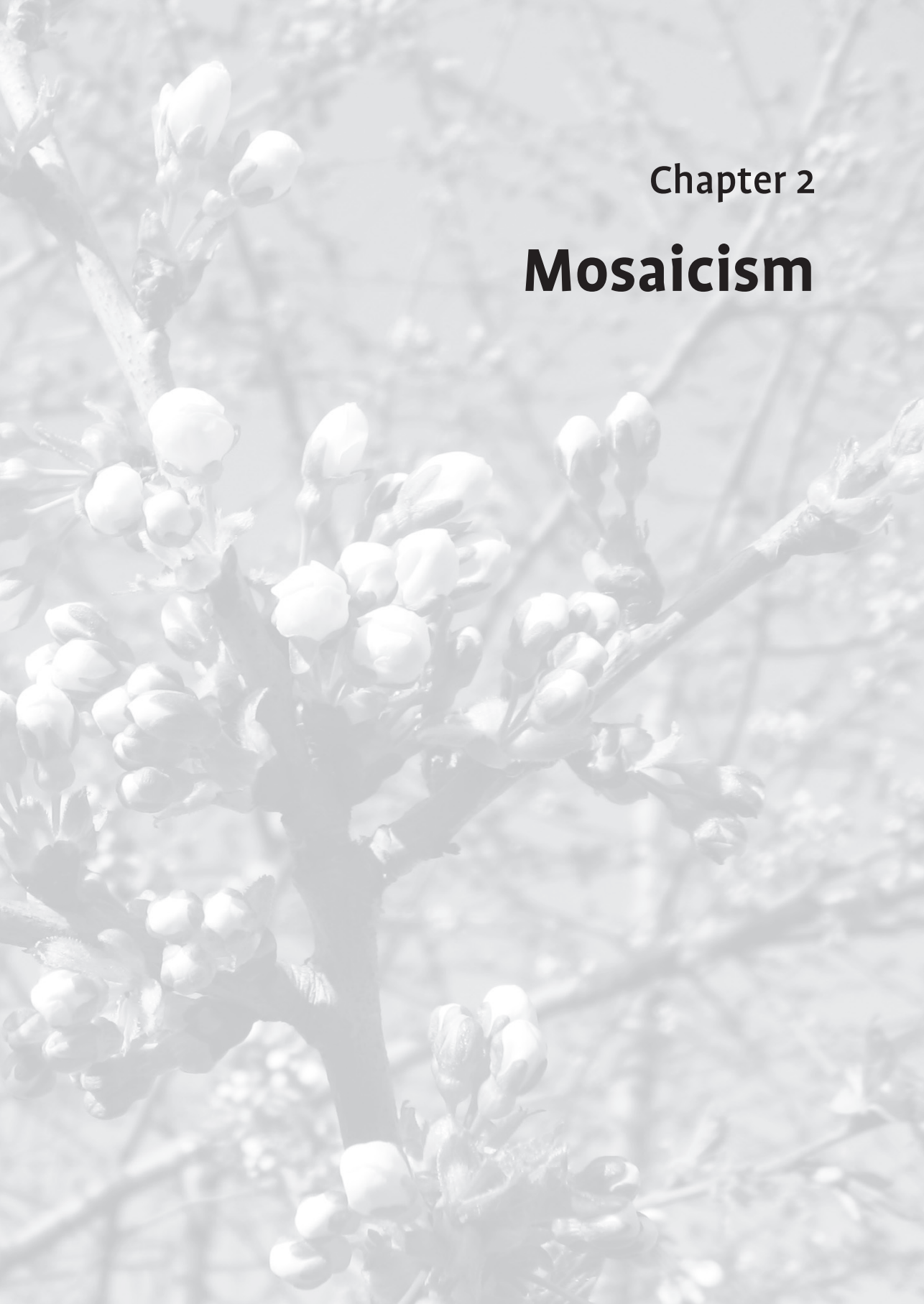

Chapter 2

Mosaicism

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Short Report

Recurrence risk due to germ line mosaicism: Duchenne and Becker muscular dystrophy

Helderman-van den Enden ATJM, de Jong R, den Dunnen JT, Houwing-Duistermaat JJ, Kneppers ALJ, Ginjaar HB, Breuning MH, Bakker E. Recurrence risk due to germ line mosaicism: Duchenne and Becker muscular dystrophy.
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The presence of multiple affected offspring from apparently non-carrier parents is caused by germ line mosaicism. Although germ line mosaicism has been reported for many diseases, figures for recurrence risks are known for only a few of them. In X-linked Duchenne and Becker muscular dystrophies (DMD/BMD), the recurrence risk for non-carrier females due to germ line mosaicism has been estimated to be between 14% and 20% (95% confidence interval 3–30) if the risk haplotype is transmitted. In this study, we have analyzed 318 DMD/BMD cases in which the detected mutation was *de novo* with the aim of obtaining a better estimate of the 'true' number of germ line mosaics and a more precise recurrence risk. This knowledge is essential for genetic counseling. Our data indicate a recurrence risk of 8.6% (4.8–12.2) if the risk haplotype is transmitted, but there is a remarkable difference between proximal (15.6%) (4.1–27.0) and distal (6.4%) (2.1–10.6) deletions. Overall, most mutations originated in the female. Deletions occur more often on the X chromosome of the maternal grandmother, whereas point mutations occur on the X chromosome of the maternal grandfather. In unhaplotyped *de novo* DMD/BMD families, the risk of recurrence of the mutation is 4.3%.

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Key words: *de novo* – Duchenne muscular dystrophy – germ line – mosaicism – recurrence risk

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A genetic disease in a child with healthy non-carrier parents is usually a result of a *de novo* mutation that has taken place during cell division (mitosis/meiosis). The mutation rate for most genetic diseases is low, and hence, the risk of a second mutation in the same gene in a specific family is negligibly small. If the mutation occurs during mitosis, a large number of cells (germ and/or somatic) may carry the mutation, thus increasing the risk for a second affected child.

The presence of multiple affected offspring from apparently non-carrier parents is due to germ line mosaicism. So far, germ line mosaicism has been reported for more than 60 genetic diseases. Recurrence risk is known for only a few of these.

Duchenne muscular dystrophy (DMD) is a lethal X-linked recessive disorder and is caused by mutations in the dystrophin gene. Mutations in this gene can also lead to Becker muscular dystrophy (BMD).

An affected boy usually inherits the dystrophin gene mutation from his mother. The carrier mother has a 25% risk of having a second affected child in each pregnancy.

In 1935, Haldane (1) postulated that for X-linked lethal recessive disorders like DMD, one in three patients has the disease as a result of a *de novo* mutation.

If one in three DMD patients is affected as a result of a new mutation, then one in three mothers is not a carrier. One would expect that in these cases, the risk for a subsequent pregnancy would be zero. However, this is not the case.

Germ line mosaicism in DMD was described by several authors in the late 80s (2–4). The estimate of the recurrence risk for non-carrier females due to germ line mosaicism of transmitting the risk haplotype varies between 14% (95% confidence interval 3–25) and 20% (11–30) (5, 6). At the

meeting of the European Society of Human Genetics in 2004, Castagni et al. presented a poster on germ line mosaicism in a group of 273 Italian families. There were only two cases where the *de novo* mutation in the dystrophin gene was transmitted twice, suggesting that previous studies may have overestimated the recurrence risk (7).

In this study, we have analyzed our proven *de novo* DMD/BMD cases with the aim of obtaining a better estimate of the 'true' number of germ line mosaics and to assess the resulting recurrence risk more precisely, which is essential in genetic counseling. The recurrence risks are specified with respect to the type of the mutation and its location within the gene.

We have also traced the origin of the mutation (maternal, maternal grandmother or maternal grandfather) by haplotype analysis of *de novo* families and have investigated whether there is a relationship between the type of mutation and its origin.

Methods

Since the availability of DNA diagnostics in 1984, more than 1500 DMD/BMD patients/families have been tested in our laboratory. Mutations in most families are known and their DNA has been stored.

The records of the patients/families were selected on the basis of a mutation detected in the dystrophin gene that was proven to have arisen *de novo*. A family was considered to have a *de novo* mutation if the mother of the patient or if the parents of a carrier mother did not have the mutation in their lymphocytes.

The risk haplotype was determined in the selected *de novo* families. We then examined the frequency of the risk haplotype transmission with or without the mutation.

In a number of healthy siblings, either haplotyping was not informative (sisters without the mutation) or DNA was unavailable (healthy brothers). Yet these siblings provide valuable information about the recurrence risk. By using Bayes' theorem as described in the supplementary materials available as part of the online article at http://www.blackwell-synergy.com, we were able to compute the expected number of siblings assumed to have the risk haplotype without the mutation.

In a number of families where the mutation must have occurred in one of the grandparents, it was not possible to establish its origin. This was usually due to the non-availability of DNA of the grandfather. The probability of the origin, and hence the number of transmitted risk haplotypes, depends on F, the number of haplotyped siblings and the number of healthy siblings with no information about the haplotype. In the supplementary materials available as part of the online article at http://www.blackwell-synergy.com, this is further explained.

Results

Among 1500 DMD/BMD patients/families known in our laboratory, 318 families were identified with proven *de novo* mutations, 272 families with DMD and 46 families with BMD.

Part A: Recurrence risk due to germ line mosaicism

The mutation was transmitted more than once in 19 cases. Table 1 gives an overview of the families with germ line mosaicism and the detected mutations.

The risk haplotype without a mutation was transmitted 108 times (data not shown) to a healthy sibling. No information about the haplotype was available from 176 healthy siblings. The a priori risk that these 176 siblings received the risk haplotype is 50% (88). By using the algorithm described in the supplementary materials, 84 siblings without haplotype information could be added to the 108 siblings with the risk haplotype.

Table 1. Summary of the mutations in the 18 proven germ line mosaic families[a]

Family number	Origin of the mutation	Deletion of exon number(s)	Duplication of exon number(s)	Point mutation
DL2	Mother	5–7		
DL26	Mother	51		
DL41	Mother	48–50		
DL43	Grandmother	4–7		
DL51	Mother	45–54		
DL114	Mother	Probe 30.1		
DL154	Grandmother	8–28		
DL202	Grandmother		3–7	
DL215	Mother		2–7	
DL389	Grandmother	52–55		
BL129	Mother	45–48		
BL138	Mother		16–34	
50173	Mother	45–52		
50796	Mother	3–7		
51526	Mother	46–49		
53224	Mother			8791G>T
53435	Mother	12–19		
61447	Mother	43		

[a]Eighteen families are shown, whereas we counted 19 cases of germ line mosaicism. In family BL138, the *de novo* mutation was transmitted three times. The exon numbers of the deletion family DL114 could not be further specified because there was insufficient DNA and no new material was available.

From the families with unknown grandparental origin, we estimated that another 11 siblings are likely to carry the risk haplotype.

In total, the number of siblings with the risk haplotype is therefore 203 (108 + 84 + 11).

The recurrence risk if the risk haplotype is transmitted is:

$$19/(203+19) = 0.086(=8.6\%)$$
$$(95\%\ \text{confidence interval}: 4.8-12.2).$$

Table 2 gives an overview of the origin and the type of mutation. The most frequent type of mutation, a deletion, was present in 246/318 families. The deletions are subdivided as proximal, middle and distal to be able to calculate the specific recurrence risks for these types of deletions.

Figure 1 shows two hot spots of deletions; most deletions are found in the distal hot spot. The graph in Fig. 2 shows the distribution of deleted exons in families with proven germ line mosaicism due to a deletion. Both hot spots can be seen. However, the distal hot spot is significantly lower compared with the distal hot spot in the entire group of *de novo* deletions (Fig. 1). Table 1 shows the families with proven germ line mosaicism: six deletions proximal and eight distal. Table 2 shows the whole group of *de novo* deletion families: 53 proximal *vs* 182 distal.

The recurrence risks for the different types of mutations were calculated in the same manner as described above for the entire group. Table 3 shows the results. No recurrence risk is calculated for a middle deletion because the total number of middle deletions was too small (11 families).

Part B: Origin of the new mutation

Table 2 shows that most families (77%) had a deletion; duplications and point mutations were found in 11% and 12%. In 232 families, the mother was not a carrier; hence, the mutation has arisen in the germ line of the mother. In 40 families, the mutation originated in the grandmother and in 27 families in the grandfather. In 19 families, the origin of the mutation could not be determined (see Methods).

Discussion

Recurrence risk due to germ line mosaicism

Hall in 1988 and Edwards in 1989 speculated that every woman has several oocytes with mutations for common genetic disorders because the 6–8 million oocytes exceed the denominator of the mutation rates for these diseases (8, 9). In the male germ line, an even greater range of mutations is expected to be present.

The result of a literature search on germ line mosaicism is added as a supplement and can be viewed online at http://www.blackwell-synergy.com in the supplementary materials.

An estimate for the recurrence risk was found for only 7 of 63 diseases: 2 with an autosomal dominant and 5 with X-linked inheritance. The recurrence risks vary as follows: 0.02% [achondroplasia (10)], 5–7% [autosomal dominant osteogenesis imperfecta (11)], 11% [RETT syndrome (12), double cortex X-linked lissencephaly syndrome (13) and hemophilia B (14)] and 13% [hemophilia A (15)].

In DMD, the reported recurrence risks vary from negligible to 14–20% if the risk haplotype is transmitted (5–7). For genetic counseling, it is important to have a reliable estimate of the recurrence risk attributed to germ line mosaicism. Our study describes the largest number of families with a *de novo* mutation known to date, and we found a recurrence risk, if the risk haplotype is transmitted, of 8.6% (95% confidence interval 4.8–12.2). In the current counseling practice, information about the risk haplotype is usually not obtained because only the presence/absence of the mutation is tested in the at-risk sibling. One should use a recurrence risk of 4.3% in these families with no information about the risk haplotype.

Table 2. Overview of the origin and type of mutation[a]

Type of mutation	Maternal	Maternal grandmother	Maternal grandfather	Unknown	Total
All deletions	183	35	14	14	246 (77%)
Proximal deletion	*35*	*10*	*6*	*2*	*53*
Middle deletion	*8*	*1*	*1*	*1*	*11*
Distal deletion	*140*	*24*	*7*	*11*	*182*
Duplication	25	3	5	2	35 (11%)
Point mutation	24	2	8	3	37 (12%)
Total	232 (73%)	40 (13%)	27 (8%)	19 (6%)	318 (100%)

[a]A deletion is defined as proximal if most deleted exons are found in the proximal hot spot (exons 3–20) and as distal if most deleted exons are distal to exon 40. The other deletions are located in the middle of the gene between exons 20 and 40.

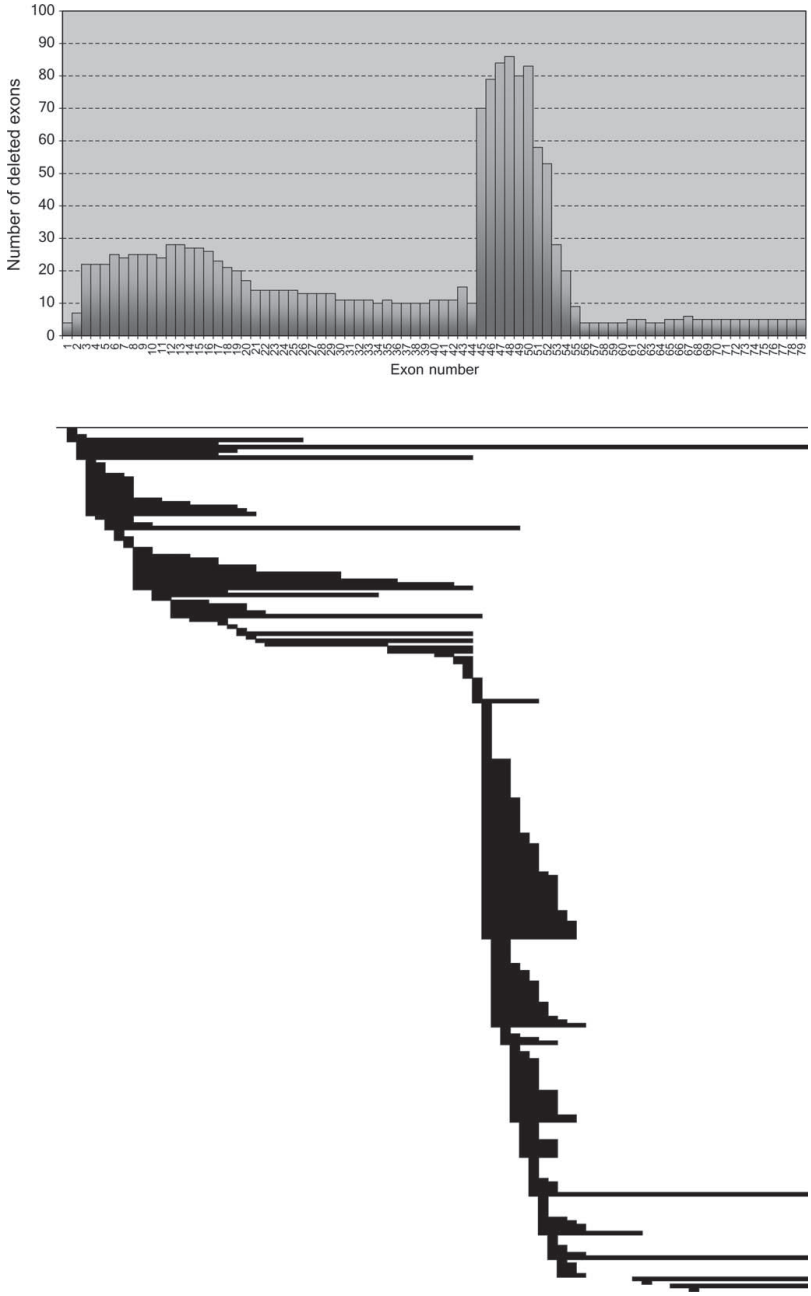

Fig. 1. Overview of the found deletions. Graphic representation of the location of 245 deletions (the border of one deletion could not be defined: DL114 del probe 30.1 because of insufficient DNA). The number of times that each individual exon is deleted is shown on the *y*-axis, and the *x*-axis shows the different exons. The lines in the lower part represent individual deletions. Summing of the individual deletions has resulted in the graph on the top.

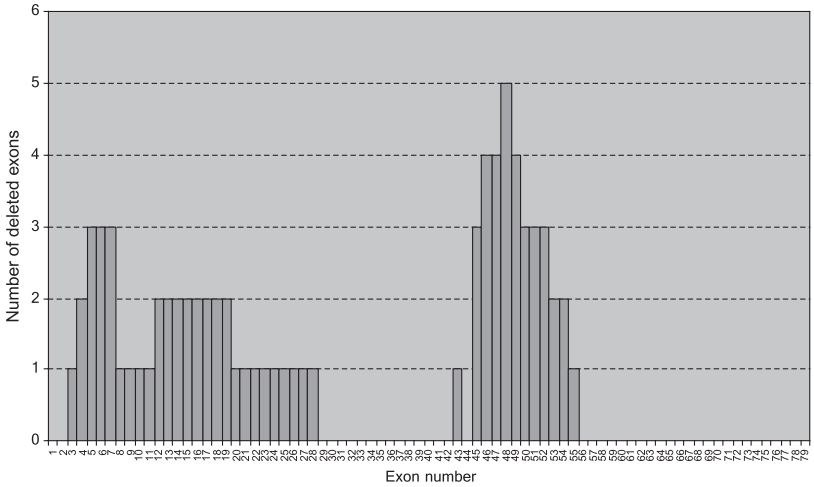

Fig. 2. Distribution of the deleted exons in 13 families with a *de novo* deletion and proven germ line mosaicism. Not included in this figure is family DL114 with a deletion of probe 30.1, this is also a proximally located deletion. The boundaries of the deletion could not be defined, however, because of insufficient DNA.

This figure is remarkably close to the 4.5% recurrence risk calculated by Van der Meulen et al. in 1995 (16). The primordial germ cell divides mitotically, so that in the *i*th generation of the germ cells, there are 2^i cells. If this process continues for a total of n cells (n may be different in females and males), then at maturity, there are 2^n germ cells. Hartl (17) showed that more complex versions of this simple model do not change recurrence risks as long as the number of gonadal generations is high enough. The recurrence risk due to germ line mosaicism can be calculated with the following formula:

$$\text{Recurrence risk} = \sum_{i=1}^{n} 1/n.(2)^{-i} \approx 1/n.$$

If the number of generations needed to form the 5–7 million oocytes is at least 22 in females (18), the recurrence risk according to this formula is $1/22 \approx 0.045 = 4.5\%$.

In the majority of the *de novo* families, the mutation originated in the germ line of the mother (in our study 232/318) or the maternal grandmother (40/318), which might explain the fact that the theoretical calculated recurrence risk is close to our empirical risk.

The mutations with proven germ line mutations are deletions in 14/18 (77%), duplications in 3/18 (17%) and a point mutation in 1/18 (6%) families. These percentages are divided as the expected ratio of mutations in the dystrophin gene, apart from the number of point mutations, which is smaller than expected. This can be explained by the fact that these type of mutations are more difficult to locate.

Table 3. Recurrence risk due to germ line mosaicism

Type of mutation	Recurrence risk (%) if the risk haplotype is transmitted (95% confidence interval)	Recurrence risk with unknown haplotype (%)
All types together	8.6 (4.8–12.2)	4.3
All deletions	8.4 (4.2–12.6)	4.2
Proximal deletion	15.6 (4.1–27.0)	7.8
Distal deletion	6.4 (2.1–10.6)	3.2
Duplication	12.1 (1.0–23.2)	6.1
Point mutation	4.4 (0–12.7)	2.2

Different mosaicism frequencies for proximal and distal deletions

If the distribution of mutations in familial and sporadic cases was identical, no difference between these groups would be expected. Passos-Bueno et al. observed that in familial cases of DMD/BMD caused by a deletion, 47% of these were found in the proximal hot spot and 53% in the distal hot spot, whereas in sporadic cases, 28% of the deletions were found to be proximal and 72% distal (19). Furthermore, they found that germ line mosaicism for DMD was present more

often in the proximal hot spot than in the distal one. These authors calculated different mosaicism frequencies for proximal and distal DMD mutations. A distinct recurrence risk of 30% was found for proximal *de novo* mutations and 4% for distal mutations. It was speculated that proximal deletions arise earlier in embyrogenesis than distal ones. This explains the higher recurrence risk because more cells would carry the mutation.

The present study confirms a difference between the recurrence risk for germ line mosaicism for proximal and distal deletions. The difference, however, is much smaller: a proximal deletion has a risk of recurrence of 15.6% whereas a distal deletion has 6.4%. Of the three families with germ line mosaicism caused by duplications, two involved also the proximal part of the gene, but it is known that duplications are found more often proximal than distal (20).

In our study, the recurrence risk due to germ line mosaicism was 12.1% for duplications and 4.4% for point mutations. These recurrence risks have relatively large 95% confidence intervals due to the small number of families in which duplications (35/318) and point mutations (37/318) were found.

We have added a flowchart (Fig. 3) for use in estimating the recurrence risk in a family with a sporadic DMD patient. To our knowledge, these recurrence risks are the most accurate at present, and this flowchart should facilitate genetic counseling. However, all 95% confidence intervals overlap, and therefore, the recurrence risks for the specific types of mutations should be used with caution.

Origin of the mutation

Since the description of the male to female ratio of mutations by Haldane in 1947 (21), many articles have been written on this subject. Usually, the ratio in DMD is assumed to be 1, which makes the risk of the mother being a carrier 2/3.

This variation of the male to female ratio of mutations depending on the type of the mutation has been described also for other diseases, for instance, in X-linked hemophilia B (22).

In 86 of the 318 DMD/BMD families (27%) in our study, the mutation arose in the grandparental germ line. This low percentage is not surprising because an unknown number of women carrying a *de novo* mutation in the dystrophin gene are

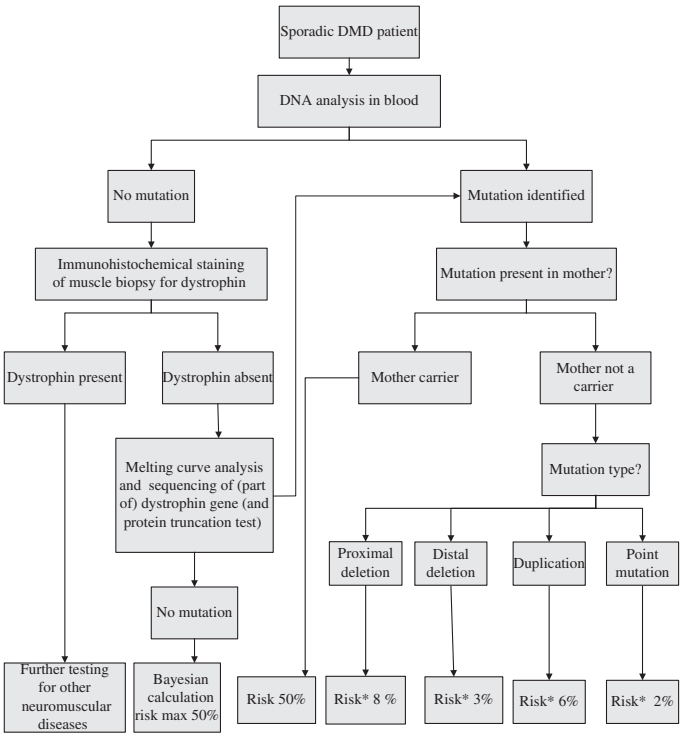

Fig. 3. Flowchart for use in counseling for the recurrence risk in a family with a sporadic Duchenne muscular dystrophy (DMD) patient. Risk* is the risk of an affected son if there is no information about the haplotype. Haplotype analysis is usually not performed because now it is possible to test for the mutation directly. The recurrence risks for the specific types of mutations should be used with caution because, as can be seen in Table 3, all 95% confidence intervals overlap.

missed if they do not pass the mutation on to a son.

Our study confirms that deletions in the dystrophin gene occur more often on the X chromosome of the maternal grandmother (35 times) than of the maternal grandfather (14 times). In a study of 81 *de novo* DMD/BMD families in 1992 (6), it was found that the mutation came from the grandmother in 49 families and from the grandfather in 32 families. The authors concluded that the mutation rate in males and females in their study did not significantly deviate from an equal mutation rate in both sexes. This study involved 97.4% deletions and only 2.6% duplications. Our study confirms this result.

Point mutations originated more often in the maternal grandfather (eight times) compared with the maternal grandmother (two times). It is in the literature a well-known phenomenon that point mutations arise more often in the male germ line. This is explained by the way germ cells in the male are formed. There are about 30 cell divisions before puberty and 1 about every 23 days thereafter. For a 30-year-old male, the number of cell divisions is 380 (23). In the female germ line, there are about 22 cell divisions (18).

At present, the mutation can be identified, and reliable testing of family members is feasible in most DMD cases. Our data indicate that in a family of a sporadic DMD patient with *unknown* mutation, the risk for a second affected boy can be as high as 8.6% if the risk haplotype is present in a subsequent male fetus. If MyoD can modify chorion villus cells in the same way as it does fibroblasts (24), we may be able to test the ability of the fetus to make dystrophin *in vitro* and thus be informed whether the fetus is affected or healthy. The couple faces a difficult decision whether to continue the pregnancy or not in case the MyoD technique fails or is not available. If they decide to terminate the pregnancy, it is important to collect muscle tissue from the fetus. Immunohistochemical staining of dystrophin should be performed on this tissue (25). If dystrophin is absent, the risk that the mother is a carrier is high (although germ line mosaicism cannot be excluded as long as the mutation is unknown) and the couple will know that their fetus was affected. If, however, dystrophin is present, the fetus was not affected with DMD. In any case, prenatal testing should be offered in a future pregnancy as there is still a recurrence risk because of possible germ line mosaicism.

Germ line mosaicism remains an important pitfall that should be considered during the counseling of families with a *de novo* mutation. The 8.6% risk of recurrence of the mutation in the risk haplotype in our large series of families indicates the need for assessing the potential DMD carrier risk for all female members of families with apparent *de novo* cases.

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Supplementary materials of the article of Helderman et al: Recurrence risk due to germline mosaicism: Duchenne muscular dystrophy. This is available as part of the online article at http://www.blackwell-synergy.com

In a number of healthy siblings either haplotyping was not informative (sisters without the mutation) or DNA was unavailable (healthy brothers). Yet these siblings provide valuable information about the recurrence risk. Bayes theorem is used as described below in the box to compute the expected number of siblings assumed to have the risk-haplotype without the mutation.

The probability that a healthy sibling has the risk-haplotype without the mutation is

$$\frac{\frac{1}{2}(1-F)}{\frac{1}{2}(1-F)+\frac{1}{2}}=\frac{1-F}{2-F}$$

Where F denotes the chance that a germ line mutation is present in the risk-haplotype and (1-F) is the chance that the risk-haplotype does not have the mutation

If F is small this probability equals ½.

The numerator gives the risk that the healthy sibling has the risk-haplotype without the mutation.

The denominator gives the possibilities of a healthy sibling: the numerator and the possibility of receiving the non risk-haplotype (=1/2)

Now the unknown parameter F can be estimated by using an EM algorithm which computes, based on a current value of F, the expected total number of haplotypes transmitted (E step) and then using these total number, the value of F is updated (M step). The expected total number of haplotypes is given by

$$19+108+176\frac{1-f}{2-f}.$$

Here the last term represents the healthy siblings for whom either haplotype was not informative or DNA was not available.
Then a new value of F is obtained by

$$f_{new}=\frac{19}{19+108+176\frac{1-f}{2-f}}.$$

These steps are repeated until convergence has been obtained. By using the algorithm described above, we calculated that 84 of the 176 siblings without information about the haplotype, probably carried the risk haplotype (so a little less than the apriori risk of 50%).

These formulas hold for families with known origin of mutation. For 19 (out of 86) families the origin was unknown. Also these families contain information about F. To include these families in the procedure, we formulated the posterior probability of origin as function of F and the observed family data.
Let NDC be the number of daughters carrying the mutation, NDH be the number of daughters carrying the healthy haplotype, NDU be the number of daughters without mutation and NSU be the number of sons without the mutation.

Then the probability of the family give the origin of mutation are given by
Prob(NDC, NDH, NDU | paternal origin)= F^{NDC} $(1-F)^{(NDH+NDU)}$

Prob(NDC, NDH, NDU, NSU | maternal origin)= $(½F)^{NDC}$ $(½-½F)^{NDH}$ $(1-½F)^{NDU+NSU}$

Using Bayes theorem and the prior probabilities of maternal origin of ⅔ and of paternal origin of ⅓, the posterior probabilities of origin can be calculated for each family.

Now given the origin, the number of transmitted haplotypes can be counted as before and the total number of transmitted haplotypes in these families is the weighted sum of the number under maternal origin and under paternal origin weighted with the corresponding posterior probabilities of origin. This total number of expected transmitted haplotypes in the family can be added to the expected total number of transmitted haplotypes given above.

In this way we estimated that in the families with unknown grandparental origin another 11 siblings are likely to carry the risk-haplotype.

The following table was published online as a supplementary file of the article of Helderman et al titled: Recurrence risk due to germ line mosaicism: Duchenne and Becker muscular dystrophy.

Overview of the literature on germ line mosaicism

Only those references were included where multiple affected offspring with a detected mutation had apparently non-carrier parents (no mutation in lymphocytes). The diseases are presented in alphabetical order, followed by the name of the gene, the type of inheritance and the reference(s). AD = autosomal dominant, AR = autosomal recessive, X-L = X-linked

Disease	Gene	AD	AR	X-L	reference
Achondrogenesis type II	COL2A1	1			(1)
Achondroplasia	FGFR3	1			(2, 3, 4)
Albright hereditary osteodystrophy	GNAS1	1			(5)
Amyloid polyneuropathy	TTR	1			(6)
Androgen insensitivity syndrome	AR			1	(7)
Angelman syndrome	UBE3A	1			(8)
Apert syndrome	FGFR2	1			(9)
Campomelic dysplasia	SOX9	1			(10)
Charcot-Marie-Tooth disease type 1 (CMT1)	MPZ/P0	1			(11, 12)
CHARGE	CHD7	1			(13)
Coffin-Lowry syndrome	RSK2			1	(14)
Craniofrontonasal syndrome (CFNS)	EFNB1			1	(15)
CRASH	L1CAM			1	(16)
Crouzon	FGFR2	1			(17)
Danon disease	LAMP-2			1	(18)
Diabetes permanent neonatal	KCNJ11	1			(19, 20)
Duchenne muscular dystrophy	dystrophin			1	(21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34)
EEC	P63	1			(35)
Epidermolysis bullosa lethal junctional (Herlitz)	LAMB3		1		(36)
Epidermolysis bullosa mild dystrophic form	COL7A1	1			(37)
Epidermolysis bullosa simplex	Keratin 5	1			(38)
Epilepsy, severe myoclonic form of infancy	SCN1A	1			(39, 40)
Fabry	alpha-gal A			1	(41)
Facioscapulohumeral myopathy	FSHD 4q35	1			(42, 43, 44, 45)
Factor X deficiency homozygous	Factor X		1		(46)
Familial Adenomatous Polyposis	APC	1			(47)
Familial hypertrophic cardiomyopathy	MYH7	1			(48)
Familial hypophosphatemic rickets (XLH)	PHEX			1	(49)
Fragile X	FraX (deletion)			1	(50)
Frontotemporal dementia with parkinsonism-17	MAPT	1			(51)
Hemoglobinopathy	beta-globin	1			(52)
Hemophilia A	Factor VIII			1	(53, 54, 55)
Hemophilia B	Factor IX			1	(56, 57, 58, 59)
Hunter	IDS			1	(60)

Disease	Gene	AD	AR	X-L	reference
Hutchinson-Gilford progeria	LMNA	1			(61)
Hyperparathyroidism–jaw tumour syndrome	HRPT2	1			(62)
Hypoparathyroidism sporadic isolated form	CASR	1			(63)
Kallmann syndrome	FGFR1	1			(64)
Lesch-Nyhan syndrome	HPRT			1	(65)
Li-Fraumeni	P53	1			(66)
Lowe syndrome	OCRL1			1	(67)
Marfan	FBN1	1			(68)
MODY 5	HNF-1beta	1			(69)
Neurofibromatosis 1	NF1	1			(70)
Ornithine transcarbamylase deficiency	OTC			1	(71)
Osteogenesis imperfecta	COL1A1/COL1A2	1			(72, 73, 73, 74, 75, 76)
Otopalatodigital syndrome (OPD) spectrum	FLNA			1	(77, 78)
Progressive external ophthalmoplegia	ANT1	1			(79)
Progressive external ophthalmoplegia	C10Orf2(Twinkle)	1			(80)
Pseudoachondroplasia	COMP	1			(81, 82)
Renal coloboma syndrome	PAX2	1			(83, 84, 85)
Resistance to thyroid hormone (RTH)	TRbeta	1			(86)
RETT	MECP2			1	(87, 88)
Subcortical band heterotopia	DCX			1	(89, 90)
Thanatophoric dysplasia type I (TDI)	FGFR3	1			(91)
Tuberous sclerosis complex	TSC1/2	1			(92, 93)
X-linked alpha thalassaemia mental retardation syndrome	ATRX			1	(94)
X-linked form of chronic granulomatous disease (CGD)	CYBB			1	(95)
X-linked dyskeratosis congenita	DKC1			1	(96)
X-linked mental retardation (XLMR)	ARX			1	(97)
X-linked mental retardation with microphthalmia and microcephaly	PQBP1			1	(98)
X-linked myotubular myopathy	MTMI			1	(99, 100)
X-linked severe combined immunodeficiency	IL2RG			1	(101, 102)

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