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RESEARCH REPORT

Geographical and Ethnic Distribution of Mutations of the Fumarylacetoacetate Hydrolase Gene in Hereditary Tyrosinemia Type 1

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Abstract Hereditary tyrosinemia type 1 (HT1) (OMIM 276700) is a severe inherited metabolic disease affecting mainly hepatic and renal functions that leads to a fatal outcome if untreated. HT1 results from a deficiency of the last enzyme of tyrosine catabolism, fumarylacetoacetate hydrolase (FAH). Biochemical findings include elevated succinylacetone in blood and urine; elevated plasma concentrations of tyrosine, methionine and phenylalanine; and elevated tyrosine metabolites in urine. The HT1 frequency worldwide is about 1 in 100,000 individuals. In some areas, where the incidence of HT1 is noticeably higher, prevalence of characteristic mutations has been reported, and the estimated incidence of carriers of a specific mutation can be as high as 1 out of 14 adults. Because the global occurrence of HT1 is relatively low, a considerable number of cases may go unrecognized, underlining the importance to establish efficient prenatal and carrier testing to facilitate an early detection of the disease. Here we describe the 95 mutations reported so far in HT1 with special emphasis on their geographical and ethnic distributions. Such information should enable the establishment of a preferential screening process for mutations most predominant in a given region or ethnic group.

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Abbreviations

BCH	Birmingham Children's Hospital
FAH	Fumarylacetoacetate hydrolase
GTR	Genetic Testing Registry
HCC	Hepatocellular carcinoma
HT1	Hereditary tyrosinemia type 1
LGCD	Laboratory of Cell and Developmental Genetics
NTBC	2-(2-Nitro-trifluoromethylbenzoyl) 1,3-cyclohexanedione
SLSJ	Saguenay-Lac-St-Jean region

Introduction

Hereditary tyrosinemia type 1 (HT1) (OMIM 276700) is an inherited metabolic disease, mainly of childhood. This pathological condition was referred to as hereditary tyrosinemia type 1 in the mid-1960s (reviewed in Mitchell et al. 2001; Russo et al. 2001), and it was later shown to result from a deficiency in fumarylacetoacetate hydrolase (FAH), the last enzyme of the tyrosine catabolic pathway (Lindblad et al. 1977; Fällström et al. 1979; Berger et al. 1981; Kvittingen et al. 1981; Tanguay et al. 1990).

HT1 is an autosomal recessive disease characterized by severe liver dysfunction, impaired coagulation, neurological crises, renal tubular dysfunctions and a high risk of hepatocellular carcinoma (HCC). Three main clinical forms of HT1 have been described: the *acute* form, which

presents itself in the first months of life and is associated with acute liver failure; the *subacute* form (second half of the first year) that manifests a similar but less severe clinical picture presenting usually with hepatomegaly or hypophosphatemic rickets (due to tubular dysfunction); and the *chronic* form which appears after the first year of age and shows a slower progression (Tanguay et al. 1990; van Spronsen et al. 1994; Bergman et al. 1998; Russo et al. 2001). Patients affected with HT1 generally show failure to thrive and hepatic damage including hepatomegaly, cirrhosis, hepatic failure and HCC. Complications associated with liver damage include jaundice, ascites and bleeding. HT1 also disrupts kidney function causing multiple tubular dysfunctions, Fanconi-like syndrome and glomerulosclerosis. In 1992, the introduction of NTBC (2-(2-nitro-trifluoromethylbenzoyl) 1,3-cyclohexanedione, also known as nitisinone) (Lindstedt et al. 1992) has proven to be highly effective in preventing the progression of liver damage, neurological crises and kidney damages (Larochelle et al. 2012; Bartlett et al. 2014). NTBC in combination with a low-tyrosine diet represents the only treatment available for this disease. However, one of the most severe complications occurring in HT1 patients remains the development of HCC (Mitchell et al. 2001). Indeed, although regular administration of NTBC in HT1 patients, combined with a protein-restricted diet, prevents liver and kidney dysfunction, recent reports have documented the presence of HCC even under therapy (de Laet et al. 2013). Effectiveness of this treatment depends on how early the disease is recognized and treated; thus, recent retrospective studies highly recommend the implementation of newborn screening in more areas (Zytkovicz et al. 2013; Dehghani et al. 2013; De Laet et al. 2013; Mayorandan et al. 2014). For example, Mayorandan and collaborators in their retrospective study point out the necessity of neonatal programmes borne by the government or health insurance companies to allow early diagnosis and access to adequate treatment. Indeed they report that patients, who were diagnosed after the neonatal period and consequently received NTBC treatment later, had a 2–12-fold higher risk (depending on age at start of therapy) of developing hepatocellular carcinoma compared to patients treated as neonates.

Detection of succinylacetone (SA) in urine, blood and amniotic fluid is the most reliable biochemical diagnostic for HT1. Assay of FAH enzyme activity in skin fibroblasts is possible but not readily available. Advent of molecular genetic testing has greatly improved the diagnostic power for this disease. Mutation analysis is not essential for clinical management but is useful for prenatal diagnosis and reproductive counselling. In fact targeted mutation analysis for diseased alleles and sequence analysis of the entire *fah* coding region can detect mutations in more than 95% of affected individuals (Sniderman King et al. 2011). The database of the GTR (Genetic Testing Registry: https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268490) reports 56 clinical tests for diagnosis and monitoring of this condition. Carrier testing for at-risk relatives and prenatal diagnosis for pregnancies at increased risk are possible if both disease-causing alleles in a family are known.

Patients and Methods

The present review is based on a current compilation of all HT1 alleles reported worldwide including those from patients identified in the Laboratory of Cellular and Developmental Genetics (LGCD), Université Laval, Quebec, Canada (Dr RM Tanguay), and the Department of Clinical Chemistry at Birmingham Children's Hospital (BCH), Birmingham, UK (Dr G Gray), mostly between 2001 and 2013 (unpublished data). Screening of genetic databases (e.g. HGMD, NCBI, ENSEMBL) and HT1 literature has been made to classify the reported mutations and to identify the ethnic group of patients. The mutations reported so far and the patients' origins are listed in Table 1.

Since there are inconsistencies in the literature of names of the mutations in this gene, we have used the Human Genome Variation Society's nomenclature for the description of sequence variations (http://www.hgvs.org/mutnomen/recs.html) as the basis of nomenclature (den Dunnen and Antonarakis 2000) and used the *fah* cDNA sequence given as GenBank accession number BT007160.1 as our reference sequence. For splice defects we have also added the historical mutation nomenclature, since this is the most common way in which they are named worldwide.

Results and Discussion

Fah Gene Characteristics and Mutations

The first mutation reported in the *fah* gene was the c.47A>T (p.Asn16Ile) in a French Canadian patient and was shown to be causative of FAH deficiency (Phaneuf et al. 1992).

The human *fah* gene is located on chromosome 15q23-q25, spans 30–35 kb and consists of 14 exons. The cDNA has an open reading frame of 1,257 bp encoding 419 amino acids (Phaneuf et al. 1991; Labelle et al. 1993). Identification of this gene (Phaneuf et al. 1991) led to mutation screening of patients and characterization of a number of disease-causing alleles, some of which were present at relatively high frequencies in specific populations (St-Louis and Tanguay 1997).

Eighty-three disease-causing mutations are presently reported on Human Gene Mutation Database (HGMD® Professional 2014.2, accessed in August 2014). Recently,

Table 1 Compilation of hereditary tyrosinemia type 1 alleles worldwide

HGVS mutation nomenclature		Effect of mutation	Origin	No. patients	Reported alleles	References
cDNA (Alias[a])	Protein					
c.1A>G	p.1Met>Val	Missense	Emirates	1	2	Al-Shamsi et al. (2014)
			Greece	1	2	Georgouli et al. (2010)
			Saudi Arabia	7	14	Imtiaz et al. (2011), Mohamed et al. (2013)
c.47A>T	p.Asn16Ile	Missense	French Canada	1	1	Phaneuf et al. (1992)
c.67T>C	p.Ser23Pro	Missense	Asia (un)	1	2	Heath et al. (2002)
c.82-1G>A	–	Splicing	Spain	1	?	Perez-Carro et al. (2013)
c.103G>A	p. Ala35Thr	Missense	Belgium	1	2	Cassiman et al. (2009)
c.185T>G	p.Phe62Cys	Missense	Japan	1	2	Awata et al. (1994)
c.191delA	–	Deletion	Turkey	1	2	Dursun et al. (2011)
c.192G>T (IVS2-1G>T)	p.Gln64His	Splicing	Asia (un)	5	10	BCH
			India	2	4	Rootwelt et al. (1994a), Rootwelt et al. (1996)
			Middle East	3	6	Rootwelt et al. (1994a), Rootwelt et al. (1996)
			Pakistan	6	11	Rootwelt et al. (1994a), Rootwelt et al. (1996)
			Pakistan	9	8	BCH
c.192+1G>T (IVS2+1G>T)	–	Splicing	Portugal	1	1	Bergman et al. (1998)
c.233G>A	p.Trp78X	Nonsense	Spain	3	4	Arranz, et al. (2002)
c.234G>A	p.Trp78X	Nonsense	Spain	1	1	Couce et al. (2011)
c.315-3C>G (IVS3-3C>G)	–	Splicing	Turkey	4	8	Dursun et al. (2011)
c.374 C>G	p.Thr125Arg	Missense	Egypt	1	2	Imtiaz et al. (2011)
c.398A>G	p.His133Arg	Missense	Asia (un)	1	2	Heath et al. (2002)
c.398A>T	p.His133Leu	Missense	Spain	1	2	Couce et al. (2011)
c.401C>A	p.Ala134Asp	Missense	Norway	2	2	Labelle et al. (1993), Rootwelt et al. (1994c), Rootwelt et al. (1996)
			Turkey	1	1	Rootwelt et al. (1994c)
c.441_448del8	–	Deletion	Turkey	1	?	Dursun et al. (2011)
c.442-1G>A (IVS4+1G>A)	–	Splicing	Egypt/Saudi Arabia	4	8	Imtiaz et al. (2011)
c.455G>A	p.Trp152X	Nonsense	China	4	3	Yang et al. (2012), Dou et al. (2013)
c.467C>A	p.Pro156Gln	Missense	Asia (un)	1	1	Heath et al. (2002)
c.473G>A	p.Gly158Asp	Missense	Germany	1	1	Bergman et al. (1998)
c.497T>G	p.Val166Gly	Missense	North America (un)	2	2	Grompe and al-Dhalimy (1993)
			Germany	1	1	Rootwelt et al. (1996)

(continued)

Table 1 (continued)

HGVS mutation nomenclature		Effect of mutation	Origin	No. patients	Reported alleles	References
cDNA (Alias[a])	Protein					
			Iran	1	1	Grompe and al-Dhalimy (1993)
			Italy	1	2	Bergman et al. (1998)
			Turkey	2	4	Dursun et al. (2011)
c.509 G > T	p.Gly170Val	Missense	Saudi Arabia	2	4	Imtiaz et al. (2011)
c.520C>T	p.Arg174X	Nonsense	North America (un)	1	1	Timmers and Grompe (1996)
			Asia (un)	1	1	Heath et al. (2002)
			Turkey	1	2	Dursun et al. (2011)
c.548_553+20del26	–	Deletion	Brno-Czech Rep	1	1	Arranz et al. (2002)
c.536A>G	p.Gln179Arg	Missense	Korea	1	?	Choi et al. (2014)
c.553+5G>A (IVS6+5G>A)	–	Splicing	America	1	1	Timmers and Grompe (1996)
c.554-1G>C (IVS6-1G>C)	–	Splicing	Yugoslavia	1	1	Bergman et al. (1998)
c.554-1G>T (IVS6-1G>T)	–	Splicing	Africa	1	2	Bergman et al. (1998)
			Brazil	1	2	LGCD
			Czech Rep	8	14	Arranz et al. (2002), Vondrackova et al. (2010)
			Europe (un)	2	2	Poudrier et al. (1999), Kim et al. (2000)
			France	3	4	Bergman et al. (1998)
			Hungary	1	2	Laszlo et al. (2013)
			Italy	2	3	Bergman et al. (1998), Arranz et al. (2002)
			Morocco	6	11	Ploos van Amstel et al. (1996), Bergman et al. (1998), Arranz et al. (2002), la Marca et al. (2011)
			North America (un)	10	13	Timmers and Grompe (1996), Poudrier et al. (1999)
			UK	1	1	BCH
			Pakistan	1	2	BCH
			Spain	36	63	Rootwelt et al. (1996), Bergman et al. (1998), Arranz et al. (2002), Couce et al. (2011)
			Turkey	11	20	Bergman et al. (1998), Dursun et al. (2011)
			Yugoslavia	1	1	Bergman et al. (1998)
			UK	4	5	BCH
			Unknown	1	2	Rootwelt et al. (1996)

c.577T>C	p.Cys193Arg	Missense	Netherlands	1	1	Ploos van Amstel et al. (1996)
c.579C>A	p.Cys193X	Nonsense	Czech Rep	1	2	Vondrackova et al. (2010)
c.607-1G>A (IVS7-1G>A)	–	Splicing	Turkey	1	2	Ploos van Amstel et al. (1996)
c.607-6T>G (IVS7-6 T>G)	–	Splicing	USA	?	?	Sniderman King et al. (2011)
c.615delTs	p.Phe205leufsX2f	Frameshift	Norway	1	1	Bliksrud, et al. (2012)
c.620G>A	p.Gly207Asp	Missense	North America (un)	1	1	Timmers and Grompe (1996)
c.648C>G (IVS8-59C>G)	p.Ile216Met	Splicing	India	3	4	Sheth et al. (2012)
c.680G>C	p.Gly227>Ala	Missense	Egypt	1	2	Imtiaz et al. (2011)
c.680G>T	p.Gly227>Val	Missense	Czech Rep	2	4	Vondrackova et al. (2010)
c.696C>A	p.Asn232Lys	Missense	Turkey	1	2	Dursun et al. (2011)
c.696C>T (IVS8-11C>T)	p.Asn232Asn	Splicing	Netherlands	1	1	Ploos van Amstel et al. (1996)
c.698A>T	p.Asp233Val	Missense	Turkey	8	15	Rootwelt et al. (1994a), Rootwelt et al. (1996), Dursun et al. (2011)
c.700T>G	p.Trp234Gly	Missense	USA	1	1	Hahn et al. (1995), Rootwelt et al. (1996)
c.707-1G>A (IVS8-1G>A)	–	Splicing	Egypt	1	2	Imtiaz et al. (2011)
			Saudi Arabia	3	6	Couce et al. (2011), Imtiaz et al. (2011)
			Spain	3	5	Arranz et al. (2002), Couce et al. (2011)
c.707-1G>C (IVS8-1G>C)	–	Splicing	Israel	8	16	Bergman et al. (1998), Elpeleg et al. (2002)
c.709C>T	p.Arg237X	Nonsense	Asia (un)	1	2	Heath et al. (2002)
			China	2	2	Cao et al. (2012)
			Morocco	1	2	la Marca et al. (2011)
			Pakistan	1	2	BCH
			Saudi Arabia	10	20	Imtiaz et al. (2011)
			Thailand	1	2	Jitraruch et al. (2011)
			Turkey	4	8	Ploos van Amstel et al. (1996), Dursun et al. (2011)
c.718 C>T	p.Gln240>X	Nonsense	Iran	1	2	Imtiaz et al. (2011)
c.726G>A	p.Trp242X	Nonsense	UK	1	1	BCH
c.744delG	p.Pro249HisfsX55	Frameshift	Norway	5	7	Bliksrud et al. (2012)
c.745C>A	p.Pro249Thr	Missense	North America (un)	1	1	Timmers and Grompe (1996)
c.775G>C	p.Val259Leu	Splicing	USA	1	1	LGCD
c.776T>A	p.Val259Asp	Missense	Turkey	1	2	Dursun et al. (2011)
c.782C>T	p.Pro261Leu	Missense	Israel	3	6	Bergman et al. (1998), Elpeleg et al. (2002)
			Israel	1	2	BCH
			Saudi Arabia	1	2	BCH

(continued)

Table 1 (continued)

HGVS mutation nomenclature		Effect of mutation	Origin	No. patients	Reported alleles	References
cDNA (Alias[a])	Protein					
			Egypt/Saudi Arabia	3	6	Imtiaz et al. (2011)
c.786G>A	p.Trp262X	Nonsense	Denmark	1	1	Rootwelt et al. (1996)
			Europe (un)	1	1	BCH
			Finland	22	40	Rootwelt et al. (1994a), St-Louis et al. (1994), Rootwelt et al. (1996), Mustonen et al. (1997)
			French Canada	1	1	LGCD
			Norway	1	1	Rootwelt et al. (1994a)
			Poland	1	1	Rootwelt et al. (1996)
			UK	2	2	BCH
			USA	3	6	LGCD
c.787G>A	p.Val263>Me	Missense	Saudi Arabia	2	4	Imtiaz et al. (2011)
c.835delC	pGln279ArgfsX25	Frameshift	Norway	2	2	Bliksrud et al. (2012)
c.836A>G (IVS9-2A>G)	p.Gln279Arg	Splicing	Spain	1	?	Perez-Carro et al. (2013)
			USA	1	1	Kim et al. (2000), Dreumont et al. (2001)
c.837+2T>C (IVS9+2T>C)	–	Splicing	Turkey	2	4	Dursun et al. (2011)
c.838-2A>G (IVS9-2A>G)	–	Splicing	Caucasus	1	1	Heath et al. (2002)
			UK	1	1	BCH
c.843 C > A	p.281Thr > Pro	Missense	Saudi Arabia	1	2	Imtiaz et al. (2011)
c.880A>C	p.Thr294Pro	Missense	North America (un)	1	1	Timmers and Grompe (1996)
			France	1	1	Bergman et al. (1998)
c.913G>C	p.Gly305Arg	Splicing	Spain	1	?	Perez-Carro et al. (2013)
c.913+5G>A	–	Splicing	Korea	1	?	Choi et al. (2014)
c.914-2A>T (IVS10-2A>T)	–	Splicing	Spain	1	1	Arranz et al. (2002)
c.938delC	p.Thr313ThrfsX60	Frameshift	Spain	1	1	Arranz et al. (2002)
c.960q1130_*1260q10539del18036	–	Deletion	Korea	3	4	Park et al. (2009)
c.961-1010del50	–	Deletion	Iran	1	2	Haghighi-Kakhki et al. (2014)
			North Europe (un)	9	8/?	Rootwelt et al. (1994d), Prieto-Alamo and Laval (1998)

c.974C>T	p.Thr325Met	Missense	Caucasus	1	1	Heath et al. (2002)
			Spain	1	1	Couce et al. (2011)
			UK	1	1	BCH
c.974_976delC AinsGC	–	Deletion	China	3	6	Yang et al. (2012)
c.982C>T	p.Gln328X	Nonsense	Spain	2	2	Arranz et al. (2002)
c.1001 C>T	p.Ser334>Phe	Missense	Saudi Arabia	1	2	Imtiaz et al. (2011)
c.1009G>A	p.Gly337Ser	Missense	Austria	1	2	Bergman et al. (1998)
			France	1	1	Rootwelt et al. (1994b)
			Iran	1	2	Haghighi-Kakhki et al. (2014)
			Norway	6	7	St-Louis et al. (1995), Bliksrud et al. (2005), Bliksrud et al. (2012)
			North Europe (un)	18	15/?	Rootwelt et al. (1994d), Rootwelt et al. (1996), Prieto-Alamo and Laval (1998)
			Portugal	1	1	Bergman et al. (1998)
			Spain	1	2	Bergman et al. (1998)
c.1022 G>C	p.Arg341Pro	Missense	Egypt	1	2	Imtiaz et al. (2011)
c.1025C>T	p.Pro342Leu	Missense	Greece	1	2	Bergman et al. (1998)
			Norway	1	1	Rootwelt et al. (1994c)
			USA	1	1	Rootwelt et al. (1996)
c.1027G>T	p.Gly343Trp	Missense	Spain	2	2	Arranz et al. (2002)
c.1027G>C	p.Gly343Arg	Missense	China	2	3	Dou et al. (2013)
			Egypt	3	6	Imtiaz et al. (2011)
c.[1035_1037del]		Deletion	China	2	3	Mak et al. (2013)
c.1043C>G	p.Ser348Gly	Missense	North Europe (un)	5	?	Prieto-Alamo and Laval (1998)
c.1056C>A	p.Ser352Arg	Missense	Asia	1	2	Heath et al. (2002)
c.1061C>A	p.Pro354Gln	Missense	Norway	1	1	Bliksrud et al. (2005)
c.1062+5G>A (IVS12+5G>A)	–	Splicing	Asia (un)	3	5	Heath et al. (2002)
			Canada	3	5	Grompe et al. (1994)
			Czech Rep	1	2	Vondrackova et al. (2010)
			Denmark	1	1	Rootwelt et al. (1994d)
			Europe (un)	23	28	Rootwelt et al. (1996)
			Finland	1	1	Grompe et al. (1994)
			French Canada	98	181	Grompe and al-Dhalimy (1993), Grompe et al. (1994), Poudrier et al. (1996), LGCD
			France	1	2	Grompe et al. (1994)
			Germany	2	3	Ploos van Amstel et al. (1996), Bergman et al. (1998)

(continued)

Table 1 (continued)

HGVS mutation nomenclature		Effect of mutation	Origin	No. patients	Reported alleles	References
cDNA (Alias[a])	Protein					
			India	2	4	BCH
			Iran	2	3	Grompe and al-Dhalimy (1993), Imtiaz et al. (2011)
			Israel	1	2	Bergman et al. (1998)
			Mexico	1	1	Grompe et al. (1994)
			Netherlands	7	10	Ploos van Amstel et al. (1996), Bergman et al. (1998)
			Norway	3	3	Grompe et al. (1994), Rootwelt et al. (1994d)
			Pakistan	2	4	Rootwelt et al. (1996), BCH
			Portugal	4	6	Bergman et al. (1998)
			Spain	6	8	Arranz et al. (2002), Couce et al. (2011), Perez-Carro et al. (2013)
			Turkey	4	10	Rootwelt et al. (1996), Bergman et al. (1998), Dursun et al. (2011)
			UK	4	8	BCH
			UK	2	2	Grompe and al-Dhalimy (1993), Rootwelt et al. (1994d)
			USA	11	13	Grompe et al. (1994), Hahn et al. (1995), Timmers and Grompe (1996), LGCD
c.1063-1G>A (IVS12 -1G>A)	–	Splicing	China	2	3	Mak et al. (2013)
c.1069G>T	p.Glu357X	Nonsense	Caucasus	1	1	Heath et al. (2002)
			French Canada	5	6	Grompe and al-Dhalimy (1993), St-Louis et al. (1995)
			Netherlands	1	1	Ploos van Amstel et al. (1996)
			Norway	1	1	Rootwelt et al. (1996)
			Poland	1	1	Rootwelt et al. (1996)
			UK	1	1	Rootwelt et al. (1994d), Rootwelt et al. (1996)
			UK	1	1	BCH
c.1090G>T	p.Glu364X	Nonsense	French Canada	7	7	Grompe and al-Dhalimy (1993), Timmers and Grompe (1996), Poudrier et al. (1999)
			UK	2	2	Rootwelt et al. (1994d), Rootwelt et al. (1996)
			USA	4	4	Timmers and Grompe (1996)
			Netherlands	2	2	Ploos van Amstel et al. (1996), Bergman et al. (1998)
			Belgium	1	1	Grompe et al. (1994)
c.1097_1099delCGT	p.Ser366del	In-frame deletion	Italy	1	1	Bergman et al. (1998)
			Netherlands	1	1	Bergman et al. (1998)
c.1100 G>A	pTrp367X	Nonsense	China	3	2	Yang et al. (2012)
c.1106G>T	p.Gly369Val	Missense	Morocco	1	1	Ploos van Amstel et al. (1996)

c.1107delG	p.Asn344Tfsx	Deletion	Turkey	1	1	Dursun et al. (2011)
c.1124T>C	p.Leu375Pro	Missense	China	2	2	Cao et al. (2012)
c.1141A>G	p.Arg381Gly	Missense	French Canada	5	5	St-Louis et al. (1995)
			Portugal	1	1	St-Louis et al. (1995)
c.1156G>C	p.Asp386His	Missense	Emirates	1	2	Al-Shamsi et al. (2014)
c.1159G>A	p.Gly387Arg	Missense	India	3	4	Sheth et al. (2012)
c.1190delA	–	Deletion	Egypt	2	4	Imtiaz et al. (2011)
c.1195G>C	p.Asn400His	Missense	Saudi Arabia	1	2	Imtiaz et al. (2011)
c.1210G>A	p.Gly404Ser	Missense	Czech Rep	1	2	Vondrackova et al. (2010)
c.1213_1214delTTinsCA	p.Phe405His	Missense	Portugal	1	1	Bergman et al. (1998)

[a] Variant designation that does not conform to current naming conventions

BCH Birmingham Children's Hospital (unpublished data), *LGCD* Laboratory of Cell and Developmental Genetics (unpublished data), *Un* Undetermined region

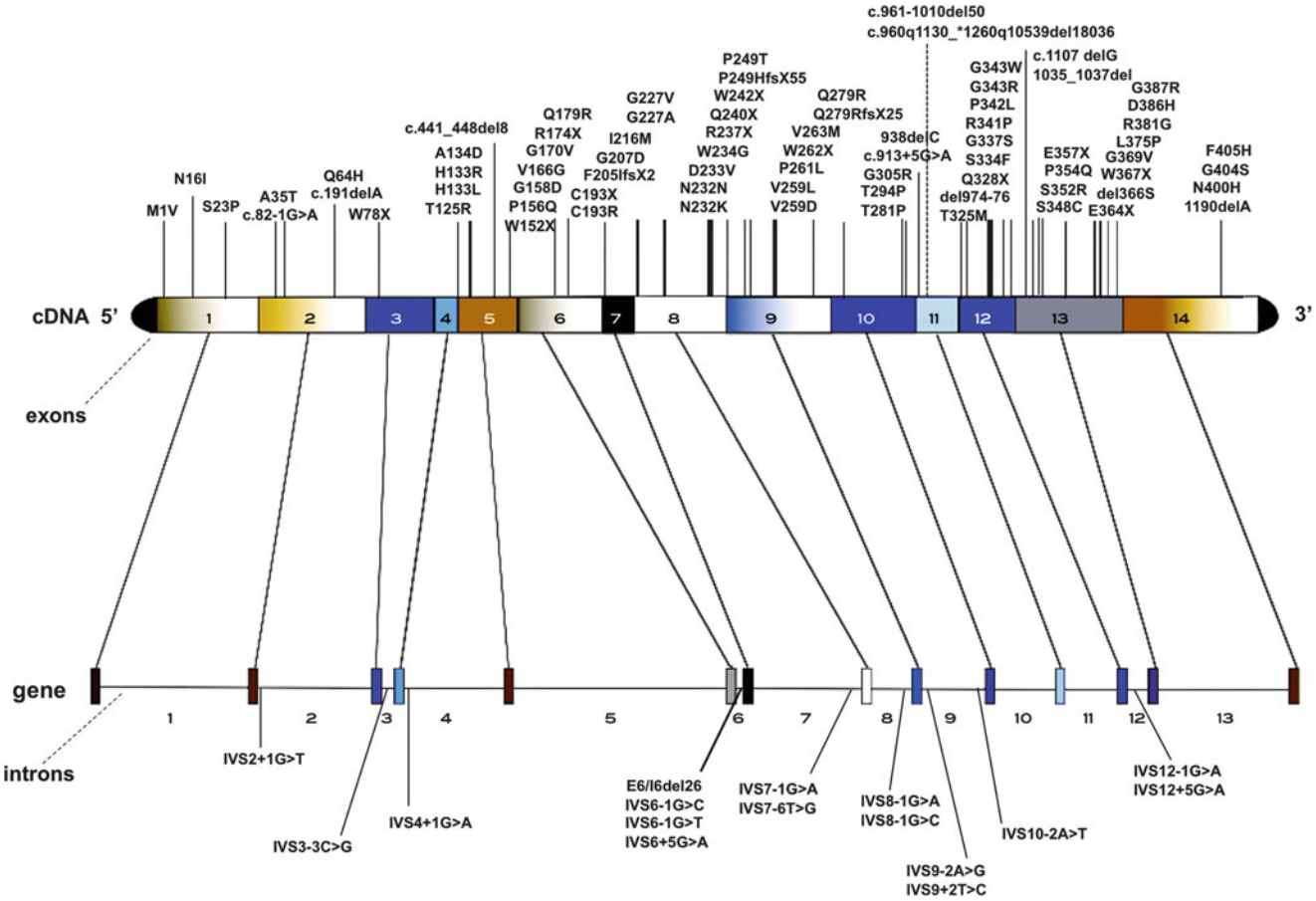

Fig. 1 Location of the 95 mutations identified on the *fah* gene. Among the known HT1 alleles causing mutations, 45 are missense mutations, 23 are splicing mutations, 13 are nonsense mutations, 10 are deletions and 4 are frameshift. Intronic mutations are illustrated at the *bottom* of the figure

two new mutations were uncovered at LGCD, Quebec, and in BCH, Birmingham (unpublished data). The first was the c.726G>A (p.Trp242X) nonsense mutation, obtained by screening one English adult patient at BCH. The second, the c.775G>C (p.Val259Leu) a potential missense mutation, was observed in an American patient at the Quebec laboratory. This patient was heterozygous for the new c.775G>C (p.Val259Leu) allele and the already reported c.554-1G>T (IVS6-1G>T) (Grompe et al. 1994). Western blot analysis of his liver obtained after transplantation revealed the absence of FAH protein and no activity was detected by enzymatic assay (data no shown). RNA analysis suggested a defect in splicing affecting exon 9, and this was confirmed using minigene constructs transfected in HeLa cells (Dreumont and Tanguay, unpublished).

Reclassification of HT1 Mutations

After cross-checking of genetic databases and the literature on HT1 from the oldest publications to the present day, we updated the number of allelic variants with the two found by our group and others recently reported (Fig. 1 and Table 1). Next we decided to reclassify them in a unique list containing number of known alleles from patients and geographical distribution of the mutations most predominant for each country (Fig. 2, and Table 1). Indeed, frequency of reported alleles and origin of patients could be useful in helping clinicians to focus on mutations specific of certain regions, facilitating the targeted detection of diseased alleles.

Overall 95 mutations are now reported within the *fah* gene in this review (Fig. 1 and Table 1). All 95 HT1 alleles are divided in 45 missense mutations, 23 splice defects, 13 nonsense mutations, 10 deletions and 4 frameshift (Table 1). In addition the missense c.1021C>T (p.Arg341Trp) sequence variant is described as a pseudodeficiency variant since individuals homozygous for this mutation are healthy (Rootwelt et al. 1994b; Bergeron et al. 2001).

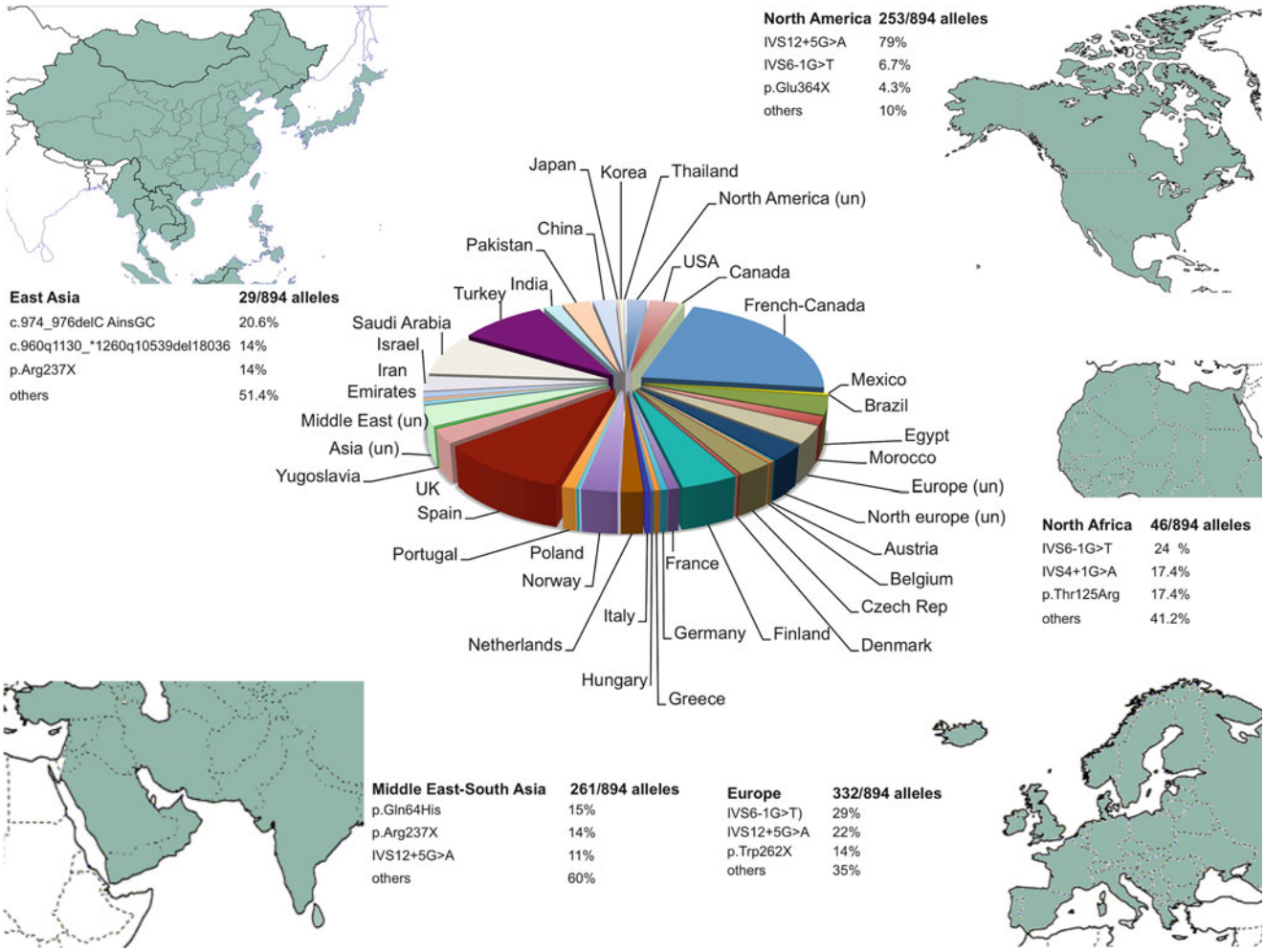

Fig. 2 Geographical distribution of the most common HT1 alleles causing mutations worldwide. *Pie chart* representing distribution of ethnic groups in HT1 alleles. Where the patient provenance was not clear, the mutation is included in the continent of origin, i.e. undefined (un) on graphic. The top three mutations and the total number of alleles for each continent are reported. There are more than 894 HT1 alleles reported worldwide. The most frequent HT1 mutation encountered is the IVS12+5G>A splice mutation, which accounts for 33.7% of all HT1 alleles, followed by the IVS6-1G>T mutation (16.4%). The French Canadian population alone accounts for as much as a third of all HT1 alleles reported. Both mutations are the most reported globally

Predominance of Ethnic Groups in HT1 Distribution

Despite the fact that the worldwide incidence of HT1 is relatively low with one affected individual in approximately 100,000 healthy individuals (Hutchesson et al. 1996), specific populations stand out as they represent small clusters of diseased alleles (Fig. 2). The population that possesses the highest incidence of HT1 is the French Canadian population of the SLSJ region, in the province of Quebec (Canada) (De Braekeleer and Larochelle 1990; Poudrier et al. 1996). The prevalence of HT1 in the SLSJ region was as high as 1/1,042 births in 1971 but dropped to 1/1,846 births in 1986, most likely due to the implementation of a screening programme for HT1 in 1970 conducted by the Quebec Network of Genetic Medicine. The most predominant mutation in this region is the c.1062 + 5G>A (IVS12 + 5G>A) accounting ~90% of all the disease-causing alleles. Furthermore, even though the Quebec population accounts for only approximately 0.12% of the world population (estimated today to number of 7 billion), it represents ~33% of all HT1 alleles worldwide. Although these data may be biased by the fact that all newborns in Quebec are screened for HT1, it is clear that this region represents the highest incidence of HT1 and that the c.1062 + 5G>A mutation is predominant in this region.

A second cluster of HT1 is found in Scandinavia (Kvittingen et al. 1981). In the Finnish population of Pohjanmaa, 1 individual out of 5,000 is affected with HT1

(St-Louis et al. 1994), whereas the overall incidence of HT1 in Finland is 1:60,000 (Mustonen et al. 1997). In this region, one single mutation (c.786G > A, p.Trp262X) represents ~88% of all reported HT1 alleles (St-Louis et al. 1994). Indeed 40 of the 46 European c.786G>A alleles have been reported in this country.

New findings show a peculiar pattern of HT1 mutations also in Norway. In a recent report, 19 Norwegian HT1 patients were investigated in the Hospital of Oslo University and three new small deletions were found: c.615delT, (p.Phe205LeufsX2), c.744delG (p.Pro249HisfsX55) and c.835delC (p.Gln279ArgfsX25). The novel mutations lead to frameshift and premature termination codons. FAH protein structure is affected, and normal folding, function and stability of the protein cannot be expected (Bliksrud et al. 2012). The c.615delT, c.744delG and the c.835delC are found in 13.5%, 3.8% and 1.9% of the alleles, respectively. Around 65% of the Norwegian HT1 patients are heterozygous for different mutations. The relatively high incidence of HT1 in Norway (1 in 74,800 live births) has not been connected with a single founder effects or high incidence of parental consanguinity as in the previous areas (Bliksrud et al. 2012).

Another cluster occurs in an immigrant population from Pakistan living in the UK, predominantly in Birmingham (Hutchesson et al. 1998). Birmingham is a city in the West Midlands Region, which has a total population of approximately 5.3 million of which nearly 3% are of Pakistani origin. We have diagnosed 44 patients from the West Midlands with this disorder of which 30 (68%) were of Pakistani origin. This is over 22-fold higher than the frequency of people of Pakistani origin in this region. Mutation analysis revealed that five out of 12 index patients (42%) in this ethno-geographic group had the c.192G>T (p.Gln64His) mutation. This mutation was not detected in patients from any other close-by region suggesting a founder effect from the region of origin of this population. Indeed the frequency of this mutation in Pakistani from the UK was comparable to that of the common pan-ethnic c.1062 + 5G>A mutation.

Most Frequent HT1 Alleles Around the World

Although Quebec, Finland, Norway and Pakistani in the UK stand out as populations with the higher frequency of HT1, reports highlight a specific tendency in mutational distribution among ethnic groups. The c.1062 + 5G>A (IVS12 + 5G>A) mutation is found frequently in patients from a wide range of ethnic groups over a large geographical distribution. Given the high frequency and wide spread of this mutation, it is likely to be a very old mutation and it was originally reported in a French Canadian patient and in two patients of Iranian origin (Grompe et al. 1994). Although this is the most frequent HT1 mutation encountered worldwide (302/894 HT1 alleles), the c.554-1G>T (IVS6-1G>T) splice mutation is also frequently observed (147/894 HT1 alleles), showing a high prevalence in the Mediterranean region and in southern Europe. In a recent cross-sectional retrospective study on 168 HT1 patients originating from Europe, Turkey and Israel, mutational analysis performed in 58/168 patients revealed the predominance of the IVS12 + 5G>A (11 patients) and IVS6-1G>T (13 patients) mutations in these ethnic groups (Mayorandan et al. 2014).

The mutation that ranks third in prevalence in Europe is the c.786G>A (p.Trp262X) nonsense mutation. This ranking is due to its predominance in the Finnish population. A number of others mutations have also been associated with specific ethnic or geographic groups, as described below (Table 1, Fig. 2). The c.1062 + 5G>A (IVS12 + 5G>A), the c.607-6T>G (IVS7-6T/G) and the c.554-1G>T (IVS6-1G>T) splicing mutations and the c.786G>A (p.Trp262X) nonsense mutation all together represent 60% of mutant alleles in the general US population (Sniderman King et al. 2011). Surprisingly, only one HT1 allele was reported until now in Mexico and this allele carried the c.1062 + 5G>A mutation most prevalent in Quebec (Table 1). 16 new cases have recently been described in Brazil (Neto et al. 2014), with only two alleles reported at this time, and these harboured the c.554-1G>T (IVS6-1G>T) mutation, most prevalent in the Mediterranean area (Table 1).

Arranz et al. in their work based on a panel of 29 patients mostly from southern Europe demonstrated a high homogeneity of the mutational spectrum in this region (Arranz et al. 2002). In a retrospective study on European HT1-affected individuals (Couce et al. 2011), mutational analysis on 34 Spanish patients reported nine different mutations in this population, documenting c.554-1G>T (IVS6-1G>T) as the most prevalent, in accordance with the previous literature (Arranz et al. 2002). Molecular genetics analysis of the *fah* gene in 11 Czech patients with HT1, diagnosed in the Medical Faculty of Charles University in Prague between 1982 and 2006, revealed three mutations not previously described: the c.579C>A nonsense mutation (p.Cys193X) and the c.680G>T (p.Gly227Val) and c.1210G>A (p.Gly404Ser) missense mutations (Vondrackova et al. 2010).

The Middle East is interesting in the sense that even though patients harbour the common c.1062 + 5G>A (IVS12 + 5G>A) and c.554-1G > T (IVS6-1G>T) mutations, many of the other mutations reported are typical to this region. One such example is the already described c.192G>T (p.Gln64His) mutation, which is thus far found only in people originating from Pakistan, the Middle East and North West India. This mutation accounts for over one

third of all HT1 alleles in these populations (Rootwelt et al. 1994a; Rootwelt et al. 1996). Another mutation that is often detected in patients from the Middle East is the c.709C>T (p.Arg237X) mutation (Imtiaz et al. 2011). In Turkey, the c.698A>T (p.Asp233Val) mutation, which has not been reported elsewhere, accounts for 20% of the reported alleles (Rootwelt et al. 1994a; Rootwelt et al. 1996; Dursun et al. 2011). Moreover, other different mutations, although not at high frequency, are peculiar for this population (Table 1).

The c.782C>T (p.Pro261Leu) missense mutation was found in 100% of Ashkenazi-Jewish examined in Israel (Elpeleg et al. 2002). Direct sequencing in 43 HT1-affected patients originating from Saudi Arabia, Egypt and Iran identified a total of 17 different homozygous mutations. Eleven of these (8 missense, 1 nonsense, 1 splice site and 1 deletion) had not been reported previously (Imtiaz et al. 2011).

Little information about the epidemiology and molecular defects in HT1 patients from East Asia is available at this time. Sakai and Kitagawa (1957) reported the first case of HT1 in a two-month-old Japanese patient, but genetic analysis was not possible at that time. The c.185T>G (p.Phe62Cys) represents the first and the only allele reported in Japan to date (Awata et al. 1994). Recent findings start to describe HT1 mutations in China. The missense mutation c.1124T>C (p.Leu375Pro) represents the first case of HT1 analysed by molecular genetics in this area (Cao et al. 2012). This mutation, affecting the secondary protein structure, decreases the stability of FAH enzyme and compromises the protein's functions. Another report represents the first case of HT1 in a two-month-old Hong Kong Chinese patient (Mak et al. 2013). Genetic analysis of this patient showed two novel mutations, the c.1063-1G>A splicing mutation and the c.1035_1037del. Recently, clinical data on 3 HT1 Chinese patients showed five mutations in the FAH gene: c.455G>A (p.Trp152X), c.520C>T (p.Arg174X), c.974_976delCGAinsGC, c.1027G>A (p.Gly343Arg) and c.1100G>A (p.Trp367X) (Yang et al. 2012; Dou et al. 2013). The c.455G>A, c.974_976delCGAinsGC and c.1100G>A mutations have not been described elsewhere. Currently, few cases of HT1 have been reported in Korea. Mutational analysis of two female neonates admitted to hospital for further work-up of an abnormal newborn screening test revealed three novel mutations (one deletion, one missense and one splice defect) that have not been reported elsewhere (Park et al. 2009; Choi et al. 2014).

To our knowledge no mutations in HT1 have yet been documented in Central America or in the Oceania continent.

Conclusions

The advent of neonatal screening, prenatal diagnosis and carrier tests for genetic disorders has shown the importance of establishing the population frequencies and ethno-geographic spread of mutations for the evaluation of future screening strategies. To highlight the prevalence of HT1 mutations in a geographical context, we compiled all reported HT1 alleles worldwide, including those not yet reported in the common databases, and another two, discovered in the screening of HT1 patients in our laboratories over a period between 2001 and 2013 (summarized in Table 1 and Fig. 2). Obvious conclusions can be drawn when we examine the incidence of HT1 worldwide (Fig. 2 and Table 1).

According to the data gathered so far, a preferential screening for those mutations in regions in which they show a higher prevalence could provide some improvement in carrier diagnostic efficiency and may enable the establishment of family pedigrees for adequate counselling in some cases. Currently, screening is carried out in Quebec, the USA and Europe (Morrissey et al. 2011; Barnby 2014). In this case it is obviously important to know the pattern of mutations in the respective populations.

However, it is necessary to bear in mind that this compilation may be partly biased by the fact that: (1) very few cases of HT1 are overlooked in some countries as in the province of Quebec due to a screening programme for HT1 established early in 1970 and (2) not all cases of HT1 are described in the literature. Many of these probably occur in countries with no or limited access to service for diagnosis of genetic disease and as a result remain undiagnosed (De Laet et al. 2013). This could lead to some geographical bias reflected in the fact that the majority of the patients whose mutations have been described are residents of Europe, the Middle East or North America. (3) Whilst we have carefully attempted to ensure that patients are not counted twice because they appear in more than one publication, this may occur in a few cases.

In summary, this report allows a detailed identification of the mutations causing HT1 worldwide, with diagnostic and methodological consequences implementing the ground-work for future carrier and prenatal testing, premarital screening and pre-implantation genetic diagnosis.

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Synopsis

Geographical and ethnic distribution of mutations in hereditary tyrosinemia type 1

Compliance with Ethics Guidelines

Conflict of Interest

Francesca Angileri, Anne Bergeron, Geneviève Morrow, Francine Lettre, George Gray, Tim Hutchin, Sarah Ball and Robert M. Tanguay declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration as revised in 2013.

Animal Rights

This article does not contain any studies with animal subjects performed by any of the authors.

Author's Contributions

AB and FA contributed equally to this review. AB, FA and SB did the literature review and contributed to the draft of the manuscript. FL, TH and SB performed mutational analysis in some patients. RMT, GM and GG designed the review and worked on the draft of the manuscript. All authors read and approved the final manuscript.

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