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Reviews

Frequency of Inborn Errors of Metabolism, Especially PKU, in Some Representative Newborn Screening Centers Around the World

A Collaborative Study

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Stimulated by published regional differences in the frequency of inborn errors of metabolism (Cahalane, 1974; Szeinberg and Cohen, 1971; Thalhammer and Scheiber, 1972), the editor of this journal asked us to organize a more widespread comparison to decide whether significant differences in the frequency of certain inborn errors of metabolism might be explained by genetic (racial) relationships. The data collected during the winter 1974/75 will be presented.

Method

The screening centers listed (Table 1) were invited by the organizer to cooperate. The centers have been selected mainly on the basis of acceptability of technique and the number of newborns tested, but the list is not complete. It was suggested to the centers that they exclude the newborns tested during periods in which they suspected that one test or the other might have been unreliable. In this way artefacts in frequency determinations arising from technical difficulties would be excluded. The centers were also asked to report only on inborn errors for which at least 70000 newborns had been tested.

Centers, being aware of regional differences within the population covered by the center, were asked to give the data separately for such regions or population groups.

The results from cooperating centers have been arranged in a geographical order beginning in eastern Europe going westward to eastern Asia.

Since separation of so-called classical PKU and Hyperphenylalaninemia (atypical PKU) is difficult, and different in various centers, it was felt worthwhile to give, not only the frequency of these two conditions, but also their ratio and the joint frequency.

Table 1. Centers asked to cooperate

Bickel, H., Heidelberg	Levy, H. L., Boston
Brandon, G. R., Portland	Menne, F., Münster
Cabalska, B., Warsaw	Naruse, H., Ichikawa
Cahalane, S. F., Dublin	Palmenstierna, H., Stockholm
Charpentier, C., Evian	Schimpfessel, L., Brussels
Clayton, B. E., London	Scriver, Ch., Montreal
Cohen, B. E., Tel Hashomer	Sereni, F., Milano
Gitzelmann, R., Zürich	Veale, A. M. O., Auckland
Grüttner, R., Hamburg	Visakorpi, J. K., Tampere
Hawcroft, J., Liverpool	Wamberg, E., Glostrup
Hyanek, J., Prague	Wilcken, B., Sydney
Komrower, G. M., Manchester	

Results

The most important disorder in the study is PKU (and Hyperphenylalaninemia) because of the greater number of centers testing, as well as for the ease and therefore reliability of the respective test techniques, mostly Guthrie's bacterial inhibition assay. Examining the data collected (Table 2) it seems rather clear that there is a higher frequency of PKU in Slavic populations than in those of mainly Germanic and Romanic (or Franconian) origin. The difference between eastern and western Austria, and possibly the one in the DDR, fits well with this observation. The Scandinavian populations, especially the Finnish, without lingual relationship to any other European nation covered by this study, show an exceptionally low frequency of PKU. The frequency in Sweden seems to indicate that, in the past, there was not only a population movement from Sweden to Finland but also in the reverse direction. Ireland has a PKU frequency comparable to that of the Slavic nations but there is no known relationship between these two groups.

Still more interesting is the difference obtaining between the populations of the northeastern and the southwestern part of Ireland. Although figures from Northern Ireland—politically part of the United Kingdom—are not included, the differences may be thought to reflect different population mixtures (Celtic and Anglo-Saxon) and also different degrees of inbreeding associated with geographical insularity. There is, however, no clear evidence from recent or past history of immigrations of conquests to explain these differences. The forces which may have prevented genetic homogenization are also not clear. Studies are being carried out by the Dublin workers in an attempt to throw further light on this phenomenon. Some differences within Great Britain, such as that from Manchester, may reflect the influence of more recent Irish immigration.

On the other side of the Atlantic, Boston and Portland reported frequencies quite comparable to most frequencies in Europe. There may be variations between the two coasts but the average frequency in the USA is of the same order. Montreal, in the French part of Canada, shows a much lower frequency of PKU than most European areas and the two US centers, and significantly lower than the French frequency. (Also the joint frequency for "typical" and "atypical" PKU is still lower than the French one.) The Montreal frequency is of the same magnitude as the Swedish. Between these two and the median frequencies (most European, USA) are the frequencies in New Zealand (European and Maori mixed) and Liverpool. (The joint frequency for "typical" and "atypical" PKU in Montreal is about the same as the PKU frequency in New Zealand.) There is no detectable relationship between Montreal and New Zealand.

Japan is the only far-East country screening for inborn errors. The frequency of PKU there is exceptionally low, comparable only with the frequency in Finland and among Ashkenazi Jews in Israel. Whether the genetic influence of Jews is large and old enough to have decreased the PKU frequency in Montreal is not known. The very low frequency among Ashkenazi Jews is a striking example of the maintenance of a genetic stock—in spite of a considerable degree of integration—by primarily religious exclusiveness and consequent failure to intermarry. The differences in Ireland may result from similar factors.

Table 2. Frequency of PKU and Hyperphenylalaninemia

Center, region	Period	Newborn tested	Method	Proven No.		Frequency		P:H ratio	Remarks P + H frequency
				PKU	HYPER	PKU	HYPER		
Warsaw	65—74/6	894891	G	115		1:7782		2.17	1:5327
Poland					53		1:16885		
Prague	68—73	132392	E+U—Chr	20		1:6618		0.91	1:3229
Prague					21		1:6303		
Greifswald, Gera,	69—74	266756	G	37		1:6351		4.63	1:5928
Frankfurt, DDR					8		1:33345		
Greifswald	69—74	619531	G	53		1:11689		5.89	1:9992
Other parts DDR					9		1:68837		
Total DDR	69—74	886287	G	95		1:9329		5.88	1:7913
					17		1:52135		
Vienna	66—74	285768	G	33		1:8659		2.54	1:6212
East Austria (excluding Vienna)					13		1:21982		
Vienna	66—74	206907	G	11		1:18809		1.00	1:9404
West Austria					11		1:18809		
Vienna Austria total	66—74	666383	G	54		1:12340		2.00	1:8226
(eastern, western plus Vienna)					27		1:24680		
Switzerland	65—74	699089	G	42		1:16644		1.45	1:9846
3 labs					29		1:24106		
Evian	67—73	1892734	G	138		1:13715		0.96	1:6712
France					144		1:13143		
Brussels		307647	G	?		?			38 PKU + HYPER
Belgium					?		?		1:8095
Heidelberg	69—74	364513	G	59				2.36	1:4330
West of Germany					25		1:14580		

Table 2 (continued)

Center, region	Period	Newborn tested	Method	Proven No.		Frequency		P:H ratio	Remarks P + H frequency
				PKU	HYPER	PKU	HYPER		
Münster Northwest Germany BRD	72—73	359875	G	33	45	1:10935	1:7997	0.73	1:4614
Hamburg Northern Germany BRD	65—74/7	245191	G	27	4	1:9081	1:61297	6.75	1:7909
Glostrup Denmark	69—73	285535	G	24	7	1:11897	1:40790	3.43	1:9211
Stockholm Sweden	65—74	907746	G	ca. 21	ca. 41	1:43226	1:22140	0.51	62 PKU + HYPER ⅓ classical 1:14641
Helsinki Finland	60—70/4	71111	G	0	0	<1:71111	<1:71111		programm stopped <1:71111
London North London	69/10—73	402434	G	18 + 4	6 + 2	1:18292	1:50304	2.75	7 cases not yet classified added in proportion of cleared 1:13414
Liverpool Liverpool	69—71	102779	G	12	1	1:8565	1:102779	12.00	1:7906
Liverpool Liverpool	72—75/5	112362	TLC blood	11	0	1:10215	<1:112362		1:10215
Manchester Manchester	65—75/5	323700	Chr blood	42	4	1:7707	1:80925	10.5	1:7037
Dublin East Ireland (Leinster, Ulster)	66—74	325935	G	61	10	1:5343	1:32594	6.10	1:4591

Dublin	66—74	206011	G	26		1:7924		8.70	1:7104
West Ireland (Connaught, Munster)					3		1:68670		
Dublin	66—74	531946	G	87		1:6114		6.10	1:5320
Total Republic Ireland					13		1:40919		
Boston	—74/4	1071423	G	77		1:13914		1.22	1:7653
Mass. USA					63		1:17006		
Portland	62—74/6	337002	G	29		1:11620		2.90	1:8641
Oregon USA					10		1:33700		
Montreal	—73	277769	Chr	7		1:39681			PKU typical 7
Canada			blood	4		1:69442			PKU atypical 4
			later G						total 1:25252
									ratio 1.75
									Pt:Pa + H = 0.39
					14		1:19840	0.78	1:11110
Auckland	69—75/3	381536	G	21		1:18168		5.25	1:15261
New Zealand					4		1:95384		
Sydney	67—74/9	353458	G	36		1:9818		2.25	1:6797
New South Wales Australia					16		1:22091		
Japan	69—75/1	210851	G	1		1:210851			8 from known
4 labs					3		1:70284		PKU families 1:52712
Tel Hashomer	64—74	180000	G	0		<1:180000			1:15000
Israel Ashkenazi					12		1:15000		
Tel Hashomer	64—74	320000	G	37		1:8649		0.82	1:3902
Israel other or Arab					45		1:7111		

G = Guthrie test, E = Efron method, Chr = paper chromatography, TLC = thin layer chromatography, U = urine.

The frequencies for *Hyperphenylalaninemia* (HPA) vary greatly and independently of those for PKU. The PKU : HPA ratio also shows a surprisingly wide range between 0.51 and 12.00. It is quite certain today that PKU and Hyperphenylalaninemia (whatever this means) arise from different genes, probably alleles. This could explain the variations in frequency but differences in definitions certainly are at least as important. Therefore it may not be very useful to analyze these variations in frequency further. It can be seen that the joint frequency of PKU plus Hyperphenylalaninemia does not vary as much as does the PKU frequency. (PKU 1:5343 to 1:43226; HPA + PKU 1:3229 to 1:15261.) This underlines the significance of differing definitions.

Of the other inborn errors of metabolism screened for in sufficient numbers today, *Galactosemia due to transferase deficiency* is of special interest, since for this disorder a significant difference in frequency within one population determined by one laboratory (technical homogeneity) has also been documented (Thalhammer and Scheiber, 1972). In contrast to PKU (and Hyperphenylalaninemia) technical difficulteis have to be kept in mind. This is true for centers where Guthrie's or Paigen's *E. coli* test is used as well as for those where the Beutler-Baluda test is the screening procedure.

The centers screening for Galactosemia are in the same geographical order as for PKU (Table 3). A frequency of Galactosemia in the order of 1:40000 is reported from a number of centres. (Hamburg, Vienna, Auckland, Prague, Stockholm and Zurich with a range of from 1:30000 to 1:65000. Allowance must be made for possibly inadequate numbers of samples.) This seems to be the frequency of the disorder in European populations. Neither significant regional differences nor ethnic trends are recognizable. The much higher frequency in Poland is probably due to the inclusion of cases with 10—20% of normal enzyme activity (double heterozygotes? Duarte variant?). Much lower frequencies in another group of centers (1:100000—1:150000) probably reflect technical and local organizational situations to a greater extent than true genetic differences. The great difference in frequencies that exists between certain American centers and several European ones, as well as New Zealand, would not be easily explainable on the grounds of genetic population differences. Yet there is one observation suggesting caution in this respect. There is a significant ($P < 0.02$) difference between eastern and western Austria and all cases have had typical symptoms and enzyme activities between 0% and less than 3% of normal.

Collected data for *Histidinemia* show quite the same situation as for Galactosemia. Technical problems with the screening procedure must also be considered here. One group of centers with frequencies found between 1:13000 and 1:19000 contrast with two others finding frequencies of less than 1:130000 and 1:150000. (Brussels frequency of 1:53000 possibly is an artefact of small numbers.) Excluding the two centers mentioned, Histidinemia seems to be evenly distributed in all of the populations screened irrespective of the tests used.

Maple syrup urine disease and *Homocystinuria* are seemingly very rare. But it should be kept in mind that some cases of leucinosis could have died (or developed severe symptoms) before blood sampling. Homocystinuria, on the other hand, is found in Sydney at later ages in such a number that one has to doubt whether methionine blood level determination in the newborn age is able to uncover at

Table 3. Frequency of Galactosemia by transferase and kinase deficiency

Center, region	Year	No. tested	Method	No. found		Frequency		Remarks
				transferase	kinase	transferase	kinase	
Warsaw Poland	69—74/6	307947	B	25	—	1:12317		enzyme some 0% some 10—20% of normal
Prague	68—73	132392	G + Chr	3	—	1:44130		technical problems
Vienna Total Austria (including Vienna)	67—74	664966	G	17	3	1:39116	1:221655	all cases typical symptoms, all fine catatacts 2. week., 11 severely ill 2. week, all enzym 0%-less than 3%
Vienna Western Austria	67—74	206907	G	11	1	1:18809	1:206907	see total Austria
Vienna Eastern Austria (excluding Vienna)	67—74	285769	G	4	1	1:71442	1:285769	see total Austria
Switzerland 3 labs	65—74	520456	G, P, B	8	0	1:65057		12 additional partial deficiency (total 1:26023)
Brussels Belgium	72—74	106511	G	0	0	<1:106511	<1:106511	

Table 3 (continued)

Center, region	Year	No. tested	Method	No. found		Frequency		Remarks
				transferase	kinase	transferase	kinase	
Hamburg Northern Germany	70—74/7	119024	G	4	2	1:29756	1:59512	
Heidelberg West of Germany BRD	69—74	300355	G, ab 71 B	7	—		1:42893	
Stockholm Sweden		907746	G	?	?	1:49000		
Dublin Ireland	72/10—74	144843	G	3	1	1:48218	1:144843	
Boston Mass. USA	—74	600000	P + B	6		1:100000		technical problems
Portland Oregon USA	65—69	132911	G	1	0	1:132911	total 1:111545	technical problems ?
	69—74/6	201724	B	2		1:100862		
Montreal Quebec Canada	—73	148872	UChr ?	1	1	1:148872	1:148872	some died before testing?
Auckland New Zealand	70/6—75/3	292626	B	9	—	1:32514		

G = Guthrie test, P = Paigen test, B = Beutler-Baluda test.

Table 4. Frequency of Histidinemia

Center, region	Period	No. tested	Method	No. found		Frequency		Remarks
				typ.	atyp.	typ.	atyp.	
Warsaw, Poland	72—73	150972	G	0		< 1:150972		technical problem ?
Prague, Prague	68—73	132392	UChr + E	0		< 1:132392		technical problem ?
Vienna, Austria	69—74	407117	G	26		1:15658		
Brussels, Belgium	72—74	106511	G	2		1:53255		
Hamburg, Northern Germany	—74/7	70871	G	0		< 1:70871		
Heidelberg West of Germany BRD	69—74	364512	G	0		<1:364512		technical problem ?
London, North	—73	239214	G	19		1:12590		
Manchester, Manchester	65—75/5	323700		21		1:15414		
Boston, Mass. USA	—74/4	396028	UChr	20		1:19801		
					2		1:198014	
Auckland, New Zealand	70/1—75/3	315617	G	23		1:13722		
					2		1:157808	
	—74/12	100000	UChr	6		1:16666		
Sydney, New South Wales Aust.	72—74/9	100000	UChr	6		1:16666		

G = Guthrie test, UChr = urine paper chromatography, E = Efron method.

Table 5. Frequency of Leuzinosis and Homocystinurie

Center, region	Period	No. tested	Method	No. found	Frequency
Leuzinosis					
Prague, Prague	68—73	132392	UChr + E	1	1:132392
Vienna, Austria	67—74	648962	G	1	1:648962
Switzerland, 3 labs	65—74	663287	G	8	1:82910
Evian, France	70—73	169342	E	0	<1:169342
Brussels, Belgium	72—74	106511	G	1	1:106511
Hamburg, Northern Germany	70—74/7	131528	G	0	<1:131528
Münster, Northwestern Germany	69—73	575215	G	1	1:575215
Heidelberg, West of Germany BRD	69—74	374512	G	2	1:182256
Dublin, Ireland	71/10—74	225746	G	0	<1:225746
Boston, Mass. USA	—74/4	932066	G	3	1:310688
Portland, Oregon USA	64—74/6	299765	G	2	1:149882
Auckland, New Zealand	69—75/3	381536	G	2	1:190768
Homocystinuria					
Warsaw, Poland	69—72	211505	G	0	<1:211505
Prague, Prague	68—73	130000	UChr + E	0	<1:130000
Vienna, Austria	68—74	573569	G	1 + 1 (1 atypical)	1:573569
Switzerland, 3 labs	65—74	564889	G	0	<1:564889
Evian, France	70—73	211540	E	1	1:211540
Brussels, Belgium	72—74	106511	G	0	<1:106511
Hamburg, Northern Germany	70—74/7	131528	G	0	<1:137528
Münster, Northwestern Germany	69—73	415935	G	3	1:138645
Heidelberg, West of Germany BRD	69—74	364512	G	0	<1:364512
London, North	—73	357976	G	3	1:119325
Manchester, Manchester	65—75/5	323700		4	1:80925
Dublin, Ireland	72/10—74	225746	G	4	1:56421
Portland, Oregon USA	67—74/6	214147	G	0	<1:214147
Boston, Mass. USA	—74/4	539677	G	3	1:179892
Auckland, New Zealand	69—75/3	381536	G	2	1:190768
Sydney, New South Wales Aust.	71—74/9	296733	UChr	1	1:296733

G = Guthrie test, E = Efron method, UChr = urine paper chromatography.

least the majority of these cases. So the data of today may not reflect the reality, that differences in frequency observed certainly also fall into the error of small numbers. The same seems to be true for *Tyrosinosis* with the exception of Montreal (less than about 1:200000 versus 1:13000). Whether this high frequency is an effect of definition, technique or inbreeding (!) has to be further clarified. *Argininosuccinic-aciduria* is screened for in only a few centers. There seems to be a significant difference between Boston on one hand and Sydney and Vienna on the other. The great difference between Boston and Sydney is of special interest because the methods used are almost identical but in Sydney urine testing is done 2 weeks

Table 6. Frequency of Tyrosinosis and other rare disorders

Center, region	Period	No. tested	Method	No found	Frequency	Remarks
Tyrosinosis						
Warsaw, Poland	72—74/6	210165	G	0	< 1:210165	(9 variants)
Prague, Prague	68—73	132392	UChr + E	3	1:44130	without enzyme determination
Vienna, Austria	70—72	189490	G	0	< 1:189490	
Evian, France	70—73	169342	E	0	< 1:169342	
Stockholm, Sweden	—74	400000	Bolinder	3	1:133333	
Brussels, Belgium	72—74	106511	G	0	< 1:106511	
Dublin, Ireland	72/3—74	199976	G	1	1:199976	
Boston, Mass. USA	—74/4	498313	G + UChr	0	< 1:498313	
Portland, Oregon USA	68—74/6	200822	G	0	< 1:200822	
Montreal, Canada	—73	232580	UChr	18	1:12921	
Auckland, New Zealand	69—75/3	381536	G	0	< 1:381536	
Sydney, New South Wales Aust.	—74/9	728040	UChr	1	1:728040	no definitive diagnosis, died before investigations complete
Arginino-succino-aciduria						
Vienna, Austria	73—74	162613	Mu	0	< 1:162613	
Boston, Mass. USA	—74/4	396028	UChr	5	1:79205	
Auckland, New Zealand	70/2—71/8	96464	Mu	0	< 1:96464	
Sydney, New South Wales Aust.	64—74/9	728040	UChr	2	1:364020	
Cystinuria						
Austria, Vienna	73/1—75/6	70400	UChr	59	(1:1100)	incomplete, Cyst/Lys/Orn high no Arg in 4—5 controls up to 6—12 months

Table 6 (continued)

Center, region	Period	No. tested	Method	No found	Frequency	Remarks
Boston, Mass. USA	—74/4	396028	UChr	25	1:15841	
Montreal, Canada		?		?	1:14084	
Sydney, New South Wales Aust.	68—72	370019 64.1% of initially positives	UChr	47	1:5069 followed for 3 years	see[a]
Prague, Prague	68—73	132392	UChr	6	1:22065	
Hartnup						
Vienna, Austria	73/1—75/6	70400	UChr	1	1:70400	
Boston, Mass. USA	—74/4	396028	UChr	22	1:18001	
Sydney, New South Wales Aust.	—74/9	728040	UChr	7	1:104005	
a1-Antitrypsin deficiency						
Portland, Oregon USA	71—74/6	95437	Mu	12	1:7953	7 additional expected 1:5000
Adenosine Desaminase defic.						
Vienna, Austria	75/1—75/10	79035	Mu	0	<1:79035	

[a] "Homozygous" is defined as: 3 years or older; at least 2 tests 1 year apart; urine Chr. cystine and lysine in excess, arginine present on at least 1 test, cystine/creatinine ration 250 mg/g or more.

later than in Boston. For an explanation one should possibly not think only about genetics.

Cystinuria in the incomplete from seems to be a rather prevalent disorder but for genetic comparisons data from more centers are needed. In *Hartnup's* disease there is an important difference in frequency between the only two centers screening which also needs further studies. The findings in Oregon about α1-*Antitrypsin deficiency* and in Vienna about *Adenosine Desaminase deficiency* are given for interest and stimulation.

Conclusions

It becomes quite clear, by comparing reliable data about frequencies of some inborn errors of metabolism in newborn populations scattered around the world, that the frequency of PKU is significantly different in different nations and races. For several of these differences the relationships and dissimilarities in the origin of present-day nations can be presumed as explanations. The examples of intra-Irish differences and those between Ashkenazi Jews and other European nations, demonstrate the possible effect of religious and social barriers. In Galactosemia by transferase deficiency, comparable observations can be made, although technical problems produce artefacts. At present there is no indication that Histidinemia has a different frequency in different parts of the world, but more data are needed. This is true also for Arginino-succinic-aciduria and Hartnup's disease where interesting differences in frequency have been observed but in too few screening centers.

The observation of significant differences in frequency of PKU and Galactosemia within such small countries as Ireland and Austria seems to indicate that comparison of frequencies in total newborn populations may only mask interesting differences by intranational equilibration. A politically defined modern nation need not necessarilly represent a genetic entity.

The study shows that the comparison of frequencies of inborn errors of metabolism is a valuable and inexpensive means of elucidating genetic relationships and dissimilarities between modern populations and of recognizing influences which define genetic compartments. This side effect of newborn screening programs could become much more fruitful if screening centers were spread more evenly arround the globe; the reliability of certain test procedures could be ensured and the number of generally sought—for disorders could be increased.

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