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Mutation Frequency of Three Neurodegenerative Lysosomal Storage Diseases: From Screening to Treatment?

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Background. The ascertainment of mutation frequencies in the general population may have impact on the population's wellbeing and respective healthcare services. Furthermore, it may help define which approaches will be more effective for certain patients based on the genetic cause of disease.

Aim of the Study. Determine the frequency of three mutations, known to be a major cause of three distinct Lysosomal Storage Diseases (LSDs).

Methods. The following pre-requisites were met: each mutation accounted for over 55% of the disease alleles among previously reported unrelated patients, all three diseases were among the most prevalent LSDs in the population under study, they all involved devastating deterioration of the nervous system, lacked curative treatment and may be fatal in childhood or adolescence. The anonymous samples used in this study were representative of the whole population; mutations were tested by PCR based methods, positive results were further confirmed. The diseases studied were Mucopolysaccharidosis type I (Hurler, MIM 607014), Tay Sachs disease variant B1 (TS, MIM 272800) and Metachromatic Leukodystrophy (MLD, MIM 250100); the mutations were, respectively, p.W402X, p.R178C and c.465+1G>A.

Results and Conclusion. Increased carrier frequencies were found for Tay Sachs disease variant B1 HEXA p.R178C mutation (1:340) and for the infantile MLD ARSA c.465+1G> A mutation (1:350) denoting higher risk for these sub-types of disease in Portugal and possibly in individuals of Iberian ancestry. Carrier screening in target populations may provide the foundations for more effective approaches to precision medicine.

Key Words: Lysosomal diseases, Gene frequency, Molecular genetics, Therapeutics, Population screening, Mucopolysaccharidoses, Sphingolipidoses.

Introduction

Lysosomal storage diseases (LSDs) are a group of rare genetic disorders in which there is a malfunction at the lysosomal level. Over 70 diseases have been described as LSDs, the causal defect can lie in acid hydrolases or in non-enzymatic proteins (such as activator or transport proteins, among others) and in the future, with the wide application of next generation sequencing, more lysosomal related diseases may be identified. As research progressed and the mechanisms of LSDs were discovered the lysosome became a target for the development of several types of therapies (1).

Population-specific and disease-specific studies are important to improve health outcomes and understand disease susceptibility in specific population groups. The comparison of the genetic characteristics of individuals from different geographic areas usually shows that mutations vary among regions, even if the related diseases remain with the same relative impact. Mutation profiles are usually population-specific denoting population history and demographics. The mutation profiles can be shaped by founder

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effects or by heterozygote advantage, biased reproductive choices and better adaptation to environmental conditions making them, often, unique. Some mutations can be found across several population groups at different frequencies, perhaps indicating recurrent mutational events or ancient common origins. However, to understand the genetic bases of diseases, comparison between different populations is necessary. In this work we first considered the top six LSDs in Portugal (2) and, based on previously reported data, we chose to study three of them.

Genetic carrier screening involved testing a sample representative of the whole population. The DNA based tests performed were precise, avoiding any pseudo-deficiency situation that could arise in a biochemical screening. In each case a single mutation accounted for over 55% of the disease alleles among the reported unrelated patients and all three diseases were prevalent in the population under study (2,3). The three disease-causing mutations that filled our pre-requisites were Metachromatic Leukodystrophy (MLD) mutation c.465+1G>A (IVS2DS+1G>A, MIM 607574.0003, rs80338815), Tay Sachs (TS) GM2-gangliosidosis variant B1 mutation c.533G>A (p.R178C, MIM 606869.0006, rs28941770), and Mucopolysacharidosis type I (MPS I) mutation c.1205G>A (p.W402X, MIM 252800.0001, rs121965019). The results obtained were then compared with those of the 1000 Genomes Project (4).

General information–Metachromatic Leukodystrophy

MIM: 607574; ORPHA: 512; Gene: ARSA; Chromosome location: 22q13

Gene product: Arylsulfatase A; Subtype: Infantile

Common mutation in this population: ivs2+1, 250100.0033

Frequency of mutated allele in unrelated patients from Portugal: 60%

Treatment available: mostly palliative; recent *ex-vivo* experiments

Metachromatic Leukodystrophy is usually caused by ARSA gene mutations (MIM 607574), which lead to a deficiency of the lysosomal hydrolase arylsulfatase A (ARSA; EC 3.1.6.8). The resulting defect originates intralysosomal accumulation of galactosylceramide sulfatide and other sulfated sphingolipids. This accumulation affects the white matter of the central and peripheral nervous systems resulting in a progressive demyelination and in a clinical picture characteristic of leukodystrophy (5). The overall incidence of MLD varies from 1 in 40.000 to 1 in 130.000 in different populations (5). Mutation c.465+1G>A is highly prevalent and in combination with p.P426L mutation accounts for about 50% of the MLD alleles in different populations (6).

General information–Tay Sachs disease

OMIM: 606869; ORPHA: 845; Gene: HEXA; Chromosome location: 15q23

Gene product: Beta hexosaminidase alpha chain; Subtype: Variant B1

Common mutation in this population: R178H, 606869.0006

Frequency of mutated allele in unrelated patients from Portugal: 59.5%

Mutation type: missense affecting normal catalytic function

Treatment available: mostly palliative; recent lentiviral based therapy experiments

Variant B1 is a rare form of GM2-gangliosidosis and is caused by a deficiency of hexosaminidase A (HEXA, EC 3.2.1.52) which results from mutations in the HEXA gene (MIM 606869). Due to the impairment of function of hexosaminidase A, GM2 gangliosides are not degraded resulting in neuronal accumulation and progressive loss of central nervous system function (7). Tay Sachs has an incidence of 1 in 112.000 births in the general populations and a carrier frequency estimated as 1:~260 (7). Specific populations may exhibit specific HEXA mutations at higher allelic frequencies (8), for example, the Ashkenazi Jews and the French Canadian are known to present specific mutations at high frequencies (9,10). Variant B1 has been reported in patients with a subacute variant phenotype, late infantile to juvenile onset, and the deficient enzyme has altered kinetic properties due to active site disturbance (11). Most variant B1 patients carry at least one c.533G>A allele and they often have traceable Portuguese ancestry (12–15).

General information–Mucopolysacharidosis type 1

MIM: 252800; ORPHA: 93473; Gene: IDUA; Chromosome location: 4p16.3

Gene product: Alpha-L-iduronidase; Subtype: Hurler syndrome

Common mutation in this population: W402X

Frequency of mutated allele in unrelated patients from Portugal: 63%

Treatment available: mostly palliative; enzyme replacement therapy and CNS system cell based therapy experiments

Mucopolysacharidosis type I (MPS I) is a rare autosomal recessive disease caused by a deficiency of alpha-L-iduronidase (IDUA; EC 3.2.1.76), an enzyme required for the degradation of the glycosaminoglycans, dermatan sulfate and heparan sulfate, due to IDUA gene mutations (MIM 252800). It is estimated that 1 in 100.000 live births is affected by MPS I (16). This disease is characterized by progressive and chronic accumulation of glycosaminoglycans (GAGs) in the lysosomes of cells due to their impaired degradation. The CNS symptoms occur mostly in MPS I Hurler subtype. Patients affected by this disease present multi-organ dysfunction which leads to extensive morbidity in most patients, and early mortality in those most severely affected (16). Mutation c.1205G>A is the most prevalent IDUA mutation in Caucasian populations (17).

In these cases, the severity of the diseases, their prevalence, their mutation profiles, and the lack of fully