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Expanded Carrier Screening for Neuromuscular Disorders

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ABSTRACT

Genetic disorders are inherited from ancestors of family who may reflect clinical symptoms or be silent asymptomatic carriers. Awareness about such disease prevalence in family and understanding its implications in living and life expectancy is very important. Symptomatic people can have their treatment for their morbidity but asymptomatic people have higher probability of missing golden chances for preventing any mishap. To their rescue, expanded carrier screening, an upcoming testing program facilitates early detection, preparedness and awareness about the potential burden that arrives uninformed. However, not yet very common, ultimate aim would be towards normalizing and eliminating social discrepancies and fear towards such trigger points. This review will be focusing on role of expanded carrier screening in neuromuscular disorders like Spinal Muscular Atrophy and Duchenne Muscular Dystrophy.

Abbreviations: PKU: Phenylketonuria; ECS: Expanded Carrier Screening; NBS: New Born Screening; PAH : Phenylalanine Hydroxylase; CF: Cystic Fibrosis; ACMG: American College of Medical Genetics and Genomics; ACOG : And American College of Obstetricians and Gynaecologists; SMA: Spinal Muscular Atrophy; SMN: Survival Motor Neuron; EMG: Electromyography; MLPA: Multiplex Ligation Dependent Probe Amplification; qPCR: Quantitative PCR; SMARD1: Spinal Muscular Atrophy With Respiratory Distress Type 1; PGT: Preimplantation Genetic Testing; IVF: *In Vitro* Fertilization; Scaav9: Adeno-Associated Virus Serotype 9; DMD: Duchenne Muscular Dystrophy; CK: Creatine Kinase; DAP: Dystrophin Associated Proteins; BMD: Becker Muscular Dystrophy; ECG: Electrocardiogram; CGH: Comparative Genomic Hybridization; RFLP: Restriction Fragment Length Polymorphism; PCR: Polymerase Chain Reaction; STR: Short Tandem Repeat; qmfPCR : Quantitative Multiplex Fluorescence PCR

Introduction

Genetic disorders are characterised by deleterious changes in nucleic acid sequence called mutation. This alteration in genetic makeup could be inherited from ancestors or acquired during the course of life [1] and can be potentially life threatening depending on various factors like age, family history, [2] ethnicity [3,4], gender, comorbidities etc. However, mutations are also proven to be beneficial [5] or neutral. The latter is considered and proved to play an important role in evolution by Kimura in his Neutral theory of Molecular Evolution where he held random genetic drift to be the reason for molecular level evolutionary changes [6]. Most genetic disorders that are passed from parents to their offspring are carried by determining units of genome called genes by the concept of inheritance. Hence, it is important that we understand its pattern of flow, phenotypic and genotypic expression and variation and the probability of passing to next potential generation. Genes have two alternate forms of themselves called alleles, each from both parents,

forms the basis of inheritance. Expression of gene can be influenced by genetics and environment [7]. Concept of inheritance first described by Gregor Johann Mendel laid the foundation for single gene disorders where one gene is affected by mutation hampering its normal function [1,7]. Effect of mutation is scrutinized up to the level of loci of the mutated gene, autosome or sex chromosome, number of mutated alleles and phenotypic expression of inherent genotype [1].

Disease phenotype can be distinguished as dominant where presence of one mutant allele will suffice the requirement to express the condition or recessive where both alleles are to be mutated to present the condition [1,8]. Autosomal dominant as in Huntington's disease refers to expression of one mutated allele in autosomes, with no carrier states, heterozygous affected or homozygous unaffected [1,7,8]. Autosomal recessive like Phenylketonuria (PKU) refers to the requirement of two mutated alleles to present a condition, homozygous affected, unaffected or heterozygous carriers [1,7,8]. Hypophosphatemic rickets is X – linked dominant identified by inheritance of one mutated allele on X chromosome with gender bias towards females [1,8]. Hemophilia A is X – linked recessive, which has inheritance of two mutated alleles with only females as carriers [1,7,8]. Heterozygous female carriers can express clinical symptoms called as lyonization due to random inactivation of either of X chromosomes [7]. Y – linked inheritance is in Y chromosome in males and transmission only between them like in non-obstructive spermatogenic failure [1]. Mitochondrial inheritance is possible in females only with all offsprings at equal risk [7].

Carrier states in inheritance can be understood as individuals with one mutated allele in the place of two, with no phenotypic expression of concerned traits, who carry the risk through generations without awareness. Identifying such hidden secrets can help us foresee and be prepared for unplanned expressions [8]. Carrier screening is a specialised program to detect carriers for inherited recessive genetic disorders [2-4,9-11] that focuses on particular age groups with a family history. It is available for premarital or pre-relationship, preconception and prenatal screening [4]. It can be for the couple or individuals who are considered to be at high risk [3], which happens when there is enough awareness about the prevailing condition in the family, else identified in preconception time, which gives more reliable data about risks and chances. It was once referred as single-disease [2], ancestry-based screening [2,9] and now widely accepted as expanded carrier screening (ECS) or pan ethnic or universal screening [2,3,9]. The traditional screening explained by Wick and Rose was typically for single disease on particular ethnic group that were considered to impact normal living [4], which lacked focus on other prevailing genetic disorders, and this emphasized the improvisation to ECS, which has multiple addressing points for various population and disorders [10,12]. It was in 1970s when Tay-Sachs's disease was first taken for carrier screening in Ashkenazi Jewish ethnic group [3,9,12].

Necessity

ECS is necessary to throw light on common and uncommon genetic disorders that run through generations, indicating high risk for acquiring the recessive condition without prior precaution. It gives possible options for alternative reproductive interventions [4], spouse or partner selection, a part of newborn screening not as a replacement [13], fall in birth rate of affected offsprings and gives equal importance to all ethnic groups. The main source of information in the genetic front is the frequency of sequence variants, which determine the effects of carrier status [2]. On the public health perspective, there is better planning of treatment strategies for the improvisation of quality of life. On gaining good reach there is observable data accumulated for rare inherited diseases. It has contributed to reduced morbidity and mortality rates [3]. In the economical perspective, this universal screening has been considered cost effective for resources invested and turnover of reliable information [2,3,9,14].

Evolution of Carrier Screening

Detection of single gene disorders was first implemented in 1963 as newborn screening (NBS) for phenylketonuria, a metabolic genetic disorder caused by mutation in phenylalanine hydroxylase (PAH) gene. [15] NBS is mandatory, non-ethnic based procedure followed to identify expressing clinical conditions and not asymptomatic carriers. First carrier screening began with Tay-Sachs disease in Ashkenazi Jewish ethnic group in 1970s. Around 1990s to 2000s the same was recommended for Cystic Fibrosis (CF) in Northern European Caucasian and Ashkenazi Jewish populations. A breakthrough ethnic barrier occurred in 2001 when American College of Medical Genetics and Genomics (ACMG) [16] and American College of Obstetricians and Gynaecologists (ACOG) established initially the guidelines for CF screening for Northern European and Ashkenazi Jewish descents, which was later improvised in 2017 to recommend CF screening to high risk categorised people (pregnant women, strong familial predisposition) and no ethnic considerations [14]. It was further refined for other conditions like Spinal Muscular Atrophy (SMA), Hemoglobinopathies, Fragile X Syndrome for the Eastern and Central European Jewish descents. However, in 2009, it took the shape of pan-ethnic screening for many genetic disorders despite of commonness and ethnic considerations [3,12]. ACMG in 2013 defined certain criteria for carrier screening which helped in identifying at risk patients who can be directed for prenatal

diagnosis and prior consent and counselling for adult-onset disorders. It also emphasizes in understanding the role of causative gene and mutation in population level screening and establishing a direct association between mutation and severity of the disorder. Quality control and proficiency tests maintains the integrity of the process [16].

Spinal Muscular Atrophy (SMA)

It is an autosomal recessive disorder caused by degeneration of motor neurons in spinal cord, leading to weakness, hypotonia and paralysis. The incidence and carrier frequencies were found to be 1 in 10,000 [17,18] and 1 in 40 respectively [19]. Its prevalence was estimated to be 1 – 2 in 100,000. Caucasian and Asian population are found to have higher frequency of heterozygous carriers [18]. Carrier status of this disorder is indicated by one copy of SMN1 gene that is involved in pathogenesis. It is clinically classified as Type – I, II, III and IV. Type I or Werdnig-Hoffmann disease can be characterised as severe form in 6 months of age by hypotonia, unable to control head movement, paradoxical breathing, bulbar denervation, aspiration pneumonia finally leading to death within 2 years of onset. Type II can be distinguished by intermediate level of impact in 7 to 18 months of age, unaided sitting, kyphoscoliosis, deep tendon reflexes, fine tremors, weak swallowing, poor bulbar and intercostal muscles leading to respiratory failure and death. Type III or Kugelberg-Welander disease can be identified as heterogeneous with ability to walk without assistance but reduced significantly before or after 3 years of age, minor muscle weakness and scoliosis [20-22]. Type IV can be found in 2nd or 3rd decade of life with mild motor impairment and walking ability in later years [20,21]. The SMA gene was mapped on chromosome 5q11.2 - q13.3 in 1990 [21].

Five years down the line, survival motor neuron (SMN) gene was found to be responsible. The SMN exist as the telomeric SMN 1 gene (SMA – determining gene) and the centromeric SMN 2 gene. They differ by a few nucleotides which causes alternative splicing of exon 7 but no alteration in amino acid sequence [20,21] SMA is supposedly diagnosed by homozygous disruption of SMN1, leaving back a copy of SMN2, which when undergoes alternative splicing produces a truncated mRNA with exon 5 and/or 7 being lost. Further, a nucleotide transition produces a non-functional protein that is degraded. This when observed in diagnosis confirms the genetic condition. [20,21]. Some of the clinical features include floppy baby, proximal weakness, swallowing and breathing difficulty in extreme cases. Nocturnal hypoventilation is also seen. Assays that help assess type of SMA include creatine kinase dose, electromyography (EMG), nerve conduction study, multiplex ligation dependent probe amplification (MLPA), quantitative PCR (qPCR) and semiquantitative assays [21]. Genetic diagnosis is initiated for homozygous deletion of SMN1 particularly exon [7], which is observed in 95% of SMA cases [21]. Single deletion, frameshift, nonsense and missense mutation of SMN1 indicate other types of SMA. SMN1 dosage analysis is conducted for identifying 95% of carrier status of individuals who may have deletion or mutation in one SMN1 copy. SMN2 copy number can be used to determine severity of the disorder however, precise prediction when used stand-alone is not reliable [21,23].

Carrier status determination apart from SMN1 dosage testing is based on remaining 5% categorised for deletion followed by its duplication onto the other SMN1 or mutation sequencing of the remaining undeleted copy [23]. Single copy of SMN1 is more indicative of type I with very poor prognosis [21]. Single strand conformation polymorphism is widely used for understanding heterozygous deletion as in cases of carriers and point mutation in undeleted allele [24,25]. Genetic counselling is a challenging profession where the professionals are trained and evaluated for their knowledge in the field of genetics and counselling skills [26]. It is offered to people categorised for risk of having a child with SMA like parents or siblings of SMA affected infant, presymptomatic individuals [23], which is assessed by SMA screening on voluntary basis, with proper informed consent and confidentiality maintained. Prenatal diagnosis is available by chorionic villus sampling in 11th to 13th week of gestation and 14th to 16th week of gestation by amniotic fluid sampling [21]. Preimplantation Genetic Testing (PGT) can be facilitated for *In Vitro* Fertilization (IVF) to identify couples at risk for pregnancy [27]. Follow up coordination plays a crucial role in management of SMA. Complications in pulmonary function makes the situation difficult to tackle. Movement to muscles like walking is necessary. Surgical intervention benefits younger age group in prevent curve progression.

Drugs are being developed for cure of SMA, which have molecular level targets. Salbutamol, a β2-adrenergic agonist is proved to increase SMN levels [28]. Riluzole's neuroprotective and neurotrophic activities is proved to promote neuron survival and expression of brain-derived neurotrophic factor [29]. Spinzara is an approved modified anti-sense oligonucleotide acting by including exon 7 for production of full-length SMN protein [30]. Adeno-associated virus serotype 9 (scAAV9) is employed for SMN1 gene replacement therapy. (21, 30) AAV9-mediated IGHMBP2 gene therapy for spinal muscular atrophy with respiratory distress type 1 (SMARD1) is under clinical trials, whose wild type has shown to increase IGHMBP2 protein levels, protect motor neurons and axons, resolve defects in neuromuscular junctions, increase myofibre calibre and causes extended life period [31].

Duchenne Muscular Dystrophy (DMD)

This X-linked recessive disorder [32,33] is reflected by weakness and loss of muscle mass at a very early stage of life [34] with limited

life expectancy up to late teens [33]. The incidence rate is about 1 in 5000 boys [35,36] and global prevalence in general population was estimated to be 2.8 cases per 1,00,000 [37]. Mortality rates of non-hispanic whites was found to be statistically high on comparison with non-hispanic blacks and hispanics. [33] Mutation in DMD gene on X chromosome Xp21.2 [32,34,37] produces dysfunctional dystrophin protein [37,38], which is essential for cytoskeletal support of sarcolemma in skeletal muscle along with glycoprotein complex. Intragenic deletions hold higher responsibility followed by duplications and small insertions. The open reading frame of DMD gene when disrupted causes DMD with nonsense protein production [32,36]. Hotspots for deletion in the largest gene of the human genome include exons 45 to 55 for deletions (36) and exons 2 to 10 duplications [39]. Proportion of affected males is higher due to recessive inheritance; however, there are chances for female asymptomatic carriers who can be potential carriers in their family [32,36,37]. Almost fully absent (32, 36, 39) or higher deficiency of functional dystrophin protein [37] hampers muscle functions and they can be characterised by loss of regenerative potential of muscle mass, increase in serum creatine kinase (CK) [36,38], inflammatory response resulting in fibrosis and altered metabolism, deficiency of dystrophin associated proteins (DAP) that ultimately distorts muscle function.

Physical observation include abnormal gait [36], difficulty or inability to walk is a crucial milestone at 18 months hinting for diagnosis of DMD [38]. Since this can be indicative at a very young age around 3 to 5 years [36], where they are supposed to be on their feet always, it becomes a point of concern. Slow and stiff movement of muscles, scoliosis [36,38], pseudohypertrophy [36], lumbar lordosis and gowers maneuver [36,37] does not enable performing normal activities. Untreated can be wheelchair bound by 11 to 12 years of age [33,36]. Motor skills impairment or delay can also be seen in a proportion [36,37]. Cardiac concerns [34] like dilated cardiomyopathy [38], arrhythmias can be seen but mostly asymptomatic [37]. Respiratory insufficiency leads to fatal end of life [34,37,38]. Biochemical aspects include elevated serum CK levels around 5,000 to 15,000 units/L and hepatic transaminases [36]. However, these symptoms in a milder version can be seen in Becker Muscular Dystrophy (BMD). Hence, a sequencing analysis can clearly reveal the exact morbidity [32]. Diagnosis relies on muscle biopsy testing [38,40] by immunostaining and western blot for detecting absence of dystrophin [32], elevated enzyme levels [38] and cardiac examinations by electrocardiogram (ECG), echocardiography and chest X-ray are performed to check for development of cardiac symptoms [34]. Genetic testing [38] by MLPA which detects deletion of 25 exons [34], comparative genomic hybridization (CGH) [41], high resolution chromosome microarray, further to which direct sequence analysis can be availed for analysis of presence of small deletions, insertions and point mutations [42] apart from deletion and duplication [36].

Carrier testing is recommended for women who are closely associated with men genetically confirmed to have DMD. This can be well appreciated in a family tree. Female relatives of those suspected carrier women of a family are considered for carrier testing. However, asymptomatic nature poses a challenge in timely identification [40]. Creatine kinase test is most reliable for this context [43]. It can also be tested by Restriction Fragment Length Polymorphism (RFLP) [44] and Polymerase Chain Reaction (PCR) of short tandem repeat (STR) loci [45]. qPCR with STR markers and for dystrophin gene was also performed in Eastern Indian population for carrier status counselling also proving statistically significant difference in frequency in different parts of population [46]. As a developed diagnostic technique, MLPA holds great value that allows reading of 79 exons of the dystrophin gene than Quantitative Multiplex Fluorescence PCR (qmfPCR) where 51 exons are examined and STR-(CA) segregation analysis for 11 markers of the gene. Carrier frequency is observed to lower than theoretical values specially for deletion mutations. MLPA gives a reliable assessment before proceeding towards any invasive procedure and is termed to be first choice in carrier screening even in female relatives who are in families of affected males to confirm their status [42]. Prenatal diagnosis [36] by chorionic villus sampling or amniocentesis can be offered for females who have tested positive for carrier status and encourage family members to take up the testing to be well informed prior to family planning.

With all the results correlated, genetic counselling essentially prepares the susceptible individuals and parents or couples likely to plan, as it gives them the opportunity to receive prior information about their next step or to take the final call [36]. Linkage studies can also aid in locating the maternal X chromosome in the fetus [32]. DMD has no definite cure but symptom management is possible. Corticosteroid therapy with prednisolone, prednisone and deflazacort can be adopted to improve muscle strength with an eye on the side effects of hormone-induced actions [32,36]. AAV mediated transfer of miniature dystrophin genes for gene therapy [47] is an upcoming development [48]. Human trials are yet to be done for dystrophin producing mesenchymal-cell transplantation [32]. Aminoglycoside inhibitors used to interrupt encountering premature stop codons [49]. Ataluren is employed to target non-sense mutations and a possible drug therapy for DMD [37,50]. Eteplirsen is an anti-sense therapy used for skipping exon 51 in defective gene to produce a shortened yet functional dystrophin protein [36,37,51] which received FDA approval in 2016 [52].

Discussion

Genetic diagnosis when offered to a larger group and a wider spectrum of genetic disorders assists in taking well-informed decisions in all facets of suspicion. There is no ambiguity with presence or absence or carrying of disease, which can break barriers of discrimination. It covers major susceptible disease carrying aspects cost effectively with minimal risks involved. Some of the challenges for ECS include lack of interest in general public, not being considered as priority but as choice and social pressure on individuals or couples especially in reproductive decisions. This necessitates appropriate genetic counselling at the right time from a valid perspective and fine-tuning to get a deeper understanding of technical background. [9] Awareness about carrier status in genetic disorders begins from understanding own family history and current scenario in their lives. Focusing attention on high-risk classified individuals with strong familial background and immediate relations who are affected gives a major cue to diagnosis. With increasing knowledge and application of principles in viable technology, diagnosis has hastened multitude with maximum sensitivity and specificity. Availability of resources, reliability on testing and reproducibility of results are exceptionally crucial for validation of findings.

Conclusion

Expanded carrier screening is an upcoming initiative that involves identifying prospective symptomatic or asymptomatic carriers of genetic disorders which when left unnoticed poses great challenges in the later part of their live(s). The shape taken by ECS in today's time will make a huge turnover in the upcoming times, provided there is support from both common public and healthcare experts. Role of a geneticist and a genetic counsellor takes a huge contribution to appropriate and timely diagnosis and planning their next step of action. The future prospects would be towards normalizing such testing and spreading awareness about keenly observing any inherited conditions in their family or acquaintances and report to concerned professionals to seek their observation and interpretation.

Conflict of Interest

Authors declare that they have no conflict of interest.

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