., Mammi,I. *et al.* (2004) Paternal origin of LMNA mutations in Hutchinson-Gilford progeria. *Clin. Genet.*, **65**, 52–54.
10. Rannan-Eliya,S.V., Taylor,I.B., De Heer,I.M. *et al.* (2004) Paternal origin of FGFR3 mutations in Muenke-type craniosynostosis. *Hum. Genet.*, **115**, 200–207.
11. Richards,F.M., Payne,S.J., Zbar,B. *et al.* (1995) Molecular analysis of de novo germline mutations in the von Hippel-Lindau disease gene. *Hum. Mol. Genet.*, **4**, 2139–2143.
12. Girard,M., Couvert,P., Carrie,A. *et al.* (2001) Parental origin of de novo MECP2 mutations in Rett syndrome. *Eur. J. Hum. Genet.*, **9**, 231–236.
13. Amir,R.E., Van den Veyver,I.B., Schultz,R. *et al.* (2000) Influence of mutation type and X chromosome inactivation on Rett syndrome phenotypes. *Ann Neurol.*, **47**, 670–679.
14. Trappe,R., Laccone,F., Cobilanschi,J. *et al.* (2001) MECP2 mutations in sporadic cases of Rett syndrome are almost exclusively of paternal origin. *Am. J. Hum. Genet.*, **68**, 1093–1101.
15. Ketterling,R.P., Vielhaber,E., Li,X. *et al.* (1999) Germline origins in the human F9 gene: frequent G:C–>A:T mosaicism and increased mutations with advanced maternal age. *Hum. Genet.*, **105**, 629–640.
16. Green,P.M., Saad,S., Lewis,C.M. *et al.* (1999) Mutation rates in humans. I. Overall and sex-specific rates obtained from a population study of hemophilia B. *Am. J. Hum. Genet.*, **65**, 1572–1579.
17. Morison,I.M., Ramsay,J.P. and Spencer,H.G. (2005) A census of mammalian imprinting. *Trends Genet.*, **21**, 457–465.