Inherited metabolic diseases in the Southern Chinese population; Diseases Spectrum and estimated incidence from recurrent mutations

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Summary (200-250 words)

Inherited metabolic diseases (IMDs) are a large group of rare genetic diseases. The spectrum and incidences of IMDs differ among populations, which has been well characterized in Caucasians but much less so in Chinese. In a setting of a University Hospital Metabolic Clinic in Hong Kong, over 100 patients with IMDs have been seen during a period of 13 years (from 1997 to 2010). The data were used to define the spectrum of diseases in Southern Chinese. Comparison with other populations revealed a unique spectrum of common IMDs. Furthermore, the incidence of the common IMDs was estimated by using population carrier frequencies of known recurrent mutations. Locally common diseases (their estimated incidence) include (1) glutaric aciduria type 1 (~1/60,000), (2) multiple carboxylase deficiency (~1/60,000), (3) primary carnitine deficiency (~1/60,000), (4) carnitine-acylcarnitine translocase deficiency (~1/60,000), (5) glutaric aciduria type 2 (~1/22,500), (6) citrin deficiency (~1/17,000), (7) tetrahydrobiopterin-deficient hyperphenylalaninemia due to 6-pyruvoyl-tetrahydropterin synthase deficiency (~1/60,000), (8) glycogen storage disease type 1 (~1/150,000). In addition ornithine carbamoyltransferase deficiency and X-linked adrenoleukodystrophy are common X-linked diseases. Findings of the disease spectrum and treatment outcome are summarized here which may be useful for clinical practice. In addition, data will also be useful for policy makers in planning of newborn screening program and resource allocation.
**Keywords** (> 3 keywords)

Inherited metabolic disease; Inborn errors of metabolism; Biochemical genetics; Fatty acid oxidation defects; Newborn screening program; Enzyme replacement therapy.

**List of Abbreviations**

- **FAOD** Fatty acid oxidation defects
- **GA1** Glutaric aciduria type 1
- **HPA** Hyperphenylalaninemia
- **IMD** Inherited metabolic diseases
- **MCD** Multiple carboxylase deficiency
- **MPS** Mucopolysaccharidosis
- **NBS** newborn screening
- **PKU** classical phenylketonuria (due to defective phenylalanine hydroxylase, PAH)
- **PTS** 6-pyruvoyl-tetrahydropterin synthase, its deficiency is a cause for HPA
- **XALD** X-linked adrenoleukodystrophy
1. Introduction

1.1 Recent Progress in IMD

Inherited metabolic diseases (IMDs) are a diverse group of disorders caused by inherited defects of various metabolic pathways. These defects in metabolic pathways lead to either accumulation of toxic side products or deficiency of essential metabolites. Some patients with severe defects may die suddenly during the first year of life or suffer from severe symptoms and syndrome. In the past, treatment options were few and prognosis was poor. However, in the recent 10 to 20 years, we witnessed a major advance and breakthrough in both screening (early diagnosis) and therapy for IMDs.  

Although individual metabolic disease is relatively rare, IMDs as a group represent a significant healthcare burden collectively. For example, collective incidences ranging from 1 in 2,500 to 1 in 4,000 have been reported in European countries and many of them could be detected early by screening at the newborn period. 

The spectrum of IMDs is well characterized in Caucasians as several clinical cohorts have been reported from Canada, Italy, England and Spain. Few studies had been carried out in other populations like Japan, India and Saudi Arabia. While the Chinese population represents 18% of the world population, few cohort studies of IMDs had been reported. A Taiwan group reported incidences of IMDs identified by newborn screening, however, information was confined only to diseases that had been included in the screening program.
It is now apparent that the spectrum of diseases is different between the Asian and European populations\textsuperscript{16-18}. Therefore, it is important to understand what are those prevalent diseases in the Chinese population.

\textbf{1.2 Development of a metabolic clinic in Hong Kong}

In January 1997, a Joint Metabolic Clinic in Hong Kong was set up at the Prince of Wales Hospital/CUHK to diagnose and provide treatments to patients with IMDs. By 2010, more than 100 patients and families had been diagnosed and treated in this metabolic clinic which covers an catchment area of a population of 1.2 million. A profile of the more common IMDs in the Chinese population in Hong Kong has also emerged from our case series database. Part of it has been described in an earlier review reported by our team\textsuperscript{16}. Several unique features are apparent in the spectrum of diseases found in the Southern Chinese. For example, primary carnitine deficiency is more common in Chinese due to presence of a founder mutation\textsuperscript{19,20}. And classical phenylketonuria (due to defective phenylalanine hydroxylase, \textit{PAH}) was relatively rare compared to another defect in causing hyperphenylalaninemia (6-pyruvoyl-tetrahydropterin synthase deficiency)\textsuperscript{16}.

The data of this case series gathered after more than 10 years’ of experiences in running the metabolic clinic will be useful for policy makers in planning of newborn screening program\textsuperscript{21,22} and resource allocation involved in both screening and long-term treatment as many IMDs have major resource implications nowadays both due to the chronic nature of the disease or disability and emerging therapy regimens which are often costly\textsuperscript{21,23-25}.  

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2. **Overview of disease spectrum and comparison with other populations (Figure 1)**

In order to allow comparison with data from Western countries, IMDs were grouped according to the conventional classification into two major categories: (A) Diseases of Small Molecules and (B) Diseases of Large Molecules. Under the category of Diseases of Small Molecules, examples include organic acidurias, defects in fatty acid oxidation pathway, inherited defects involved in metabolism of amino acids, primary lactic acidosis and defects in the urea cycles. On the other hand, various storage diseases with tissue deposition of large polymeric molecules, like in mucopolysaccharidoses, glycogen storage diseases and other organelle diseases are grouped into Diseases of Large Molecules. Figure 1A shows the proportional distribution of the 2 categories which turns out to be largely even. In order to make comparison with incidence data from the Western countries, diseases are further subdivided according to Applegarth et al\(^7\). It is interesting to note that the case-mix would become fairly similar if two highly prevalent IMDs in Caucasians were excluded, namely classical PKU and galactosemia\(^7\).
3. Diseases of small molecules

3.1. Organic acidurias (Figure 2)

The prevalences of three common organic acidurias stand out from the rest as multiple unrelated patients were diagnosed in our clinic. They are (1) glutaric aciduria type 1, (2) multiple carboxylase deficiency and (3) propionic aciduria. A particularly high prevalence of glutaric aciduria type 1 and multiple carboxylase deficiency was found in Southern Chinese when compared to Northern Chinese in Shanghai or Beijing or Caucasian populations (Figure 2). All the three locally prevalent organic acidurias can be treated with dietary and pharmacological interventions and could lead to good prognosis.

3.1.1. Glutaric aciduria type 1 (GA1)

Early prophylactic treatment of patient with Glutaric aciduria type 1 before acute neurological crisis is the key advance in treatment of this disease. In Western countries and in Taiwan where universal newborn screening (NBS) is carried out, it is straightforward to start prophylactic treatment once the NBS result is confirmed. On the other hand, it is difficult to identify pre-symptomatic patients of GA1 in regions without universal NBS. The importance of pre-symptomatic treatment cannot be overemphasized as neurological sequel cannot be reversed after acute neurological crisis. In the clinic, one case was picked up by clinical suspicions due to the associated phenotype of big head (head circumference >95 percentile). The patient has been treated with dietary intervention and has been well on the latest follow-up at 9 years old.
Our early study found that IVS10-2A>C mutation was a recurrent mutation\textsuperscript{31}. Screening of the IVS10-2A>C mutation showed that population carrier rate was as high as 1/120 (95% Confidence Interval, CI = 0.0002 to 0.0456) suggesting a disease incidence of \(~1 / 60,000\). Subsequent regional newborn screening in China confirmed a similar disease incidence at 1/64,708\textsuperscript{32}. This mutation was also found in Taiwan Chinese patients\textsuperscript{33-35}.

3.1.2. Multiple carboxylase deficiency (MCD)

Multiple carboxylase deficiency could be due to defect in either one of the 2 genes: holocarboxylase synthetase (\textit{HLCS}) deficiency and biotinidase deficiency. This disease is characterized by life-threatening metabolic decompensation during infancy. Treatment response is excellent if the patient could overcome the acute crisis. Again, NBS will be an excellent cost-effectiveness way to diagnose this disorder. In Caucasian population, biotinidase deficiency screening had been implemented on filter paper blood spot sample for decades even before the era of NBS by tandem mass spectrometry\textsuperscript{36}. In this case series, only one case of biotinidase deficiency was diagnosed while \textit{HLCS} deficiency was the cause in another 4 MCD patients. In terms of phenotype, we did not find any key difference between biotinidase and \textit{HLCS} deficiency, and therefore, a definitive diagnosis by enzyme assay or mutation analysis will be required. Our collection of MCD cases is highly responsive to treatment with biotin. And prognosis is excellent.

3.1.3. Other organic acidurias
Propionic acidemia and methylmalonic acidurias are the most common types of organic aciduria in the global populations (Figure 2). However, the prevalence of both diseases are low in our population.

In summary, two unique features are described for the spectrum of organic acidurias. First, the predominant etiology of MCD in Southern Chinese is $HLCS$ deficiency, while biotinidase deficiency was more common in Northern China (Shanghai and Beijing) and Caucasian populations. Second, the prevalence of methylmalonic aciduria was low in Southern China when compared to the rest of the World. These early impression requires further confirmation after NBS implementation in the future.

3.2. **Fatty acid oxidation defects** (FAOD)

3.2.1. **Primary carnitine deficiency**

Our group has a long-term research interest in FAOD in Chinese. We are among the first to identify the causative gene ($SLC22A5$, also known as $OCTN2$) in primary carnitine deficiency due to defect of the plasma membrane carnitine transporter $^{19, 37, 38}$. Patients with this transporter defect have very low intra-cellular level of carnitine. As the same transporter is used for active re-absorption of free carnitine in the proximal renal tubule, the defect also leads to a severe renal wasting of carnitine and in turn the free carnitine in circulation is also low. Therefore, a very low free carnitine and total carnitine
are the hallmarks for diagnosis of this potentially life-threatening disease. Patients respond extremely well to high dose carnitine replacement and the very first three cases diagnosed in America showed favorable prognosis.

This defect is highly relevant to Southern Chinese population due to the presence of a common mutation, R254X. The population carrier frequency of R254X was 1/125 (95% CI=0.0002 to 0.0438) in Southern China. This disease was also the most prevalent disease among all FAOD in a Taiwan newborn screening program.

3.2.2 **Carnitine-acylcarnitine translocase deficiency**

Carnitine-acylcarnitine translocase (CACT) deficiency is characterized by early onset of severe metabolic decompensation and poor prognosis. Many studies suggested poor treatment outcome and prognosis. It is also a common cause of unexplained death in early infancy period or sudden infant death. Few patients with good treatment response were reported recently, however long term follow-up is required to confirm these initial favorable response.

Stanley et al reported the first patient of this disease who was born to an American Chinese family in 1992. Interestingly, this patient shared a recurrent splicing mutation (IVS2-10T>G) with another Chinese patient from a British-Chinese family. Later, this mutation was also found in other local Chinese cases of sudden death. Therefore, this recurrent mutation may be present at a high frequency in the Southern Chinese population.

All 3 patients in this case series presented with severe metabolic crisis in early infancy and succumbed to the disease. Early onset of cardiac arrhythmia was frequently found. Therefore, it might serve as a clinical marker to raise the suspicion of pediatrician
about this differential diagnosis in patients with early onset metabolic crisis. Although prognosis may not be favorable in the index case, it is very important to make the diagnosis as it will enable pre-natal diagnosis in subsequent pregnancy.

3.2.3 Multiple acyl-CoA dehydrogenase deficiency / glutaric aciduria type 2

Another common FAOD in Chinese is multiple acyl-CoA dehydrogenase deficiency. The defect may be caused by mutation in one of its subunits encoded by three genes (electron transfer flavoprotein alpha-subunit, \textit{ETFA}; electron transfer flavoprotein beta-subunit, \textit{ETFB}, and ETF dehydrogenase, \textit{ETFDH}). The spectrum of mutations and their distribution among these 3 genes in our local patients had been reported \textsuperscript{48}. Remarkably, one of the mutation in \textit{ETFDH} (A84T) was found to be a common mutation in subsequent studies \textsuperscript{49, 50}.

3.2.4 Very long-chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency

VLCAD deficiency may present with both neonatal (early-onset) and adult form. We diagnosed adult patients referred from another catchment area who presented with severe myopathy. Therefore, they did not appear in the statistics reported here (Table 1). However, this is an important diagnosis to recognized as it may present with highly variable phenotypes ranging from sudden death in its neonatal form to cardiomyopathy or even isolated myopathy in adult patients \textsuperscript{51}. Blood carnitine profiling is the key investigation for making the diagnosis.

3.2.5 Medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency
MCAD deficiency is very common in Caucasian with an incidence of 1 in 17,000, however, it is extremely rare in Asian. The high incidence in Caucasian is due to the presence of a common mutation (c.985A>G). Although this mutation was first found by Japanese research team, it was not present in many Asian populations\textsuperscript{14,52}. Only two patients were diagnosed in the Taiwan NBS program over 9 years which suggested an incidence of 1 in 660,000 for Southern Chinese\textsuperscript{14}.

### 3.2.6 Short-chain acyl-coenzyme A dehydrogenase (SCAD) deficiency and other variants of uncertain phenotype

SCAD deficiency is a defect in the final step of the fatty acid oxidation spiral and SCAD handles acyl-CoA of 4 to 6 carbons in length. It is not unexpected that SCAD patients may have milder phenotype and present at variable age (from newborn to 50 years old)\textsuperscript{53}. Both phenotype and severity of disease are highly variable. Some patients present with metabolic acidosis. On the other hand, asymptomatic cases were also reported in families with clinically affected sibs. Histologic features of myopathy and lipid storage disease had been found in some patients\textsuperscript{54}. A common polymorphism in \textit{ACADS} gene, c.625G>A, was found across ethnic groups. Previous reports suggested that individual homozygote for this polymorphism had a wide spectrum of clinical manifestations ranging from asymptomatic carrier to myopathy\textsuperscript{55}.

A polymorphism in the \textit{CPT2} gene was also common in Asian population (c.1055T>G or F352C)\textsuperscript{56}. This polymorphism encodes for a carnitine palmitoyltransferase 2 protein that is believed to be thermolabile. Therefore, it might lead to a phenotype of transient \textit{CPT2}
deficiency and raised serum acylcarnitine ratio only during febrile illness. Subsequent study in Japan showed that this polymorphism might be associated with higher mortality in patients with acute encephalopathy\textsuperscript{57}.

3.3 Aminoacidopathies

3.3.1 Citrullinemia type 2 or citrin deficiency

The most common aminoacidopathy found in our series is citrin deficiency, also known as neonatal onset type 2 citrullinemia (#MIM:605814) or neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD). This defect in the aspartate/glutamate carriers functioning as aspartate-malate NADH shuttle across the mitochondrial membrane was first reported in adult patients with neuro-psychiatric symptoms and hyperammonemia called adult-onset type II citrullinemia (CTLN2, #MIM:603471)\textsuperscript{58}. Only until 2001, the neonatal form was firstly recognized in patients presented with conjugated hyperbilirubinemia during neonatal or early infancy\textsuperscript{59}. We diagnosed 7 patients and citrin deficiency represented the most common IMD in this series. Galactouria was a frequent finding among our patients. This is a particularly important diagnostic marker relevant to Asian population, as the incidence of classic galactosemia is very low in Southern Chinese\textsuperscript{60}, it can serve as a surrogate marker for citrin deficiency. Recently, a second-tier molecular test approach has been proposed for this disorder\textsuperscript{61}.

3.3.2 Hyperphenylalaninemia (HPA)
A strong geographic differentiation was found in disorders leading to HPA. As already mentioned in the earlier review, classic phenylketonuria due to mutations in \textit{PAH} gene, (PKU, #MIM:261600) was less common in Southern Chinese when compared to Caucasian. On the other hand, a higher proportion of HPA was caused by deficiency of 6-pyruvoyl-tetrahydropterin synthase (\textit{PTS}, #MIM:261640) leading to tetrahydrobiopterin-deficient HPA. Hsiao KJ’s team studied mutations and causes of tetrahydrobiopterin-deficient HPA in Taiwan and found common recurrent mutations in \textit{PTS} genes which explained the high regional prevalence\textsuperscript{62}. They showed that PTS deficiency was more prevalent among the Southern Chinese while classic PKU was more common among Northern Chinese\textsuperscript{63}. Two patients with \textit{PTS} deficiency were also diagnosed and treated in this case series. Both of them also carried the common mutations. Similarly, two patients with classic PKU were also seen in the clinic.

\subsection*{3.3.3 Other aminoacidopathies}

A variety of other aminoacidopathies were also seen but they were diagnosed in single families. And no definitive statement about their prevalence could be made. These disorders included cystinuria and pyridoxine-responsive homocystinuria due to \textit{CBS} mutations\textsuperscript{64}.

\subsection*{3.4 Urea cycle defects}

Ornithine transcarbamylase (OTC) deficiency represents the most common urea cycle defect in our clinic and it is also the case in other Asian populations\textsuperscript{65}. In addition to the typical presentation of OTC deficiency, we also found variant phenotypes; including symptomatic female carrier\textsuperscript{16} and mild phenotype in a male patient with intermittent
hyperammonemia\textsuperscript{66}. These patients illustrate the complexity and the range of phenotypic variation in this X-linked disorder.

4 Disease of Large Molecules (including Storage and Organelle Diseases) and others

4.1 Glycogen Storage Diseases (GSD)

Almost all types of hepatic glycogen storage diseases had been diagnosed in Hong Kong. All patients are characterized by a huge hepatomegaly. Among the various types, Glycogen storage disease type 1 is important to recognize as patients may suffer from life-threatening hypoglycemia. All type 1 patients experienced hyperlipidemia, lactic acidosis and high blood uric acid concentration.

The main difference between type 1 and other types of hepatic GSD is that the other types (particularly type VI and IX) are presented with milder phenotype\textsuperscript{67, 68}. These (non-type 1) patients have a huge hepatomegaly to the same extent as type I GSD patients, but they might presented late (even undiagnosed after infancy) and without hypoglycemia. Pompe disease (GSDII) represented a special type of glycogen storage disease to recognize and enzyme replacement therapy is useful particularly in late-onset patients\textsuperscript{69, 70}.

4.2 Lysosomal Storage Diseases (LSD)

Lysosomal storage diseases (LSDs) are a group of approximately 50 known genetic disorders which are due to deficiency of a particular enzyme or enzymes causing abnormal storage of naturally occurring molecules inside lysosomes\textsuperscript{4, 5, 71, 72}. Up until
2010, there were 31 patients with various types of LSDs that have attended our clinic. These included 21 patients with Mucopolysaccharidoses (6 MPS I, 5 MPS II, 5 MPS III, 1 MPS IV & 4 MPS VI), 5 patients with Mucolipidosis II (I-cell disease), 1 patient with Niemann Pick type B, 3 patients with Niemann-Pick type C disease (NP-C) and 1 patient with infantile Pompe disease. It is worth pointing out that Gaucher disease was not included in our case series though patients were found Hong Kong and in other parts of China.  

4.3 Primary lactic acidosis

A variety of mitochondrial diseases have been diagnosed. Both mitochondrial respiratory chain defects (RCD) and pyruvate dehydrogenase (PDH) deficiency can lead to primary lactic acidosis. For the patients with confirmed diagnosis of PDH deficiency with enzyme assay on cultured fibroblast, they had distinctive features compared to other patients with respiratory oxidation chain defects. These features include early-onset of lactic acidosis (particularly in male PDH deficiency patients as it is a X-linked disease), persistently very high level of blood lactic acid concentration (> 6 mmol/L) and presence of specific CNS structural abnormality which could be picked up on CT scan or MRI (such as corpus callosum agenesis).

4.4 Others IMDs

4.4.1 Peroxisomal diseases

X-linked adrenoleukodystrophy (XALD) was the most common peroxisomal diseases. It is an X-linked disease due to mutation in the ABCD1 gene encoding for a
protein required for importing very-long chain acylCoA dehydrogenase into the peroxisomes. Therefore, patients have abnormally high level of very-long chain fatty acid in the circulation which is also a reliable diagnostic marker. It is important to diagnose this condition early as pre-symptomatic patients carrying mutations need to be monitored closely for onset of white matter changes, signifying imminent leukodystrophy. Definitive treatment such as bone marrow transplantation is required as early as possible when such changes are evident \(^75\). As majority of our XALD patients already had severe neurological involvement at the time of presentation, they were not suitable candidates for hematopoietic stem cell transplant. Five patients underwent transplant and three of them showed no further deterioration in their neurological status at 5-year follow up. One patient died shortly after transplant because of relentless disease progression.

### 4.4.2 Neurogenetic disorders

Various defects involving synthesis and metabolism of neurotransmitters were also found. They included tyrosine hydroxylase deficiency and GTP cyclohydrolase 1 deficiency, some of them had been reported in previous case series analysis \(^76\). Two patients with glucose transporter defect had been reported \(^77\). In addition, it was also important to recognize that patients with hyperphenylalaninemia caused by \(PTS\) mutations also suffered from deficiency of neurotransmitters dopamine and serotonin \(^78\) and they would be benefited by treatment with L-dopa/carbidopa/5-hydroxytryptophan plus BH4 with marked clinical improvement.
5 Discussion

5.1 Difference in spectrum of IMDs between Northern and Southern Chinese

Hong Kong is located at the southern coastal part of China and is densely populated with more than 7 million residents. About 95% of the population is Han Chinese\(^{79}\). A large proportion of them are descendants of the past episodic influxes of people from neighboring South China provinces, in particular, Guangdong. Therefore, the population genetic make-up is mainly that of Southern Chinese.

It is now generally accepted that genetic difference exists between the Northern and Southern Chinese. It has been hypothesized that Northern Chinese are descendants of settlements from taken North migration route, while the Southern Chinese are the offsprings of another migration event using routes through Southeast Asia\(^ {80,81}\). There are now ample evidences supporting genetic differentiation between Southern and Northern Chinese based on different genetic markers, such as SNPs and mitochondrial haplotypes\(^ {81,82}\). Geographically, an arbitrary dividing line has been placed in the Qinling Mountains and Huai River, but recent evidence supports for Yangtze River being a division.

Such genetic differentiation is also reflected in different spectrum of common IMDs in Southern Chinese as compared with that in Northern Chinese as well as in Caucasian. For example, classic PKU is less common in Southern Chinese. In contrast, the incidences of PKU are comparable between Northern Chinese and Caucasians\(^ {17}\). Likewise, methylmalonic and isovaleric acidaemia are among the most frequent organic acidurias found in Northern Chinese but not so frequent in Southern Chinese\(^ {17}\).
Our data on Southern Chinese will provide more in-depth comparison when more data from centers in Northern China become available.

5.2 Estimation of the incidence of common IMDs in Southern Chinese

An important reason to estimate the incidence of IMDs is for planning and implementation of NBS and treatment service. At the moment, the main application of NBS is targeted to small molecule diseases. Therefore, estimates of incidence of these IMDs are particularly of interest.

However, reliable disease incidence cannot be determined from the crude incidence rate from case series data like this study. Without a territory-wide registry or NBS, it is not possible to have an unbiased denominator to figure out disease incidence. As a result, a tendency of overestimation is common in case series data. For example, if we assume these patients were collected over the course of 13 years in this catchment area, the resulting incidence rate will be several folds higher than figures reported in other populations. Many reasons lead to overestimation in case series, including cross-catchment area referral, inclusion of prevalent cases which had not been diagnosed (backlog effect) and immigration of children particularly those born to non-local residence.

As an alternative we used observed population carrier (heterozygote, 2pq) frequencies of common mutations to calculate the homozygote frequencies \( q^2 \) as estimates of disease incidence. Table 2 summarizes IMDs with recognized common recurrent or founder mutation in Southern Chinese. Seven of them could be picked up by NBS using tandem mass spectrometry. Incidences of these 7 IMDs range from 1 in
17,000 to 1 in 60,000. They are consistent with incidence determined from a newborn screening program in Taiwan. All together, ~1 in 5,400 live births would have one of these locally “common” IMDs. We estimate that ~15 newborns with IMDs might be benefited from a universal NBS every year given the current annual birth rate at ~ 80,000 in Hong Kong.

This figure is also comparable to that in the USA in which a high coverage NBS has been in place. As MCAD deficiency and galactosemia are not prevalent in Southern Chinese, we compared to the incidence of small molecular diseases in US population after removal of both entities, which would become ~1 in 7,000. Recently, not only small molecule diseases are screened by NBS, storage diseases like Pompe disease and LSD are also potential diseases for screening. Expanding the NBS to cover large molecular diseases will allow early diagnosis and treatment of these patients.
**Acknowledgement**

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Figure Legends

Figure 1. Prevalence of two categories of Inherited Metabolic Diseases in Hong Kong Chinese. (1A) The proportion of two major categories of IMDs. (1B) Diseases subgroups.

Figure 2. Comparison of prevalence of various organic acidurias among Southern Chinese, Northern Chinese and Caucasian populations. Data are extracted from references 7, 9, 17, 26.
Table 1. Diagnoses and spectrum of IMDs of patients seen in a metabolic clinic in Hong Kong.

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<th>Diseases of Small Molecules</th>
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<td>Disease</td>
<td>Frequency</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Niemann Pick Type B</td>
<td>1</td>
</tr>
<tr>
<td>Niemann Pick Type C</td>
<td>3</td>
</tr>
</tbody>
</table>

**Organelle Diseases**

**Primary lactic acidosis**
- Pyruvate dehydrogenase deficiency  2
- Complex I deficiency             2
- Complex IV deficiency            1
- Leigh’s disease                   3
- Kearns Sayre syndrome             2

**Peroxisomal diseases**
- Adrenoleukodystrophy             15
- Peroxisomal biogenesis disorder   1

**Neurogenetic Disorders**
- Tyrosine hydroxylase deficiency  4
- GTP cyclohydrolase 1 deficiency  1
- Glucose transporter defect       2
- Vanishing white matter disease   1
Table 2. Recurrent or founder mutations found in IMDs among Southern Chinese

<table>
<thead>
<tr>
<th>Disease / Gene</th>
<th>Mutation</th>
<th>Carrier frequency*</th>
<th>Estimated incidence</th>
<th>Expected cases per 100,000 newborns</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic acidurias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutaric aciduria type 1/ GCDH</td>
<td>IVS10-2A&gt;C</td>
<td>1 / 120 Hong Kong</td>
<td>1 in 60,000</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td>Multiple carboxylase deficiency/ HLCS</td>
<td>R508W</td>
<td>known recurrent mutation@</td>
<td>1 in 60,000</td>
<td>1.67</td>
<td>85</td>
</tr>
<tr>
<td>Fatty acid oxidation defects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Carnitine deficiency / SLC22A5 (OCTN2)</td>
<td>R254X</td>
<td>1 / 125 Hong Kong</td>
<td>1 in 60,000</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td>Carnitine-acylcarnitine translocase / SLC25A20</td>
<td>IVS2-10T&gt;G</td>
<td>known recurrent mutation@</td>
<td>1 in 60,000</td>
<td>1.67</td>
<td>46, 47</td>
</tr>
<tr>
<td>Glutaric aciduria type 2/ ETFDH</td>
<td>A84T (c.250G&gt;A)</td>
<td>7 / 520 Shanghai</td>
<td>1 in 22,500</td>
<td>4.44</td>
<td>48, 86, 87</td>
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<tr>
<td>Aminoacidopathies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrin deficiency/ SLC25A13</td>
<td>851-854del IVS6+5G&gt;A</td>
<td>1 / 65 China</td>
<td>1 in 17,000</td>
<td>5.88</td>
<td>88</td>
</tr>
<tr>
<td>Tetrahydrobiopterin-deficient HPA (PTS deficiency) / PTS</td>
<td>N52S (c.155A&gt;G), P87S (c.259C&gt;T)</td>
<td>known recurrent mutation@</td>
<td>1 in 60,000</td>
<td>1.67</td>
<td>62, 63, 89</td>
</tr>
<tr>
<td>Storage Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycogen storage disease type 1a/ G6PC</td>
<td>c.727G&gt;T (also known as c.648G&gt;T)</td>
<td>2/385 Hong Kong</td>
<td>1 in 150,000</td>
<td>0.67</td>
<td>90, 91</td>
</tr>
</tbody>
</table>

Note: * population carrier frequencies are gathered from published references and location of the studies are shown.
@Some diseases with known recurrent mutations in Southern Chinese but no observed carrier frequency data are assigned population carrier frequencies of 1/120 and incidence of 1 in 60,000.
^ This data is extracted from a Shanghai sample.
References


