

Recurrence of perinatal lethal osteogenesis imperfecta in sibships: Parsing the risk between parental mosaicism for dominant mutations and autosomal recessive inheritance

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Purpose: Recurrence of lethal osteogenesis imperfecta in families results from either dominant (parental mosaicism) or recessive inheritance. The proportion of these two mechanisms is not known, and determination of the contribution of each is important to structure genetic counseling for these families. **Methods:** We measured the recurrence rate of lethal osteogenesis imperfecta after the birth of an affected infant. We determined the rate of parental mosaicism in a subset of families in which we had identified dominant mutations. In 37 families in which two or more affected infants were born, we identified mutations and determined the proportion that resulted from recessive inheritance. **Results:** The recurrence rate after the first affected pregnancy was 1.3%. The rate of parental mosaicism in families in which a dominant mutation was identified in a first affected child was 16%. In 37 families with two affected infants, 26 had dominant mutations, seven had recessive mutations, and we failed to find mutations in four. The overall recurrence rate for couples after two or more affected infants was 32%; 27% for families with parental mosaicism, 31% for recessive mutations, and 50% for families with no identified mutation. **Conclusions:** In most populations, recurrence of lethal osteogenesis imperfecta usually results from parental mosaicism for dominant mutations, but the carrier frequency of recessive forms of osteogenesis imperfecta will alter that proportion. Mutation identification is an important tool to assess risk and facilitate prenatal or preimplantation diagnosis. *Genet Med* 2011;13(2):125–130.

Key Words: *osteogenesis imperfecta, recurrence risk, recessive, parental mosaicism*

In the introduction of the modern classification of osteogenesis imperfecta (OI), OMIM# 166200, Sillence et al.¹ asserted that the perinatal lethal form of OI (OI type II), OMIM# 166210, was a recessively inherited disorder, based on observed consanguinity and recurrence with a segregation ratio of close to 25%. Subsequent studies from several groups observed that the recurrence risk was usually less than 10%,² and molecular genetic studies identified heterozygous mutations in type I collagen genes.^{3–6} Notably, recurrence occurred in some instances in

which one parent had affected children with two partners, an observation difficult to explain by recessive inheritance. Studies on the molecular basis of OI in several families then showed that recurrence of OI type II could result from parental mosaicism for dominant mutations in type I collagen genes.^{7,8}

The initial estimates of recurrence^{9,10} usually resulted from analysis of retrospective data in which ascertainment was probably biased toward families with recurrence. The measured rate of recurrence of OI type II in an unbiased population was 2% after the birth of an affected infant born to unaffected parents.¹¹ These observations did not, however, identify the cause of recurrence in consanguineous families.

In 2006, the second phase of this story began to unfold with the identification of biallelic mutations in *CRTAP*, OMIM# 610854,^{12–15} closely followed by the recognition of recessive mutations in genes that encode proteins that interact with *CRTAP*: *LEPRE1*, OMIM# 610915^{15–17} and *PPIB*, OMIM# 259440 (unpublished data).^{18,19} In an unselected set of 63 infants with lethal OI, 60 (95%) resulted from mutations in type I collagen genes, with the remainder in the then recognized recessive genes.²⁰

The birth of a second affected child places a family into one of two groups—one in which a parent is mosaic for a dominant mutation or a group in which each parent is a carrier of a recessive form of OI. The calculated recurrence risks for these two groups differ—as high as 50% for families in which one parent is mosaic (depending on the proportion of germ cells that carry the mutation) and 25% for families in which each parent is a carrier. Because the maximum recurrence risk is different in the two circumstances and because approaches to diagnosis differ, it is important to determine the proportion of families that can be attributed to each group and how mutation identification can clarify the risk of recurrence in each family and facilitate prenatal counseling, prenatal diagnosis, or preimplantation diagnosis.

METHODS

Subject selection

As a follow-up to the study by Pepin et al.,¹¹ we identified all prenatal samples submitted to the Collagen Diagnostic Laboratory (CDL) at the University of Washington from June 1996 to August 2009 and measured the recurrences after the identification of lethal OI in one affected infant or pregnancy, and after two or more affected pregnancies. We made the diagnosis of OI type II if the infant died within a month of delivery, if the radiologic picture was consistent with the diagnosis, if the referring physician had made the clinical diagnosis, if the ultrasound during pregnancy was described as consistent with OI type II, or if a mutation was identified that had previously been found in an infant with this condition.

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Second, we identified 216 infants (or pregnancies) in the CDL Repository with lethal OI, in which a type I collagen mutation had been found. We had DNA available from 37 parental pairs of the 216 affected infants to determine whether a parent was mosaic for the mutation.

Finally, to measure the proportion of pregnancies that could be attributed to dominant or recessive mutations, we identified a separate set of 37 families in which there were two or more affected pregnancies born to unaffected parents from the CDL Repository (approved by the Institutional Review Board of the University of Washington). The sequences of the coding and splice site regions of *COL1A1*, *COL1A2*, *CRTAP*, *LEPRE1*, and *PPIB* were determined to identify the causative mutations.

Analysis of candidate genes

RNA or genomic DNA was extracted from cultured dermal fibroblasts using the QIAamp[®] RNA or DNA Mini Kit (Qiagen, Chatsworth, CA), and cDNA was synthesized using the Super-Script[®] First Strand kit (Invitrogen, San Diego, CA). The coding sequences and flanking intron regions of *COL1A1* and *COL1A2* were amplified in 17 and 23 fragments, respectively, and sequenced in multiple reactions. The coding sequences of *CRTAP* and *LEPRE1* were amplified and sequenced as described.¹⁵ The coding sequences and flanking intron regions of *PPIB* were amplified and sequenced using five products. The sequence traces were analyzed with Mutation Surveyor[®] software. The primers and reaction conditions are available on request from the authors.

Determination of recurrence risk

The recurrence rate in all classes of sibships was calculated by excluding the first affected infant(s) in the sibship and then

counting the subsequent affected and unaffected infants in subsequent births.

RESULTS

Recurrence rate of lethal OI among prenatal diagnosis samples

Between June 1996 and August 2009, 76 families, in which there was one previously affected pregnancy, requested prenatal diagnosis studies. In each instance, either biochemical analysis (60 families) or genetic analysis (16 families, Table 1) had confirmed the clinical diagnosis of OI type II in the first affected pregnancy. In the 76 pregnancies we studied, there was one recurrence (1/76, 1.3%) (Table 2). Seven families in which there were two previously affected pregnancies requested prenatal diagnosis, and in those, there were two recurrences (2/7, recurrence rate of 29%). Finally, for three families in which there were three previously affected, two of the three pregnancies were affected (67% recurrence rate). These rates are similar to those previously identified.¹¹

Parental mosaicism for dominant mutations

We identified mutations in type I collagen genes (*COL1A1* or *COL1A2*) in 216 index patients with OI type II. In 37 of these families, DNA from blood or fibroblasts derived from the parents was sequenced around the site of the mutation identified in the affected child to determine whether the causative mutation was present in a subset of alleles in one parent. In 6 of the 37 families (16%), one parent was found to be mosaic (four mothers and two fathers). Of those six, two (both mothers) were noted to have clinical features of mild OI.

Table 1 Mutations identified in families with one previously affected infant with lethal OI in which prenatal diagnosis was done by mutation identification

Family	Genes	Mutations	Proteins	Triple helix	Outcome	References
1	<i>COL1A1</i>	c.797G>A	p.Gly266Glu	Gly88Glu		This article
2		c.1310G>A	p.Gly437Asp	Gly259Asp		This article
3		c.2110G>A	p.Gly704Ser	Gly526Ser		This article
4		c.2308G>T	p.Gly770Cys	Gly592Cys		20
5		c.2461G>C	p.Gly821Arg	Gly643Arg		20
6		c.2471G>C	p.Gly824Ala	Gly646Ala		This article
7		c.2533G>A	p.Gly845Arg	Gly667Arg		This article
8		c.2588G>T	p.Gly863Val	Gly685Val		This article
9		c.3065G>T	p.Gly1022Val	Gly844Val		20
10		c.3150_3158dup	p.Pro1051_Ala1053dup	Pro873_Ala875dup		This article
11		c.4237G>A	p.Asp1413Asn	N/A		This article
12		c.4237G>A	p.Asp1413Asn	N/A		This article
13	<i>COL1A2</i>	c.1971+1_+32del (IVS32+1_+32del)			Exon 32 skip	This article
14		c.1127G>A	p.Gly376Asp	Gly286Asp		This article
15		c.1360G>T	p.Gly454Cys	Gly364Cys		This article
16		c.1631G>T	p.Gly544Val	Gly454Val		20

Table 2 Prenatal diagnosis of OI type II in the period of 1996–2009

Previous affected	Mode of diagnosis	No. tested	No. affected	Measured recurrence rate (%)
1	Biochemical	60	0	0
	DNA based	16 ^a	1	6.3
	Total	76	1	1.3
2	Biochemical	3	1	33
	DNA based	4 ^b	1	25
	Total	7	2	29
3	Biochemical	2	2	100
	DNA based	1 ^c	0	0
	Total	3	2	67

^aTwelve *COL1A1* and four *COL1A2* (Table 1).

^bThree *COL1A1* and one *LEPRE1*.

^c*CRTAP*.

OI, osteogenesis imperfecta.

Proportion of dominant compared with recessive inheritance after recurrence

By searching our Repository, we identified an additional 37 families in which two or more affected infants had been born to unaffected parents. We sequenced five candidate genes, *COL1A1*, *COL1A2*, *CRTAP*, *LEPRE1*, and *PPIB*, to identify causative mutations (Table 3). Cultured fibroblasts from all but one of these infants produced some abnormal type I collagen molecules in which the constituent chains were overmodified and migrated slowly during gel electrophoresis. In 26 of the 37 (70%) families (67 children with 56 affected), we found mutations in a type I collagen gene, *COL1A1* (15) or *COL1A2* (11) (Table 3). In 7 of the 37 (19%) families (27 children with 18 affected), we found homozygosity or compound heterozygosity for mutations in *CRTAP* (3), *LEPRE1* (3), or *PPIB* (1). We failed to find mutations in the remaining four (11%) families (14 children with 11 affected) (Table 3).

Determination of recurrence risk

At the time we ascertained the 37 families in which there were two or more children with OI type II, there had been 108 pregnancies, of which 85 were affected (Table 4). After accounting for ascertainment, the overall rate of recurrence in these families was 32% (11/34). In families with parental mosaicism for dominant mutations, the recurrence rate was 27% (4/15); in families with recessive mutations, the recurrence rate was 31% (4/13); and in families with no mutation identified, the recurrence rate was 50% (3/6). Because the number of families is small, the measured rates serve as estimates that could change if sample size is increased.

Mosaicism among parents with recurrent OI due to dominant mutations

In 26 families, in which two or more affected infants were born, a type I collagen mutation was identified in an affected child. We studied parental blood samples from 16 of those families to determine the proportion in which we could identify the mutation found in the child and whether there was a higher

rate of mosaicism in one gender. Among those 16, we identified the mosaic parent in 15 (seven mothers and eight fathers) families. Two of the parents were assigned as mosaic on the basis of family structure (i.e., they had affected children with different partners—one mother and one father). The status was determined by DNA analysis in the remaining 13 among whom we identified mutations in 12. Among the 15 parents determined to be mosaic, three had signs compatible with mild OI (one of the fathers⁸ and two mothers). The extent of mosaicism in blood and fibroblast DNA varied, but in only one family did the proportion of affected alleles approach 50% of the total in blood DNA. The proportion of affected alleles in germ cells was not measured.

DISCUSSION

In 1979, Sillence et al.¹ recognized both dominant and recessive modes of inheritance in families with OI and thought that the perinatal lethal type, OI type II, was recessively inherited, an insight that has proved to be partially correct. Counseling of families at risk for recurrence of lethal genetic disorders in the context of simple Mendelian inheritance is straightforward. For dominant lethal disorders, the risk for unaffected parents to have a second affected child depends on whether one parent is mosaic for the mutation and the proportion of germline progenitor cells that carry the mutation. For recessive disorders, the risk to have an affected child after the birth of a first affected child is 25% with each pregnancy.

Evidence that parental germline mosaicism caused recurrence of lethal OI in sibships with unaffected parents arose in the 1980s and made counseling complex.^{5,8} For a parent with an affected allele in his or her germline, the risk to pass this altered allele depends on the proportion of germ cells that carry the mutant allele. This risk reflects the proportion of cells with the mutant allele allocated to the primordial germline during embryonic development of the parent. The recurrence risk would be 50% to have an affected child with each pregnancy if all allocated cells have one copy of the mutant allele. Generally, parents with germline mosaicism are themselves phenotypically normal (reminiscent of recessive inheritance) and, thus, unaware of the initial risk to have an affected child.

As an aid to prenatal diagnosis and counseling, we set out to determine the proportion of families in which recurrence resulted from parental mosaicism for dominant mutations or autosomal recessive inheritance, the recurrence risk within each of the two groups, whether the mosaicism was more likely to affect one parent than the other, how often mosaicism was detectable in the parents of affected infants, and whether we could estimate the number of cells allocated to the germline.

We found that the primary recurrence rate for perinatal lethal OI, regardless of cause, was 1.3%, similar to what we had recognized more than a decade ago. Among families with a first affected child in which we identified a mutation in a type I collagen gene and studied parental DNA, we documented that in approximately 16% of the families, one parent was mosaic in somatic cells (and in the germline as demonstrated by birth of an affected child).

We studied 37 families in the Repository in which there were two or more affected pregnancies with perinatal lethal OI born to unaffected parents to identify those with dominant mutations and those with recessive mutations. We expected these families to fall into two groups—one in which a parent was mosaic for a dominant mutation in a type I collagen gene and a second in which both parents were carriers for recessive mutations. In the affected infants or pregnancies from 37 families we studied, 26 had dominant mutations in type I collagen genes, 7 had recessive

Table 3 Molecular analysis in families with two previously affected infants with lethal OI

Family	Genes	Mutations	Proteins	Triple helix	Outcome	PTC	Mosaic parent	References		
17	<i>COL1A1</i>	c.1426G>C	p.Gly476Arg	Gly298Arg			ND	20		
18		c.1661G>C	p.Gly554Ala	Gly376Ala			ND	20		
19		c.1778G>A	p.Gly593Asp	Gly415Asp			Mother	20		
20		c.2002G>A	p.Gly668Ser	Gly490Ser			ND	This article		
21		c.2192G>T	p.Gly731Val	Gly553Val			Mother ^a	This article		
22		c.2228G>A	p.Gly743Asp	Gly565Asp			ND	This article		
23		c.2290G>A	p.Gly764Ser	Gly586Ser			ND	This article		
24		c.2461G>C	p.Gly821Arg	Gly643Arg			Mother	20		
25		c.2552G>A	p.Gly851Asp	Gly673Asp			Father	20		
26		c.2725_2733del	p.Pro909_Gly911del	Pro731_Gly733del			Father	21		
27		c.3182G>A	p.Gly1061Asp	Gly883Asp			Father	7		
28		c.3325G>A	p.Gly1109Ser	Gly931Ser			ND	This article		
29		c.3831C>G	p.Asp1277Glu	N/A			ND	This article		
30		c.3150_3158del	p.Pro1051_Ala1053del	Pro873_Ala875del			Mother	This article		
31		c.4238_4248dup	p.Ser1417Metfs*14	N/A		Frame shift	Exon 52	Mother ^b	This article	
32		<i>COL1A2</i>	c.1033_1035del ^c	p.Val345del	Val255del			Mother	This article	
33			c.1684G>T	p.Gly562Cys	Gly472Cys			Father	8	
34			c.2144G>A	p.Gly715Asp	Gly625Asp			Father	20	
35			c.2234G>A	p.Gly745Glu	Gly655Glu			Father	This article	
36			c.2360G>A	p.Gly787Asp	Gly697Asp			Mother	This article	
37			c.2701G>A	p.Gly901Ser	Gly811Ser			Father	This article	
38			c.2981G>A	p.Gly994Asp	Gly904Asp			Both normal	This article	
39			c.3070G>C	p.Gly1024Arg	Gly934Arg			ND	This article	
40			c.3115_3116delinsTT	p.Gly1039Phe	Gly949Phe			ND	This article	
41			c.3260 G>A	p.Gly1087Asp	Gly997Asp			ND	This article	
42			c.2133+5G>A (IVS35+5G>A)				Alters splicing		Father ^b	This article
43			<i>CRTAP</i>	c.[24_31del] + [24_31del]	p.Ala10Serfs*148		Frame shift			15
44				c.[471+2C>A] + [471+2C>A]			Alters splicing			22
45				c.[879delT] + [879delT]	p.Phe293Leufs*16		Frame shift			12
46	<i>LEPRE1</i>		c.[1080+1G>T] + [1080+1G>T]			Alters splicing			This article	
47			c.[1080+1G>T] + [1080+1G>T]			Alters splicing			15	
48			c.[1080+1G>T] + [1080+1G>T]			Alters splicing			15	
49	<i>PPIB</i>	c.[120delC] + [313G>A]	p.[Val42Serfs*16] + [Gly105Arg]					Unpublished data		
50		No mutation identified								

(Continued)

Table 3 Continued

Family	Genes	Mutations	Proteins	Triple helix	Outcome	PTC	Mosaic parent	References
51		Nomutation identified						
52		Nomutation identified						
53		Nomutation identified						

^aObligate mosaic by family structure, confirmed by DNA testing.

^bObligate by family structure.

^cThis mutation could also be described as c.1035_1035+2del. OI, osteogenesis imperfecta.

Table 4 Measured recurrence rates after two affected pregnancies

Genes	70% (26/37), Autosomal dominant		19% (7/37), Autosomal recessive			11% (4/37), Unknown Unknown
	<i>COL1A1</i>	<i>COL1A2</i>	<i>CRTAP</i>	<i>LEPRE1</i>	<i>PP1B</i>	
Families	15	11	3	3	1	4
Probands	30	22	6	6	2	8
Additional affected	0	4	3	1	0	3
Unaffected	3	8	4	3	2	3
		4/15		4/13		3/6
Recurrence risk (%)	27		31			50

sive mutations, and we failed to find mutations in the remaining 4 families. In the 26 families in this group with parental germline mosaicism for dominant mutations in type I collagen genes, we studied parental sets in 16 and identified the mutation-bearing cells in somatic sources in 13 of them; in two (one mother and one father), the parent was an obligate mosaic by family structure, and we did not study them. In one, we could not identify the mutant allele in DNA derived from blood from either parent. We can conclude that in the majority of families, the mutation occurred early in parental embryogenesis before allocation of cells to the germline, rather than after allocation. A measured recurrence rate of 27% indicates that on average approximately half of the germ cell precursors carry the mutation and could be consistent with a very small number of cells set aside for the germline. Studies in mice are consistent with a very small precursor pool.^{21,22} With one exception among those we studied, in DNA from blood in the mosaic individuals, between 10 and 20% of alleles carried the mutation, but this does not serve to refine the recurrence risk or allow any better estimate of the number of cells allocated to the germline.

The measured recurrence rate after the birth of a child with perinatal lethal OI (1.3–2%) is consistent with the observation that approximately 5% of pregnancies with this form of OI result from the recessive forms²⁰ and an overall rate of parental mosaicism of approximately 16% in the families with dominant mutations. In this context, the expected recurrence rate would be close to 4%, similar to what we have observed. In a population with a significantly higher carrier rate for recessive mutations, the predicted recurrence rate would increase in proportion to that rate. If the carrier rate for the West African *LEPRE1* mutant allele is 1/200,²³

then the calculated recurrence risk, assuming that the rate of parental mosaicism would remain the same, is approximately 8% in that population in which the majority of recurrences would be from the recessively inherited group.

Our study indicates that mutation identification is an important tool for diagnosis and counseling because it allows separation of families into one of three at risk groups: those with a very low risk (well below 0.1% in the absence of parental somatic mosaicism or recessive inheritance), those with a risk of up to 50% in the presence of parental mosaicism (that could be refined by measure of the frequency of the allele in sperm if the father is mosaic), and those with a 25% risk if both parents are carriers of a recessive mutation. The major limitation of this study is that the number of recurrent families is relatively small, and changes in the proportion of recessive forms of OI in the studied population could change the distribution among the three groups. Nonetheless, mutation identification is a key to providing accurate genetic counseling for both early prenatal and preimplantation diagnosis.

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