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The spectrum of inherited mutations causing HPRT deficiency: 75 new cases and a review of 196 previously reported cases

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Abstract

In humans, mutations in the gene encoding the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) are associated with a spectrum of disease that ranges from hyperuricemia alone to hyperuricemia with profound neurological and behavioral dysfunction. Previous attempts to correlate different types or locations of mutations with different elements of the disease phenotype have been limited by the relatively small numbers of available cases. The current article describes the molecular genetic basis for 75 new cases of HPRT deficiency, reviews 196 previously reported cases, and summarizes four main conclusions that may be derived from the entire database of 271 mutations. First, the mutations associated with human disease appear dispersed throughout the *hprt* gene, with some sites appearing to represent relative mutational hot spots. Second, genotype–phenotype correlations provide no indication that specific disease features associate with specific mutation locations. Third, cases with less severe clinical manifestations typically have mutations that are predicted to permit some degree of residual enzyme function. Fourth, the nature of the mutation provides only a rough guide for predicting phenotypic severity. Though mutation analysis does not provide precise information for predicting disease severity, it continues to provide a valuable tool for genetic counseling in terms of confirmation of diagnoses, for identifying potential carriers, and for prenatal diagnosis.

Abbreviations: HPRT, hypoxanthine-guanine phosphoribosyltransferase; HRH, HPRT-related hyperuricemia; HRND, HPRT-related neurologic dysfunction; LND, Lesch–Nyhan disease; LNV, Lesch–Nyhan variants; NA, not available; NS, not specified

1. Introduction

The enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) plays an important role in the purine salvage pathways, where it mediates the recycling of hypoxanthine and guanine into the usable nucleotide pools [1]. The human enzyme is encoded by a single gene that has nine exons spanning approximately 45 kb on the X-chromosome at Xq26-27 [2–7]. A single restriction fragment length polymorphism with three alleles has been identified in the *hprt* gene [8,9]. The restriction endonuclease *Bam*HI generates a 22/25 kb pair, a 12/25 kb pair, and a 18/22 kb pair [8]. The frequency of heterozygous females varies from 29 to 49% among different populations [8,10–12].

Mutations of the human *hprt* gene are responsible for a wide spectrum of disease that may be divided into three overlapping clinical phenotypes [1,13–15].

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The most mildly affected cases demonstrate only marked overproduction of uric acid, with resultant hyperuricemia, nephrolithiasis, and gout. Cases with intermediate severity display the uric acid overproduction, along with neurological abnormalities that range from only minor clumsiness to disabling neurological dysfunction. The most severely affected cases display uric acid overproduction, disabling neurological dysfunction, and behavioral abnormalities that include impulsive and self-injurious behaviors. This latter and most severe form of the disease is known as Lesch–Nyhan disease while the less complete phenotypic manifestations are designated Lesch–Nyhan variants.

The entire *hprt* gene with all intronic sequences has been cloned and sequenced [16], and efficient methods have been developed to precisely define potential mutations. As a result, the *hprt* gene has provided a valuable model for understanding the molecular mechanisms of mutation both in vivo and in vitro [17,18]. A growing database of information concerning mutations associated with human disease has made it possible to attempt to correlate different mutations with different elements of the disease phenotype. Since the most recent and comprehensive reviews of mutations associated with human HPRT deficiency have been presented [13,19], much additional work has been done. Prior reviews therefore each contain fewer than half of the currently defined mutations. In this article, we describe the molecular basis for 75 new cases of HPRT deficiency. We also review 196 previously reported cases and summarize the conclusions that may be derived from this extensive body of literature.

2. Materials and methods

2.1. Literature review

The Medline database through January 2000 was reviewed for articles describing mutations in the *hprt* gene that included the keywords *hypoxanthine-guanine phosphoribosyltransferase*, *Lesch–Nyhan*, or *Kelley-Seegmiller*. Additional cases were identified by reviewing the reference lists of these articles and prior reviews. Some of the mutations were also found in electronic databases: Online Mendelian Inheritance in Man (www3.ncbi.nlm.nih.gov), the Cardiff Human Gene Mutation Database (www.uwcm.ac.uk), and release six of the HPRT mutation database [20]. Each case or family is listed as a single occurrence, taking into consideration that some mutations were reported more than once. When mutations from different sources provided identical results, potential duplications were identified by comparing the initials of the case and city of origin where available. Some mutations evaluated by cDNA analysis alone were not included in the final summary, since it was not possible to distinguish deletions from splice site mutations.

2.2. New mutations

Mutations in the coding region of the *hprt* gene were characterized from blood lymphocytes or fibroblasts as previously described [21,22]. Cells were lysed and cDNA was synthesized with reverse transcriptase. The cDNA was amplified in two phases by the polymerase chain reaction (PCR). The first phase consisted of 30 cycles with an upstream primer recognizing bases 60 to 41 and a downstream primer recognizing bases 702–721. The second phase consisted of 30 cycles with an upstream primer recognizing bases 36 to 17 and a downstream primer recognizing bases 682–701. The PCR products were sequenced directly with a Taq DyeDeoxy Terminator Cycle Sequencing kit from Perkin-Elmer and a model 272A ABI automated sequencer. Mutations in non-coding regions were characterized by multiplex PCR amplification of genomic DNA [23] followed by sequencing. The mutations are presented with the cDNA being numbered with the A in the AUG start codon as the first base, and the initial methionine being numbered as the first amino acid. Since alternative numbering schemes have often been used, the original mutations in some prior reports required renumbering to be consistent with the currently used conventions.

2.3. Cases

For the purposes of this summary, the cases were grouped into one of three categories based on their clinical features. Cases with HPRT deficiency leading to uric acid overproduction only were designated HPRT-related hyperuricemia (HRH). A group with intermediate severity was designated HPRT-related hyperuricemia with neurologic dysfunction (HRND).

These cases had hyperuricemia with varying degrees of neurological abnormality but no self-injurious behavior. Cases with the full spectrum of disease including hyperuricemia, neurological dysfunction, and self-injurious behavior were designated Lesch–Nyhan disease (LND).

In most prior reports the clinical information provided made it possible to assign cases to one of the three disease categories. Although cases with HRH or HRND are sometimes described with the eponym Kelley-Seegmiller syndrome, this designation is not uniformly applied in the literature [1] and was therefore not used here. Cases described as Kelley–Seegmiller syndrome were reassigned to HRH or HRND if sufficient clinical information was presented, or listed in the tables as Lesch–Nyhan variants (LNV). Cases described as clinical variants of LND or 'mild' LND because of apparently normal cognition or absence of self-injury were designated HRND. Some reports with insufficient clinical information were listed in the tables as NA (not available). It should be noted that several cases were reported more than once, and clinical reassessment has occasionally led to the reassignment of the patient category.

Among the 75 new cases, 68 had the typical clinical features of LND including hyperuricemia with severe extrapyramidal and sometimes pyramidal motor dysfunction, cognitive disability, and recurrent self-injurious behavior. Five others had hyperuricemia with neurologic disability, but had never exhibited any self-injury (HRND). One patient had hyperuricemia with no obvious neurological or behavioral abnormalities (HRH). One was a female with a phenotype indistinguishable from that observed in males with LND.

3. Results

The 75 new cases are listed in Tables 1–6 in boldface type, together with 196 previously described cases for a total of 271 cases with 218 different mutations. A summary of all the mutations is provided in Tables 7–9 and depicted schematically in Figs. 1–4. Overall, a total of 200 cases were associated with the LND phenotype, 63 were associated with less severe forms of the disease (HRH or HRND), and eight could not be categorized from the clinical information presented (NA).

When all the mutations are considered together, 171 cases had single base substitutions, accounting for the majority of the total mutations (63.1%). Of the substitutions, 115 resulted in single amino acid substitutions (Table 1 and Fig. 1), 25 produced nonsense codons resulting in premature termination of protein translation (Table 2 and Fig. 2), and 31 resulted in splicing errors (Table 3). Transitions at four CpG dinucleotide sites comprised 14.6% of the single base substitutions and 9.2% of all the mutations. Excluding this unique class of G:C to A:T transitions, other transitions and transversions occurred at similar frequencies, although both types of single base substitutions were more frequent at G:C base pairs (69.6%) than at A:T base pairs (32.3%). Single base substitutions accounted for the majority of cases with HRH or HRND (87.3%).

There were also 65 cases with deletions of one or more bases, representing 24.0% of the total mutations. The majority occurred in coding regions (Table 4 and Fig. 3), though four were associated with splicing errors (Table 3). Approximately half of the deletions were large, defined as the loss of one or more exons. Of the large deletions, only two of eight showed identical sequence at the break point. The majority of small deletions of only 1–3 base pairs occurred in single base runs or repeated sequences. Only two deletions were associated with HRH or HRND. One occurred at the extreme 3′ end of the coding region and the other occurred at the 5′ end.

There were 20 insertions of one or more bases, representing 7.4% of the total mutations. Of the insertions, 18 resulted in a frame shift and one resulted in a splicing error (Tables 3 and 5). The last insertion, the only case with HRND, was associated with a three base pair addition that resulted in the introduction of a single additional amino acid without disturbing the normal reading frame. A total of eight insertions occurred at single base runs or repeated sequences, while a repeat was created in two cases. The most frequent insertion was the addition of a G in the run of 6 Gs from base position 207–212 in exon 3.

There were six cases with duplications, including a new one consisting of eight nucleotides (ATGCCCTT) from positions 572–579 that was derived from cells cultured from one of the original index cases [24]. There were four additional cases with more complex mutations (Table 6). Two of these were two single base substitutions separated by one base

Table 1
Point mutations leading to amino acid substitutions

Name	Case	Mutation	Exon	Base	Codon	Result	Source
1151, JR	LND	G>A	1	3	1	met>ile	[28]
LN49, JT	**LND**	**G>A**	**1**	**3**	**1**	**met>ile**	**New**
NS[a]	HRND	G>C	1	3	1	met>thr	[53]
Gravesend	HRH	G>A	1	20	7	gly>asp	[30]
HB	HRND	T>G	1	23	8	val>gly	[22]
LN8, GA	**LND**	**T>A**	**2**	**29**	**10**	**ile>asn**	**New**
Urangan, GL	HRND	G>A	2	46	16	gly>ser	[54]
FG	LND	G>A	2	47	16	gly>asp	[22]
Mashad	LNV	A>T	2	59	20	asp>val	[30]
NS[a]	HRH	G>T	2	68	23	cys>phe	[55]
JS	HRND	C>G	2	69	23	cys>trp	[22]
Yonago	HRH	C>A	2	73	25	pro>thr	[56]
AS	**LND**	**T>C**	**2**	**95**	**32**	**leu>ser**	**New**
LN72, CF	**LND**	**G>C**	**2**	**96**	**32**	**leu>phe**	**New**
LN24, JJ	**LND**	**C>T**	**2**	**113**	**39**	**pro>leu**	**New**
Huelva, LN-H	LND	G>A	2	118	40	gly>arg	[41]
Detroit, KM	LND	T>C	2	122	41	leu>pro	[57]
Isar, KM	LND	A>T	2	124	42	ile>phe	[27]
Heapy	NA	T>C	2	125	42	ile>thr	[30]
Santona	LNV	T>C	2	125	42	ile>thr	[41]
NS[a]	LNV	G>A	2	134	45	arg>lys	[58]
RJK 2163, TD	LND	G>A	2	134	45	arg>lys	[23]
GLA 7292	LND	G>A	2	134	45	arg>lys	[59]
LN59, CC	**LND**	**G>A**	**2**	**134**	**45**	**arg>lys**	**New**
LN11C, MC, MC	**LND**	**A>G**	**3**	**140**	**47**	**glu>gly**	**New**
LN40-3, CC	**LND**	**A>T**	**3**	**140**	**47**	**glu>val**	**New**
AG	HRH	G>A	3	143	48	arg>his	[22]
DD	HRH	G>A	3	143	48	arg>his	[22]
Madrid II	LNV	G>A	3	143	48	arg>his	[41]
LW	HRND	G>C	3	148	50	ala>pro	[22]
1265, RS	LND	C>T	3	149	50	ala>val	[28]
Toronto, LP	HRH	C>G	3	151	51	arg>gly	[36,60]
Banbury	NA	G>C	3	152	51	arg>pro	[30,59]
Tsou	*HRH*	G>A	3	152	51	arg>gln	[61]
TE	HRH	G>A	3	157	53	val>met	[22]
MG	HRH	T>C	3	158	53	val>ala	[22]
Japan1	LND	A>C	3	160	54	met>leu	[43]
Montreal	HRND	T>C	3	170	57	met>thr	[62]
Toowong, PH	LNV	G>A	3	173	58	gly>arg	[54]
Case #2	LND	G>C	3	190	64	ala>pro	[63]
GH	LND	C>A	3	191	64	ala>asp	[46]
LN56, JW	**HRH**	**C>T**	**3**	**193**	**65**	**leu>phe**	**New**
CT	**LND**	**T>C**	**3**	**194**	**65**	**leu>pro**	**New**
LN-J	**LND**	**T>C**	**3**	**196**	**66**	**cys>arg**	**New**
LN53, EC	**LND**	**T>G**	**3**	**203**	**68**	**leu>arg**	**New**
NS[a]	LND	G>A	3	208	70	gly>arg	[56]
Utrecht	LND	G>A	3	208	70	gly>arg	[64]
AL	**LND**	**G>C**	**3**	**208**	**70**	**gly>arg**	**New**
M	LND	G>T	3	208	70	gly>trp	[65]
New Haven, DG	LND	G>A	3	209	70	gly>glu	[57]
955-2, JP	LND	G>A	3	209	70	gly>glu	[28]
1510, JF	LND	G>A	3	209	70	gly>glu	[28]
Yale, KT	LND	G>C	3	211	71	gly>arg	[66,67]

Table 1 (*Continued*)

Name	Case	Mutation	Exon	Base	Codon	Result	Source
DW, SW	**LND**	**G>T**	**3**	**212**	**71**	**gly>val**	**New**
NS[a]	HRND	G>T	3	212	71	gly>val	[58]
Madrid I	LNV	G>T	3	212	71	gly>val	[41,64]
Tachikawa, HK	HRH	A>G	3	215	72	tyr>cys	[68]
Seoul, Y27C	HRH	A>G	3	215	72	tyr>cys	[69,70]
LN58, SJ	**LND**	**T>G**	**3**	**221**	**74**	**phe>cys**	**New**
DW	LND	C>A	3	222	74	phe>leu	[22]
Perth, BB	LND	C>A	3	222	74	phe>leu	[54]
Flint, RJK 892, AC	LND	C>A	3	222	74	phe>leu	[29,71]
1522, GH	LND	C>A	3	222	74	phe>leu	[28]
Taichung	LND	C>G	3	222	74	phe>leu	[72]
Swan, DW	HRH	C>G	3	232	78	leu>val	[54]
Case #3	LND	T>A	3	233	78	leu>gln	[63]
Arlington, MS, WB	LNV	A>T	3	239	80	asp>val	[57]
Munich, IV	HRH	A>G	3	310	104	ser>arg	[36,60]
DB	HRH	C>T	4	329	110	ser>leu	[60]
London, GS	HRH	C>T	4	329	110	ser>leu	[36,60]
DW	**HRND**	**C>G**	**4**	**371**	**124**	**thr>ser**	**New**
375[c]	LND	T>A	5	389	130	val>asp	[28]
Midland, RJK 896, JH	LND	T>A	5	389	130	val>asp	[29,32]
RJK 1784	LND	T>C	5	392	131	leu>ser	[29]
LN-C, LN30, SM	**LND**	**T>G**	**5**	**395**	132	**ile>ser**	**New**
Runcorn	NA	T>C	5	395	132	ile>thr	[30]
Ann Arbor, KC, TC	HRH	T>G	5	396	132	ile>met	[33]
Zaragoza I	LNV	G>A	5	397	133	val>met	[41]
NS[a]	HRH	A>T	6	404	135	asp>val	[58]
Yeronga, SB	HRH	A>G	6	404	135	asp>gly	[19]
JG	**LND**	**T>A**	**6**	**407**	**136**	**ile>lys**	**New**
Tokyo, YY	LND	G>A	6	419	140	gly>asp	[31,68,73]
Niigata, DS	HRH	G>T	6	472	158	val>phe	[69]
Milwaukee, RJK 949, JM	HRH	G>T	6	481	161	ala>ser	[29,57]
LN3, CJW	**LND**	**C>A**	**6**	**482**	**161**	**ala>glu**	**New**
Farnham	NA	C>G	7	486	162	ser>arg	[30,59]
Brisbane, FC	HRH	C>T	7	503	168	thr>ile	[39]
Marlow	LNV	C>T	7	527	176	pro>leu	[30,59]
RJK 2185	LND	G>T	7	529	177	asp>tyr	[23]
LN4, LN14, ADC	**LND**	**G>A**	**8**	**539**	**180**	**gly>glu**	**New**
1734, BF, JF	HRH	T>C	8	548	183	ile>thr	[22,28]
Case #1	HRND	T>C	8	563	188	val>ala	[63,74]
LN36, JJN	**LND**	**G>T**	**8**	**565**	**189**	**val>leu**	**New**
LN73, AS	**LND**	**G>C**	**8**	**568**	**190**	**gly>arg**	**New**
JM	HRND	T>G	8	578	193	leu>arg	[46]
EC	**LND**	**G>T**	**8**	**580**	**194**	**asp>tyr**	**New**
LN46, FD	**LND**	**G>C**	**8**	**580**	**194**	**asp>his**	**New**
Kinston, RJK 2188, ES	LND	G>A	8	580	194	asp>asn	[23,37,60]
Moose Jaw	HRH	C>G	8	582	194	asp>glu	[40]
Dirranbandi, CC[b]	HRH	A>G	8	584	195	tyr>cys	[19]
NS[a]	HRND	A>G	8	586	196	asp>asn	[58]
LN15, Brasil	**LND**	**A>T**	**8**	**590**	**197**	**glu>val**	**New**
New Brighton, RJK 950, EC	LND	T>G	8	595	199	phe>val	[29,57]
BT, LN39	HRND	G>C	8	599	200	arg>thr	[75]
RB	HRH	G>A	8	601	201	asp>asn	[22]
GM	LND	G>T	8	601	201	asp>tyr	[22]
Ashville, PC	HRH	A>G	8	602	201	asp>gly	[38]

Table 1 (*Continued*)

Name	Case	Mutation	Exon	Base	Codon	Result	Source
H768	LND	C>T	9	610	204	his>tyr	[76]
RJK 1874	LND	C>G	9	610	204	his>asp	[29]
RJK 2079	LND	C>G	9	610	204	his>asp	[23]
BM	**LND**	**A>G**	**9**	**611**	**204**	**his>arg**	**New**
779, JD	LND	A>G	9	611	204	his>arg	[28]
Reading	LND	G>A	9	617	206	cys>tyr	[30,59]
RJK 1727	LND	G>A	9	617	206	cys>tyr	[29]
LN27, AH	**LND**	**G>A**	**9**	**635**	**212**	**gly>glu**	**New**

[a] Designates a mutation for which no identifying information was provided for nomenclature.
[b] Quoted in prior review [19] but not published in primary literature.
[c] A subsequent re-analysis of this case provided a different result shown as DL in Table 6.

(Salamanca and Japan2). Both were T to G combined with G to A, and occurred near the intron/exon boundary. Salamanca occurred near the exon 2 splice acceptor site and Japan2 near the exon 8 splice donor site. A third compound mutation was also proximal to a splice donor site in exon 5 (LN-9). In this mutation there was a net deletion of GTAA preceding the gtaagt exon 5 splice donor site. These three compound mutations may reflect the unique structure of intron/exon boundaries. Another compound mutation was a five base deletion together with a six base insertion in exon 6: 428-431delTGCAG,

Table 2
Point mutations leading to premature stop

Name	Case	Mutation	Exon	Base	Codon	Result	Refs.
754-4, DD	LND	C>T	3	151	51	arg>stop	[28]
AS	LND	C>T	3	151	51	arg>stop	[22]
Estrie, LN-N	LND	C>T	3	151	51	arg>stop	[26]
Fujimi, TH	LND	C>T	3	151	51	arg>stop	[68,73,77]
Kanagawa, KF	LND	C>T	3	151	51	arg>stop	[68]
LN-E, CDS	**LND**	**C>T**	**3**	**151**	**51**	**arg>stop**	**New**
MS, LN40-2	LND	C>T	3	151	51	arg>stop	[22]
NS[a]	LND	C>T	3	151	51	arg>stop	[78]
Sagamie, LN-O	LND	C>T	3	151	51	arg>stop	[26]
Shefford	NA	C>T	3	151	51	arg>stop	[30,59]
TB, LN68	**LND**	**C>T**	**3**	**151**	**51**	**arg>stop**	**New**
RJK 1930	LND	C>T	4	325	109	gln>stop	[23]
PW	LND	C>G	4	368	123	ser>stop	[22]
1321, LN11D, JG	LND	C>T	7	508	170	arg>stop	[28]
LN48, AJ	**LND**	**C>T**	**7**	**508**	**170**	**arg>stop**	**New**
Almodovar	LND	C>T	7	508	170	arg>stop	[41]
B	LND	C>T	7	508	170	arg>stop	[65]
GS	HRND	C>T	7	508	170	arg>stop	[27]
LN40-5, JC	**LND**	**C>T**	**7**	**508**	**170**	**arg>stop**	**New**
JG810	LND	C>T	7	508	170	arg>stop	[76]
NB	LND	C>T	7	508	170	arg>stop	[79]
North Mymms	LND	C>T	7	508	170	arg>stop	[30,59]
RJK 974	LND	C>T	7	508	170	arg>stop	[29]
DB	**LND**	**A>T**	**8**	**602**	**201**	**asp>vAl**	**New**
KB	**LND**	**G>T**	**9**	**634**	**212**	**gly>stop**	**New**

[a] Designates a mutation for which no identifying information was provided for nomenclature.

Table 3
Point mutations leading to splicing errors

Name	Case	Mutation	Result	Refs.
JLY	HRND	IVS1+1G>A	Inclusion of IVS1+1 to 49 in mRNA	[46]
MM	**LNV**	**IVS1+1G>T**	**Inclusion of IVS1+1 To 49 in mRNA**	**New**
LN11B, LR	**HRND**	**IVS1+1G>T**	**Inclusion of IVS1+1 to 49 in mRNA**	**New**
LN5, BN	**LND**	**IVS1-2A>G**	**E2 excluded**	**New**
RJK 1760, CB	LND	IVS1-2A>T	E2 excluded	[23]
JC	**HRND**	**IVS2+1G>A**	**E2 excluded**	**New**
LN35, CO	**LND**	**209G>T**	**Exclusion of 208-318**	**New**
Keio	LND	IVS3+1G>T	E3 excluded, multiple mRNAs	[80]
Q109X	LND	325C>T	E4 excluded	[70]
LN66, MD	**LND**	**IVS3-2A>G**	**E4 excluded**	**New**
JR, RR	**LND**	**IVS4+1G>T**	**E4 excluded**	**New**
TL	HRH	IVS5+1229A>G	Multiple mRNAs	[22]
Richelieu, LN-M	**LND**	**IVS5-1G>A**	**E6 excluded, 403delG**	**New**
DB	**HRND**	**IVS5+1G>A**	**Aberrant mRNA**	**New**
NS[a]	LND	IVS6+1G>A	E6 excluded, multiple mRNAs	[58]
Chermside, RW	LND	IVS6+1G>A	E6 excluded, multiple mRNAs	[81]
DL[b]	**LND**	**IVS7+1G>A**	**E7 excluded**	**New**
RJK 1934	LND	IVS7+5G>A	E7 excluded	[23]
LN67, MP	**LND**	**IVS7+5G>A**	**E7 excluded**	**New**
NS[a]	LND	IVS7+5G>C	E7 excluded	[58]
NS[a]	LND	IVS7-1G>A	E8 excluded	[58]
Sevilla	LND	IVS7-2A>G	E8 excluded	[41]
533-9T>A	LND	IVS7-9T>A	E8 excluded	[70]
Shinagawa, TS	LND	538G>A	E8 excluded	[68]
RJK 888, GM 7092	LND	IVS8+5G>A	E8 excluded	[23,29,82]
LN-I, Peru	**LND**	**IVS8+5G>T**	**E8 excluded**	**New**
LN29, JR	**LND**	**IVS8+6T>G**	**E8 excluded**	**New**
LN33	**LND**	**IVS8+6T>C**	**E8 excluded**	**New**
NS[a]	LND	IVS8+6T>C	E8 excluded	[58]
RJK 906, GM 1899	LND	IVS8-2A>T	17 bp of E9 excluded	[23,29,82]
AS	LND	IVS8-2A>G	17 bp of E9 excluded	[46]

[a] Designates a mutation for which no identifying information was provided for nomenclature.
[b] Previously reported as 375 with a different result shown in Table 1.

insAGCAAA. This mutation created an unusual seven base repeated sequence: GGCAAAACA A[TG CAG] ACT>GGCAAA ACA A[AGCAAA] ACT. There was also another mutation in this sequence, 429insGCA, which changed the TG CAG to TG[GCA] CAG. No other mutations have been reported in this region of exon 6.

Since the disease is inherited in an X-linked recessive manner, nearly all cases were males. However, five females with a typical LND phenotype have been identified (Table 6). One of these female cases had a nonsense mutation in the paternal allele together with non-random inactivation of the maternal allele, the second had a nonsense mutation in the maternal allele together with non-random inactivation of the paternal allele, the third had complete deletion of the maternal allele with non-random inactivation of the paternal allele, and the fourth had a nonsense mutation together with reduced expression from the second allele for unknown reasons. A new female case had a splicing mutation with non-random X-inactivation leading to somatic mosaicism.

A screening study for low blood HPRT among 1000 normal volunteers has led to the identification of one asymptomatic individual with 37–46% residual HPRT activity resulting from a point mutation changing histidine to arginine at codon 60 [25]. Whether this case should be considered as a rare polymorphism or an asymptomatic mutant is not clear, so it was omitted from the tables.

Table 4
Deletions

Name	Case	Mutation	Sequence context	Result	Refs.
Illinois, RJK 951, RT, WE	LNV	(−)12-(+)1delGCC...	CGCCCG[GCC...TTA] TGGCG	13 bp deleted; alternate start	[29,42,82]
LN11E, AE, HE	**LND**	**E1**		**1 exon deleted**	**New**
SS	**LND**	**E1**		**1 exon deleted**	**New**
M97/1	LND	E1		1 exon deleted	[76]
G 137	NA	E1–3		3 exons deleted	[83]
LN12	**LND**	**E1–3**		**3 exons deleted**	**New**
RJK 853, McA	LND	E1–9		Whole gene deleted	[23,84]
RR, JR	**LND**	**E1–9**		**Whole gene deleted**	**New**
FE, 1423[b]	**LND**	**82–84delTAT**	**CAT [TAT] GCT**	**1 amino acid coded by E2 lost**	**New**
RJK 1939, LN7, BB	LND	125delT	CTA A[T]T ATG (2 base run)	Frame shift in E2	[23]
MG	**LND**	**E2**		**1 exon deleted**	**New**
C96/12	LND	Tandem genomic deletion involving E2		Partial E2 deletion	[76]
AN	**LND**	**E2–3**		**2 exons deleted**	**New**
G 316	NA	E2–3		2 exons deleted	[83]
II-2	LND	E2–3		2 exons deleted	[85]
NS[a]	LND	E2–3		2 exons deleted	[86]
Adachi, NT	LND	E2–3		2 exons deleted	[68]
Ca	LND	E2–9		8 exons deleted	[65]
NS[a]	LND	IVS2+1delG	GAC AG[G] taa (2 base run)	Splice error; E2 excluded	[58]
RJK 2108, RK	LND	156–195delATG...	CGAGA [TGTG...CCTC] TGTGT (4 base sequence)	40 bp deleted in E3	[23]
NS[a]	LND	156delT	CGA GA[T] GTG	1 bp deleted in E3	[58]
Zu	LND	196–197delTG	CTC [TG]T GTG (run of 3 TG pairs)	2 bp deleted in E3	[65]
LN28	**LND**	**247–248delAA**	**ATC [AA]A GCA (3 base run)**	**Frame shift in E3**	**New**
NS[a]	LND	289–290delGT	ACT [GT]A GAT	Frame shift in E3	[58]
289delGT	LND	289–290delGT	ACT [GT]A GAT	Frame shift in E3	[70]
Cheltenham	LND	289–290delGT	ACT [GT]A GAT	Frame shift in E3	[30,59]
RJK 1332, RC	LND	289–290delGT	ACT [GT]A GAT	Frame shift in E3	[29]
NS[a]	LND	307–308delAA	CTG [AA]G AGC	2 bp deleted in E3	[58]
RJK 1747, JM	LND	317–318delGT	TAT T[GT] gtg (run of 2 GT pairs)	Frame shift in E3	[23]
Case 2 or 4	LND	319–322delAATG	tag[AAT G]AC	Splice error; E4 excluded	[63,74]
G 323	LND	E3		1 exon deleted	[83]
P-JG	LND	E3–9		7 exons deleted	[27]
Andorra	LND	319–384delAAT...		Exon 4 deleted	[41]
Murcia	LND	333–334delAG	AC[A G]GG GAC	Frame shift in E4	[41]
Asturias	LND	342delA	GAC AT[A] AAA (4 base run)	Frame shift in E4	[41]
CC	**LND**	**322–389delGAC**...		**67 bp deletion spanning E4–5**	**New**
Co	LND	E4		1 exon deleted	[65]
LN52, FI	**LND**	**E4**		**1 exon deleted**	**New**
LN40-1, PB	**LND**	**E4**		**1 exon deleted**	**New**
RT	**LND**	**E4**		**1 exon deleted**	**New**
LN1, PB	**LND**	**E4–5**		**2 exons deleted**	**New**
NS[a]	LND	E4–6		3 exons deleted	[86]
JS, RJK 849	LND	E4–9		6 exons deleted	[84]
LN62, JO	**LND**	**E4–8**		**5 exons deleted**	**New**
LN10	**LND**	**E4–9**		**6 exons deleted**	**New**
RJK 2019	LND	391delT	GTC [T]TG ATT (2 base run)	Frame shift in E5	[23]

Table 4 (*Continued*)

Name	Case	Mutation	Sequence context	Result	Refs.
Henryville, LN-D	LND	IVS5+1delG	GAA [g]ta agt	Splice error; 66 bp of I5 included, multiple mRNAs	[21]
RS	**LND**	**E5**		**1 exon deleted**	**New**
LN-K, MD-H	**LND**	**E5–6**		**2 exons deleted**	**New**
NS[a]	LND	435–436delTT	AC [T T]TG CTT (3 base run)	2 bp deleted in E6	[58]
LNF, LI	**LND**	**460–470delAAT**...	**AG TAT [AAT**...GAT**] GGTCA (2 base sequence)**	**11 bp deleted in E6**	**New**
RJK 984	LND	E6–9		4 exons deleted	[87]
RJK 1894, PK	LND	514–516delGTT	AGT [GTT] GGA	1 amino acid coded by E7 lost	[23]
ZH	**LND**	**519–520delAT**	**GG[A T]AT AAG (run of 2 AT pairs)**	**2 bp deleted**	**New**
DL	LND	E7		1 exon deleted	[22]
GM 3467	LND	E7–9		3 exons deleted	[84]
NS[a]	LND	E7–9		3 exons deleted	[86]
Michigan, DA	LND	535–537delGTT	gTT [GTT] GGA (run of 2 GTT triplets)	Val179 lost	[57]
RJK 855	LND	536–538delTTG	gTT G[TT G]GA (run of 2 TTG triplets)	Val 179 lost	[29,82]
Case 5	LND	IVS8-16 to E9+58 del	tttct[gga...AGTT] CAAGT	Deletion of splice acceptor with cryptic splice acceptor	[63]
GLA 791	LND	548delT	GAA A[T]T CCA (2 base run)	Frame shift in E8	[59]
Brierly Hill	NA	617–618delGT		Frame shift in E9	[30]
631delA	LND	629delA	AGT G[A]A ACT (3 base run)	Frame shift in E9	[70]
Evansville, RJK 894, BS, FE	LND	643–663delAAA...	AAGCA[AAA...CAG] AGTTC	21 bp deleted in E9	[23,57,82]
Japan 3	HRH	648–698delCAA...	AAATA[CAA...CTA] TTGAC	51 bp deleted in E9	[43]

[a] Designates a mutation for which no identifying information was provided for nomenclature.
[b] Previously reported incorrectly as 80–82delATT [28].

4. Discussion

To date, the molecular genetic basis of a total of 271 cases of varying degrees of HPRT deficiency has been determined. Mutation analysis has proven valuable for confirmation of diagnoses, carrier detection, preimplantation testing, and prenatal diagnosis. In addition, there has been considerable interest in determining potential relationships between the mutations and the disease phenotype. The conclusions that may be derived from this extensive body of literature are summarized below.

4.1. Mutational hot spots

Though mutations responsible for human disease appear throughout the *hprt* gene, several sites appear to represent mutational hot-spots (Table 9). The C to T substitution changing arginine to stop at codon 51 has emerged 12 times in apparently unrelated patients (Tables 2 and 6). This mutation occurs at a CpG motif, and is likely to be related to the frequent methylation of cytosine residues in these motifs, with subsequent deamination of 5-methylcytosine to produce thymine [26]. A similar C to T mutation has been identified in another 11 cases at another CpG motif at codon 170 (Tables 2 and 6), presumably via the same mechanism. Three similar mutations occur at a CpG at nucleotide 143 and a fourth at nucleotide 152.

Other relative hot-spots for mutation include four cases with C222A (Table 1), four with G134A (Table 1), four with 289-290delGT (Table 4) and four with 212insG (Table 5). The molecular mechanism for the last mutation is likely to be strand slippage, since it

Table 5
Insertions

Name	Case	Mutation	Sequence context	Result	Refs.
Chicago, DM	LND	55insT	GAC C[T]TT GAT (2 base run)	Frame shift in E2	[57]
Coorparoo, JG	LND	71insT	TGC AT[T]A CCT	Frame shift in E3	[81]
Zaragoza II, LN-H	LND	100insGG	GAA AGG G[GG] TG (6 base run)	Frame shift in E2	[41]
IJ	LND	212insG	AAG GGG GG[G]C (6 base run)	Frame shift in E3	[27]
1650, CW	LND	212insG	AAG GGG GG[G]C (6 base run)	Frame shift in E3	[28]
RJK 866, CW	LND	212insG	AAG GGG GG[G]C (6 base run)	Frame shift in E3	[29]
34MM/95	LND	212insG	AAG GGG GG[G]C (6 base run)	Frame shift in E3	[76]
NS[a]	LND	214insG	GGC T[T]AT AAA	Frame shift in E3	[58]
LN55, CM	**LND**	**219insA**	**TAT AAA[A] TTC**	**Frame shift in E3**	**New**
CT	**LND**	**288insA**	**ATG ACT[A] GTA**	**Frame shift in E3**	**New**
Codicote	LND	298insT	GAT TTT[T] ATC (4 base run)	Frame shift in E3	[30,59]
310insG	LND	310insG	CTG AAG[G] AGC	Frame shift in E3	[70]
LN34, TS	**LND**	**371insTT**	**ACT TT[TT]A ACT (3 base run)**	**Splice error; E4–5 excluded**	**New**
Cartagene, LN-H	LND	405insA	GAT[A] ATA ATT (creates ATA repeat)	Frame shift in E6	[41]
AB	**LND**	**405insA**	**GAT[A] ATA ATT (creates ATA repeat)**	**Frame shift in E6**	**New**
RW, TW	HRND	429insGCA	ATG [GCA] CAG ACT	E6 codes for an additional amino acid	[22]
1656, CW	LND	436insT	ACT TT[T]G CTT (3 base run)	Frame shift in E6	[28]
1266, PW	LND	511insGT	CGA A[GT]GT GTT (run of 2 GT pairs)	Frame shift in E7	[28]
NS[a]	LND	556insT	GAC A[T]AG TTT	Frame shift in E8	[58]
NS[a]	LND	594insTA	GAA TA[TA]C TTC (creates TA repeat)	Frame shift in E8	[58]

[a] NS designates a mutation for which no identifying information was provided for nomenclature.

Table 6
Other mutations

Name	Case	Mutation	Result	Refs.
GM 6804	HRND	Duplication I1	13.7 kb duplicated with rare reversion	[44,60]
Salamanca, AA, JA	HRND	T128G and G130A	2 amino acids altered in E2	[22,41]
LN26	**LND**	**Duplication E2–E3**	**2 exons duplicated**	**New**
GM 1622, DM	HRND	Duplication E2–E3	2 exons duplicated with rare reversion	[22,45,44]
LN9	**LND**	**398–402delTGGAA; insG**	**5 bp replaced with 1 bp in E5**	**New**
RJK 1210, LN40-4, GB	LND	428–432delTGCAG, insAGCAAA	6 bp substituted for 5 bp in E6	[29]
Japan2	HRND	T536G and G538A	2 amino acids altered in E8	[43]
HJ	HRND	Duplication E7–8	2 exons duplicated	[88]
PJ	**LND**	**Duplication E7–8**	**2 exons duplicated**	**New**
MW	**LND**	**dup572–579ATGCCCTT**	**8 bp duplication**	**New**
Paris	Female LND	Maternal X inactivated; paternal T459G stop mutation	Both alleles dysfunctional	[89]
FLN	Female LND	Paternal X inactivated; maternal gene deleted	Both alleles dysfunctional	[90]
LN54, RM	**Female LND**	**Mosaic paternal X inactivation; maternal IVS8+4A>G**	**Both alleles dysfunctional**	**New**
S	Female LND	Paternal X inactivated; maternal C508T stop mutation	Both alleles dysfunctional	[91]
NS[a]	Female LND	One X allele nonfunctional C151T stop mutation	Both alleles dysfunctional	[92]

[a] Designates a mutation for which no identifying information was provided for nomenclature.

Table 7
Summary of mutations causing HPRT deficiency

Mutation	LND (*n*=200)	LNV (*n*=63)	NA (*n*=8)	Total (*n*=271)
Single base substitution				
Missense	63	48	4	115
Nonsense	23	1	1	25
Splice error	25	6	0	31
Deletion				
Coding sequences	56	2	3	61
Splice error	4	0	0	4
Insertion				
Coding sequences	18	1	0	19
Splice error	1	0	0	1
Others				
Duplication	3	3	0	6
Substitutions	2	0	0	2
Females	5	0	0	5
Double	0	2	0	2

occurs in a series of six guanines [27–29]. Additional mutations reported for three cases each have included G143A, G209A and G212T (Table 1).

4.2. Mutations altering enzyme kinetics

Several investigators have proposed that clinically relevant mutations associated with altered enzyme kinetics might cluster in evolutionarily conserved regions of the gene that encode important functional domains of the HPRT enzyme, such as the binding site for the co-substrate phosphoribosylpyrophosphate [28,30–33]. This binding site, initially determined by comparing sequence homologies among several phosphoribosyltransferases, extending from amino acid 129–140, was subsequently confirmed by X-ray crystallography [34,35]. Though initial work confirmed a clustering of mutations at this site [23,36–40], a review of all currently available mutations associated with an altered affinity for the purine bases or phosphoribosylpyrophosphate indicates that most are located outside the binding site identified by X-ray crystallography [34,35]. These observations suggest that mutations distant from the active site may nevertheless have a significant influence on enzyme function as a result of conformational changes that indirectly alter the active site.

Table 8
Summary of HPRT mutation types

Mutation	Number	Percent of category	Percent of total
Single base substitution	171	100	63.1
Transitions	101	59.1	
CpG(G:C>A:T)	25	14.6	
G:C>A:T	47	27.5	
A:T>G:C	29	17.0	
Transversions	70	40.9	
G:C>C:G	20	11.7	
G:C>T:A	25	14.4	
A:T>C:G	10	5.8	
A:T>T:A	15	8.8	
Deletion	65	100	24.0
1 base pair	8	12.3	
2 base pairs	12	18.5	
3 base pairs	4	6.2	
>3 base pairs	10	15.4	
>exon	33	50.8	
Insertion	20	100	7.4
1 base pair	15	75.0	
2 base pairs	4	20.0	
3 base pairs	1	5.0	
Others	15	100	5.5
Duplications	6	40.0	
Double mutations	7	46.7	
Substitutions	2	13.3	

Table 9
Summary of most frequent HPRT mutations

Mutation	Number	Percent of category	Sequence context
Single base substitution	171		
CpG			
G143A	3	1.8	GAA CGT CTT
C151T	11	6.4	GCT CGA GAT
C508T	10	5.8	CCA CGA AGT
Transitions			
G134A	4	2.3	GAC AGg taa
G209A	3	1.7	AAG GGG GGC
Transversions			
G212T	3	1.7	GGG GGC TAT
C222A	4	2.3	AAA TTC TTT
Small deletions	34		
289–290delGT	4	11.8	ACT [GT]A GAT
Small insertions	19		
212insG	4	21.1	AAG GGG GG[G]C

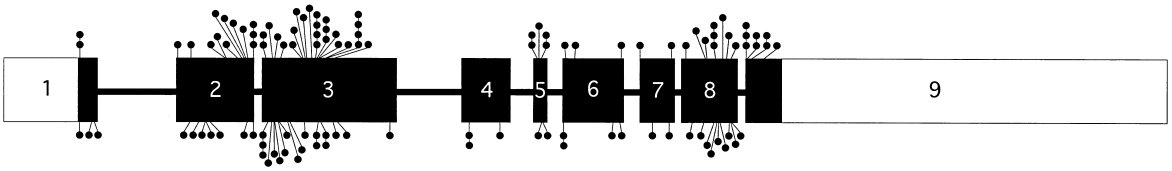

Fig. 1. Single *hprt* base substitutions leading to single amino acid substitutions. The nine exons of the gene are shown as individual boxes, with the coding regions in black and the non-coding regions pale. Individual point mutations are shown as circles. Those associated with the LND phenotype are shown above the gene, while those associated with HRND or HRH are shown below the gene.

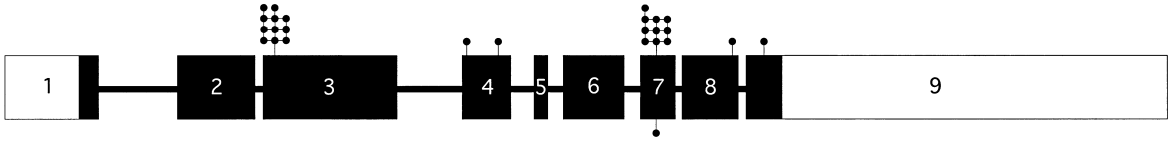

Fig. 2. Single *hprt* base alterations leading to premature stop. Individual nonsense mutations are shown as circles. Those associated with the LND phenotype are shown above the gene, and the single nonsense mutation reported in a case with HRND is shown below the gene.

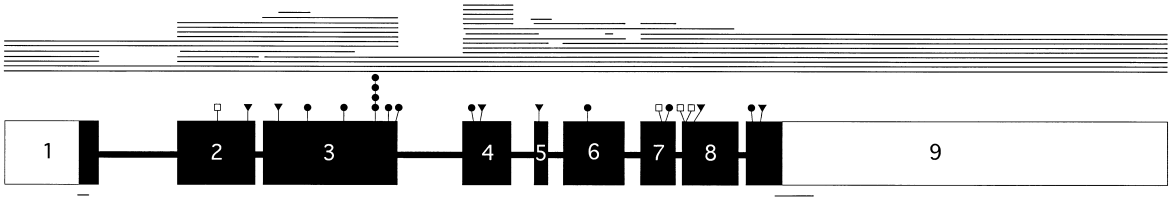

Fig. 3. Deletion mutations in the *hprt* gene. Single base deletions are shown as triangles, two base deletions are shown as circles, three base deletions are shown as squares, and large deletions are shown as a horizontal line spanning the deleted segment. Deletions associated with the LND phenotype are shown above the gene, while the two deletions associated with HRND are shown below the gene.

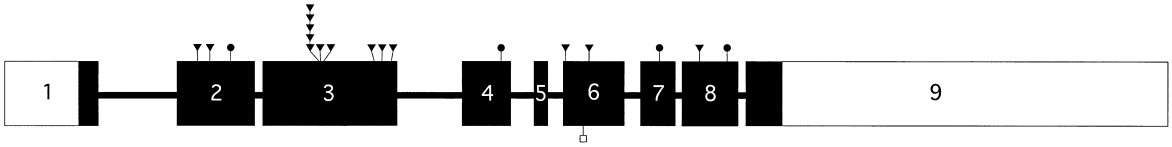

Fig. 4. Insertion mutations in the *hprt* gene. Single base insertions are shown as triangles, two base insertions are shown as circles, and three base insertions are shown as squares. Insertions associated with the LND phenotype are shown above the gene, while one insertion associated with HRND is shown below the gene.

4.3. Genotype–phenotype correlations

Several investigators have attempted to correlate different sites or types of mutations with various aspects of the disease phenotype [22,41]. Such correlations are of interest because they may allow genetic counselors to predict phenotypic severity for cases identified by prenatal screening or for cases identified in the early postnatal period. Genotype–phenotype correlations may also provide clues towards pathogenesis by pointing to specific functional domains of the HPRT enzyme that might be responsible for different elements of the clinical phenotype.

The available mutations do not suggest an association between specific sites of mutation and the presence or absence of various clinical features such as hyperuricemia, neurologic dysfunction, or self-injurious behavior (Figs. 1–4). However, the less severe forms

of the disease might be expected to be associated with mutations predicted to allow some residual enzyme function, since the severity of disease depends on the amount of residual HPRT enzyme activity [1,13,14]. Cases with the full spectrum of disease associated with LND generally have less than 1.5% of residual enzyme activity in cultured fibroblasts, while those with HRND have 1.5–8% residual activity, and those with HRND have more than 8% residual activity. Though some exceptions have been reported, the measurement of residual enzyme activity in cultured fibroblasts provides a reasonable approximation for stratification of disease severity. Indeed, the large majority of cases lacking the full spectrum of clinical features associated with LND have point mutations leading to amino acid substitutions rather than nonsense mutations, deletions, insertions, or substitutions (Figs. 1–4). This is to be expected if the severity of disease is determined by the residual enzyme activity encoded by the mutant gene, since these point mutations are less likely to disrupt enzyme function than other types of mutations. This observation provides a rough guide for predicting disease severity, since nonsense mutations, deletions, insertions, or substitutions are likely to be associated with severe HPRT enzyme deficiency and therefore the full spectrum of clinical features associated with LND.

There are multiple examples where different point mutations have altered the same codon to produce different amino acid substitutions (Table 1). In most cases, alterations of the same codon produced similar phenotypic results. For example, LND was associated with the replacement of glycine at codon 70 by arginine, glutamic acid, or tryptophan in six unrelated cases. Replacement of histidine by aspartic acid, arginine, or tyrosine at codon 204 also caused LND in five unrelated cases. In other cases, amino acid substitutions at a single codon have led to very different phenotypic consequences. This phenomenon may be explained by the effect of the substitution on residual enzyme function, since conserved amino acid substitutions are likely to have a less influential effect on the conformation of the HPRT protein than non-conserved substitutions. For example, the non-conservative replacement of leucine by glutamine at codon 78 caused LND, while the more conservative replacement by valine caused HRH. Similarly, the non-conservative replacement of aspartic acid by either asparagine or histidine at codon 194 caused LND while the more conservative replacement by glutamic acid caused HRH. The non-conservative replacement of aspartic acid by tyrosine at codon 201 caused LND, while the more conservative replacement by glycine acid caused HRH. These examples confirm that the location of the mutation has a less significant influence on phenotypic outcome than the predicted effect of the mutation on HPRT protein conformation and residual enzyme function.

A few of the less severely affected cases with deletions, insertions, or other structural alterations seem to represent exceptions to the concept that disease severity depends on the amount of residual enzyme activity, since these types of mutations predict a complete loss of functional HPRT enzyme activity. However, careful analysis provides two explanations for several of the apparent discrepancies. First, it is important to recognize that HPRT deficiency is associated with a continuous spectrum of disease severity. The severity of disease is classified into three groups for heuristic value but is not meant to imply the existence of absolutely distinct subtypes of disease. As a result, some cases fall between group designations and are readily misclassified. For example, 11 cases with a nonsense mutation at codon 170 predicting a complete loss of HPRT enzyme activity had typical LND; but another case with exactly the same mutation was reported as having HRND because of the absence of self-injury by age 10 (Table 2). Since self-injury is sometimes delayed until as late as 18 years of age [1], the classification as HRND in this case might have to be revised after the appearance of self-injury at a later age. Moreover, the potential for late appearance of self-injury also raises the possibility that some typical LND cases may never develop self-injury during their relatively shortened lifespans [1]. Thus, one explanation for rare cases having intermediate disease severity together with molecular mutations predicting complete loss of HPRT enzyme activity is that our current classification for disease severity does not provide absolutely distinct categories. In particular, there may be rare cases with complete absence of HPRT enzyme activity who have all the typical features of LND except for self-injurious behavior.

A second explanation for some of the apparent discrepancies between disease severity and mutations predicting complete loss of HPRT enzyme activity

is that some of these mutations may permit residual enzyme function via unique molecular mechanisms. For example, most cases with deletion or insertion mutations demonstrate the full spectrum of features associated with LND (Fig. 3), presumably because the mutation causes significant disruption of the reading frame and a dysfunctional protein product. However, two relatively mildly affected cases had deletion mutations. One case (Illinois) had an early deletion, but a functional mRNA was transcribed from a downstream GUG start codon [42]. The other case (Japan3) had a 51 base pair deletion predicted to produce an HPRT protein missing only the last two amino acids [43]. Two cases from another family (RW, TW) with a three base pair insertion might also express some residual enzyme activity since the mutation predicts the addition of a single amino acid without disturbing the normal reading frame [22].

Cases with partial gene duplication mutations might also be predicted to have the full spectrum of clinical features associated with LND, since they are likely to disrupt the reading frame and result in dysfunctional protein products. However, partial gene duplications in two cases with HRND (GM 1622, GM 6804) have been demonstrated to have high rates of reversion in vitro [22,44,45]. A similar reversion of the duplication in vivo could result in significant residual HPRT enzyme activity depending on the extent of somatic mosaicism. Since the extent of molecular reversion may vary in different tissues, and particularly in the brain, predictions concerning the phenotypic severity are difficult to make. The phenotypic outcome of splice site mutations may also be difficult to predict, since some of these mutations (JLY, TL) may permit a small proportion of correctly spliced transcripts that are translated into functional enzyme molecules [22,46]. The fidelity of splicing associated with these mutations can not be readily quantified in vivo, again making predictions concerning disease severity difficult.

These unusual examples of ‘unstable’ duplicaton or splicing mutations demonstrate that the molecular mutation may have unexpected consequences on phenotypic outcome, presumably by allowing for some residual enzyme function. Such unstable mutations are also likely to confound results of enzyme assays of intact fibroblasts, since the biopsy site for the fibroblast cultures may provide a sample that is not representative of the extent of molecular mosaicism or residual gene transcription in other tissues such as the brain. This problem is likely to be even more severe for enzyme assays conducted with lymphocytes, where a selection against HPRT-deficient cells will skew the population towards normalcy and result in anomalously high values [47–51].

Although phenotypic predictions may be difficult for new cases with novel mutations, some predictions might be possible when a new case is found to have a mutation similar to a previously described case. In other words, the same mutation might be predicted to have the same phenotypic consequences among different cases. In most cases, the same molecular mutation has resulted in similar disease states in different cases. In some cases, however, significant differences in the severity of the disease have been noted among different members of the same family [21,40,47,52]. For example, the onset of self-injury in two cousins with LND (Henryville) caused by the same splicing mutation varied from 6 to 16 years of age [21]. Another family with four mildly affected males (Moose Jaw) with a point mutation also displayed clinical variability; two had a learning disability, one had a speech impediment, and one was neurologically normal [40,52]. Though these cases were categorized as HRH, the mild neurological features in some suggest that they could be considered in the HRND group. More profound clinical differences were reported for two brothers in a clinical report of another family [47]. One was considered normal while the other had cognitive dysfunction, dysarthria, gait dysfunction, and seizures. These observations indicate that the molecular mutation may not reliably predict disease severity, since the expression of the disease appears to be modified by additional genetic or environmental factors.

4.4. Conclusions

There has been enormous progress in the characterization of the molecular genetic basis for individuals with HPRT deficiency, and four main conclusions emerge from the currently available database of 271 mutations. First, mutations occur throughout the *hprt* gene, with isolated areas that appear to represent mutational hot spots. Second, genotype–phenotype correlations provide no indication that specific disease features associate with specific mutation locations. Third, cases with less severe clinical manifestations

typically have mutations that are predicted to permit some degree of residual enzyme function. Fourth, the nature of the mutation provides only a rough guide for determining phenotypic severity, since certain types of mutations may have unpredictable effects on residual enzyme function, and since similar mutations sometimes produce dissimilar results. Identification of mutations for individual cases provides a valuable tool for confirmation of the diagnosis, for identifying relatives who might be potential carriers, for preimplantation testing, and for prenatal diagnosis. Because the nature of the mutation cannot always be used as a precise guide for predicting future disease severity, concurrent measurements of HPRT enzyme activity in intact cell preparations may provide valuable additional information for genetic counseling.

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