Genetics and Genetic Counselling Relevant to Mitral Valve Prolapse

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Introduction

Mitral valve prolapse (MVP) is the most prevalent valvular abnormality worldwide, with atrial displacement of either the posterior, anterior, or both leaflets, and is usually benign without any long-term sequelae [1]. In some cases, it results in sufficient incompetence manifesting with symptoms, or the regurgitation is severe to warrant intervention because of secondary structural abnormalities, and in some cases, there is an association with ventricular arrhythmias and sudden cardiac death (SCD) [2, 3]. Multiple studies show a familial component in approximately one-third of cases prompting research into genetic heritability [4, 5]. The observed family history can be higher in MVP associated with other syndromic (usually monogenic) conditions, such as aortopathies, connective tissue diseases, and dilated cardiomyopathy. Herein we describe the genetics of MVP and aspects of counselling for probands and family members [4–6].

Genetics

Broadly speaking the clinically relevant genetics of MVP can be considered in the context of one of the following 4: (1) Syndromic conditions without connective tissue disease; (2) Syndromic conditions with connective tissue diseases (CTD);

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(3) MVP and arrhythmia in genes associated with non-ischaemic cardiomyopathies or ion channel diseases; and (4) Multi-factorially inherited with certain single nucleotide polymorphisms (SNPs) [7]. Each of these associations can manifest with a range of phenotypes, including multi-system involvement where MVP is one component, or with predominantly cardiovascular (CV) manifestations, or as a result of cascade clinical family screening. The patient can thus take very different trajectories and the patient journey can mean contact with cardiologists and cardiac surgeons may be late when the clinical and genetic evaluation has already taken place, or, may be early in the disease where CV manifestations are the only features, and this should prompt an evaluation to ensure there are no syndromic associations and no features of CTD. Clinical guidelines acknowledge the high familial pattern of MVP, which may be genetic for e.g. trisomies 18 (Edwards syndrome), 13 (Patau syndrome), and 15, or Mendelian CTD which are usually autosomal dominant. However, in the absence of these syndromes and CTDs, MVP can still show a familial pattern, and guidelines recommend cascade clinical evaluation of family members [8, 9].

The current known genes and single nucleotide polymorphisms are summarized in Fig. 11.1 [7].

Syndromes associated with connective tissue disease include Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, Williams-Beuren syndrome, Pseudoxanthoma elasticum, Larsen-like syndrome, and Borrone dermato-cardioskeletal syndrome. These are discussed in Chap. 10 on genetics and reviewed elsewhere [7].

Familial MVP

In addition to the high observed prevalence of MVP in syndromic genetic conditions, isolated familial forms of MVP have long been recognised. The first published report suggested an X-linked recessive inheritance with only male phenotypic expression in a 3-generational family with polyvalvular disease [10]. Subsequent familial studies have suggested 60% heritability, with notable age- and sex-dependent phenotypic expression and reduced penetrance. These studies support autosomal dominant inheritance, with linkage studies identifying three loci: MMVP1, MMVP2, and MMVP3.

MMVP1 was identified through linkage study mapping to chromosome 16p12.1–p11.2, although the gene and protein remain elusive [11].

MMVP2 in a 5-generation family mapped to locus 11p15.4, following which a missense variant (p.R2513H) in the *DCHS1* gene was discovered in the same family. This variant was found in an unrelated family who also expressed MVP. The gene product is a signal peptide belonging to the cadherin family with loss of function impairing cell polarity during valve development in mice [12].

MMVP3 was identified in a 3-generation family with MVP and linkage to chromosome 13q31.3–q32.1 [8]. The gene and protein were unknown until a recent publication describing a deleterious missense mutation in a cilia gene, *DZLP1* [13].

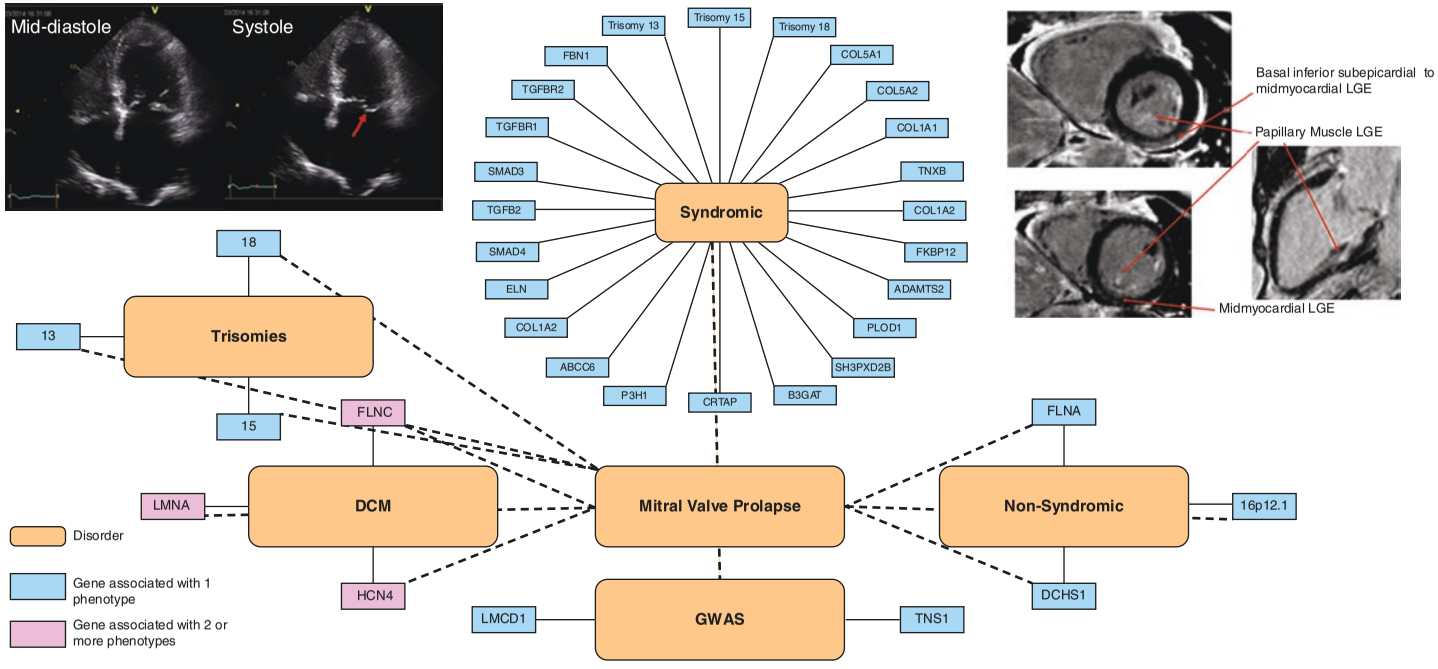

Fig. 11.1 Schematic of the complexities of MVP genetics [7]. The implicated genes have been organized into those associated with syndromic conditions and a higher frequency of MVP than that seen in the general population, those associated with familial non-syndromic forms, and genome-wide association studies. The red arrow on the apical four-chamber two-dimensional echo tracing in late systole shows the posterior mitral valve leaflet prolapsing into the left atrium. The red arrows on the T1 late gadolinium enhancement images point to areas of hyperenhancement indicating fibrosis in cases of MVP with ventricular arrhythmias

The authors functionally validated their findings in a mouse model which developed myxomatous MVP as an adult, and then validated findings in a large human cohort of MVP with a GWAS study, identifying cilia gene variants.

In a family with X-linked inheritance, there was a P637Q mutation in the *FLNA* gene [14]. More recently, families with muscular dystrophy and MVP have been described. The type of MV prolapse is unusual and may be unique to *FLNA*-related MVP: myxomatous leaflets with paradoxical restriction of leaflet motion in diastole.

Cardiomyopathies and Ion Channelopathies (FLNC, LMNA, HCN4, *SCN5A*)

Genetics of non-ischaemic dilated cardiomyopathy (DCM) is complicated with wide phenotypic expression, with a certain subset having a higher propensity for arrhythmia [15]. These arrhythmia prone DCMs have been recognized as left-dominant arrhythmogenic cardiomyopathies, as well as being described as arrhythmogenic DCM. Recently, left ventricular non-compaction (LVNC) and sinus node dysfunction with MVP have been described in persons with *HCN4* variants [16]. The *FLNC* gene encodes for gamma filamin which crosslinks actin filaments—defects in FLNC cause skeletal myopathy and truncating variants have recently been recognized as causing arrhythmias and DCM. The frequency of MVP and the association with SCD, MVP, and cardiomyopathy-related genes are unknown and an active area of research. Recently *SCN5A* and *LMNA* pathogenic variants were reported in unrelated families with arrhythmic MVP [17, 18]. Recognized risk factors for sudden cardiac death in MVP include the following: female sex, family history of sudden death, documented ventricular tachycardia, ventricular premature complexes, syncope, T wave inversion in the inferior leads, fibrosis (at post-mortem or on cardiac MRI with late gadolinium enhancement of the papillary muscles, basal LV segments), Pickelhaube sign (on lateral wall tissue Doppler), high strain, mitral annular disjunction, curling and paradoxical septal annular expansion. Thus, it is foreseeable that MVP with arrhythmia and structural abnormalities, a family history of sudden cardiac death, may become an indication for clinical genetic testing.

Sporadic and Common MVP

The vast majority of MVP is multi-factorially inherited, and do not meet clinical indications for genetic testing. Genome-wide association studies have been performed, given the large familial component observed, and have identified 7 significant loci [19, 20]. Of these, two candidate genes were discussed: *TNS1* on Chr2 and *LMCD1* on Chr3 [21]. Both genes have plausibility with a role in valvular development, although further genomic and functional studies are essential to discern their implication in the genetic risk of MVP, and to identify causal genes in the remaining associated loci. More powerful association studies are likely to

identify additional risk loci and serve to build MVP polygenic risk score with potential clinical use.

Genetic Counselling

Counselling is a crucial component prior to any form of genetic testing to ensure relevant aspects are discussed *a priori* to requesting tests, rather than addressing potential issues that can arise after the test results are returned. The increased availability of multiple private companies offering clinical tests and direct-to-consumer tests have made availability better than it has ever been. This coupled with decreasing costs and a patient-driven desire to know have increased demand for genetic counselling. This is usually provided by genetic counsellors, who are specialized healthcare professionals with dual training in medical genetics and counselling, bridging the gap of genetic testing and interpretation for probands, family members, and clinicians (Table 11.1). However, the increased demand on genetic counsellor services means these are not always available and counselling can be delivered by any competent member of an inherited cardiovascular clinic. In addition to providing expertise in cardiac genetics and psychosocial aspects of counselling, genetic counsellors often also re-evaluate genetic test results at follow-up for variants which

Table 11.1 Summary of roles of genetic counselling services

Risk assessment	• Collect detailed medical and multi-generational family history • Assess the risk of inherited cardiovascular conditions in probands and family
Education	• Describe features, risk factors, and genetics of inherited cardiovascular conditions • Discuss screening, prevention, and management options relevant to the suspect conditions(s)
Genetic testing	• Identify and coordinate appropriate genetic test options • Discuss the benefits and limitations of genetic tests • Address concerns over out-of-pocket costs and insurance (private or state) coverage • Address concerns over "luxury" insurance and potential discrimination
Result interpretation	• Review literature, curation panel data, and laboratory information to provide accurate, contemporary information • Collaborate with providers to apply genetic information to probands and family members
Result disclosure	• Explain genetic test results and implications for patient and family • Provide written documentation for probands, families, and providers
Patient-centered counselling	• Address patient and family concerns regarding the condition • Discuss implications for family planning and reproductive options when relevant • Facilitate family communication about diagnosis and testing options • Identify resources for additional support and information

Modified from Arscott et al. [22]

Table 11.2 Benefits of including a genetic counsellor in the inherited cardiovascular conditions team

Domain	Selected examples
Clinical efficiency	Time saving for the busy cardiologist (before, during, and after the clinic): • Request and review appropriate family records (autopsy reports, genetic test results, screening evaluations, etc.) • Facilitate efficient genetic testing (appropriate sample, paperwork, billing process) • Navigate post-mortem genetic testing cases (sample retention, communication with coroners, DNA banking, etc.)
Keeping current	Ongoing knowledge of changes in: • Genetic testing options • Dynamic interpretation of genetic variant • Availability of appropriate research studies • Updated practice guidelines for inherited arrhythmias
Specific expertise	Contributes unique knowledge to care team: • Gene/variant level knowledge • Familiarity with scenarios affecting test selection • Communicating detailed genetic test results • Awareness of family planning options
Interpersonal communication	Enhanced connection with patient family: • Communicate with patients and other members of the multidisciplinary team • Establish rapport with patients and their families • Demonstrate an understanding of family and cultural values with regard to genetic testing • Instill confidence in care team and increase adherence to recommendations • Empower families to play active role in their care
Patient support	Serve as patient advocate: • Promote informed decision making • Assessment of competency to consent, supporting vulnerable people (e.g. children and those with mental health issues) • Provide psychosocial counselling • Identify and refer to local and national support resources • Facilitate communication for appropriate family care (written letters, referrals to other specialized centres, etc.)
Liability	Reduce liability for the health care team: • Provide and document informed consent for genetic testing; document genetic testing results and recommendations • Integrate family history and genetic testing information into patient care • Discuss concerns regarding genetic discrimination, particularly with predictive genetic testing

Modified from Spoonamore and Ware [23]

may have been re-classified, as well as providing input to variant curation panels. Clinical practice guidelines, consensus, and scientific statements incorporate genetic counselling into their recommendations to provide these additional services (Table 11.2).

Definition of Genetic Counselling

The National Society of Genetic Counsellors defines genetic counselling as the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease [24]. The process integrates the following:

- Collection of detailed family history; its interpretation to assess the risk of disease occurrence or recurrence.
- Education of the probands and family regarding inheritance, testing, management, minimizing risk, resource availability, and research.
- Counselling to promote informed choice and where applicable interventions.

Genetic counselling can occur at differing time points including pre-conception and older age. Most consultations will be outpatient based involving cardiologists, paediatrics, and sometimes the obstetrician (for pre-conception or prenatal).

Generation of Referrals for Genetic Counselling

Clinical genetic testing for isolated MVP is not recommended. However, there are a number of scenarios where genetic testing may be indicated:

- Patient with MVP and suspected syndromic conditions.
- As part of evaluation for suspected aortopathies and connective tissue disorders in both probands and family members.
- Probands with MVP and other structural abnormalities such as a cardiomyopathy.
- Probands with MVP who have survived a cardiac arrest.
- Pathology services evaluating sudden unexpected death cases with MVP.
- Family members of patients with sudden death where aortopathy, connective tissue disease, inherited arrhythmia or cardiomyopathy suspected, which may have MVP.

Clinical Evaluation of Family Members

Clinical cascade evaluation can be done with focused clinical examination auscultating for mid-systolic click and pan-systolic murmur. Echocardiography, once expensive and difficult to obtain is now widely available. A limited study with two views parasternal long axis and apical 4 chamber can be sufficient to assess for MVP in an adult adequately hydrated patient. Handheld ultra-sound can make this very easy to do rapidly, without sending patients to cardiac echocardiography laboratory, and can be done in outpatient settings. The main reasons guidelines do not recommend evaluation of family member's is the cost-effectiveness, lack of data supporting use. Guidelines do recommend family members of patients with bicuspid aortic valve are evaluated but do not mention MVP [25, 26]. However, it is our usual practice to take a minimum three-generational family history, explain to the patient the familial nature of both MVP and sudden cardiac death, and recommend adult first-degree family members undergo a single clinical evaluation for MVP. Guidelines may change to reflect this in the future as increasing evidence is published.

What Should Be Included in Counselling

Genetic counselling usually involves three phases: pre-test counselling, testing, and interpretation of results, which are best delivered in a centre with experience in diagnosis, management, and prognostication of inherited cardiovascular conditions. The discussion should include a comprehensive medical and family history (including multi-generational pedigree, obtaining medical records, clinical test results, post-mortem reports, and death certificates) advantages and disadvantages of proceeding with genetic testing, availability of types of genetic tests, risks and benefits of each type of test, incidental findings and return of results, and options for research studies where no pathogenic variant is found (Table 11.1). Once this has taken place and appropriate time provided to process information, the appropriate test can be selected and biospecimens provided (usually blood sample but cheek swabs are reliable alternative).

Once test results are back, a follow-up visit should be arranged, and return of results should take place, as agreed prior to sending biospecimens. For example, if whole exome sequencing is used, and agreed to not disclose incidental findings, then this should not be brought up. The return of results is usually limited to pathogenic or likely pathogenic results. However, a great proportion of tests are returned under the variant of uncertain or unknown significance (VUS) and these are not usually disclosed. Disclosure can require that this be placed on the medical records. Reclassification of variants should be discussed which may include research-based functional studies as well as testing selected family members to determine co-segregation of the variant with phenotype. This is a powerful tool to aid with variant reclassification of VUS to benign or pathogenic. Thus, the role of the genetic counsellors and genetic testing in a multidisciplinary inherited cardiovascular conditions clinic occurs at different stages on the patient's journey (Fig. 11.2).

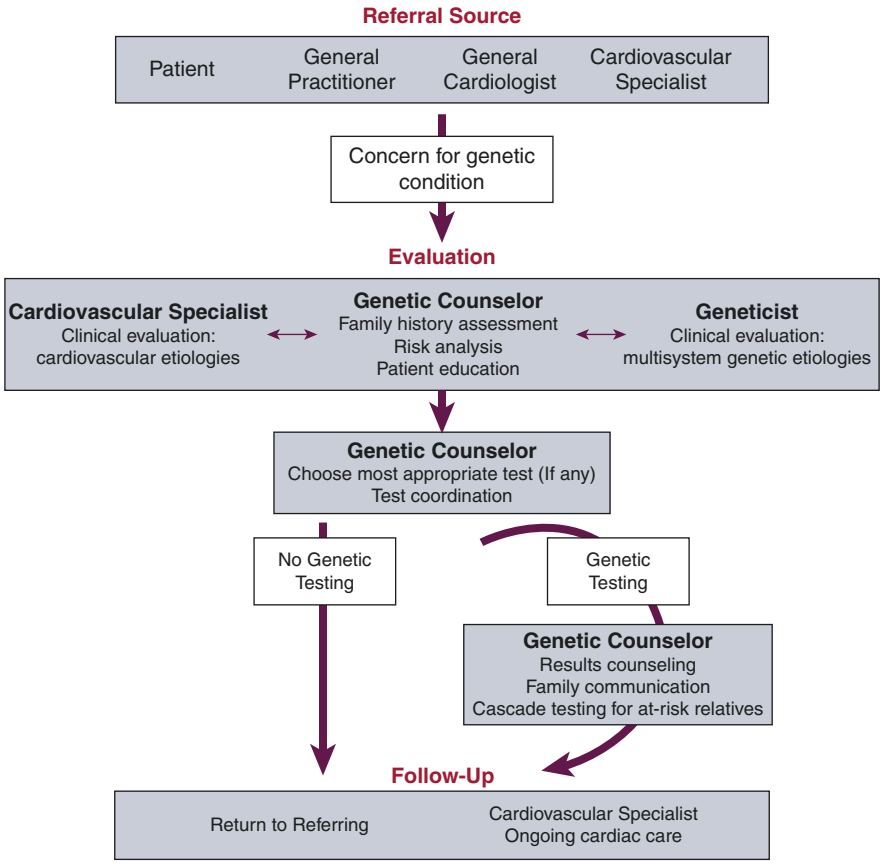

Fig. 11.2 Main roles of genetic counsellors (modified from Arscott et al. [22])

Types of Genetic Tests

The types of genetic tests available is dependent on appropriate local laboratory services, as well as services offered by private companies. This ranges from classic Sanger sequencing (one nucleotide at a time) to next generation (massively parallel) sequencing which can be a targeted panel, whole exome (WES), or whole genome sequencing (WGS). Dependent on the country, not all next generation WES or WGS are approved for clinical testing, and validation with a clinical test is sometimes required. In the USA, a clinical test has to be Clinical Laboratory Improvement Amendments (CLIA)-approved, and in the UK has to be in a Clinical Pathology Accreditation (CPA)-approved laboratory. The over-arching principle in selecting a genetic test is based on pre-test probability. Whilst, requesting an increasing number of candidate genes may intuitively increase the likelihood of identifying a causative pathogenic variant, it also increases the likelihood of genetic noise and VUS. Thus,

the selection of the type of genetic test has to be carefully balanced understanding the breadth and depth of commercial tests available.

There is also a large discrepancy with test results depending on the vendor, the technique, the sequencing platform, and variant classification. In 2015, the American Council of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) proposed classification of variants into 5 classes: Pathogenic (Class 5) >95%, Likely Pathogenic (Class 4) >90%, Variant of Uncertain significance (Class 3) 10–90%, Likely Benign (Class 2) <10% and Benign (Class 1) <5% [27]. The laboratory will provide a classification but this is often with a disclaimer that requires additional evaluation and should be interpreted in the clinical context i.e. requires accurate phenotyping of the probands family members. Thus, clinicians will reclassify the variant based on additional data, and many genetic counsellors contribute actively to variant classification in multidisciplinary clinics.

Most hospitals and private companies now use next generation technologies and focus on a selected panel of tests. For MVP, this will be driven by the associated syndromic, aortopathy, connective tissue disease and in rare cases with a personal and/or family history of sudden cardiac death. Best practice is to confirm any genetic sequence identified with next generation tests with Sanger sequencing. Laboratories also commonly offer tests for larger chromosomal deletions or duplications, which can be missed by typical polymerase chain reaction-based sequencing approaches.

If a candidate gene or panel test returns negative, then there are a number of options for further genetic testing. Again, this will be driven by the suspected clinical phenotype with regards to MVP. The first line is to do an extended panel which can usually be done with the same initial sample. If this returns negative, then approaches include WES and WGS. Whole exome sequencing includes all of the approximately 20,000 human genes and represents approximately 2% of the human genome. This can be combined with "parent-proband trios" to help narrow down the list of candidates to *de novo* mutations. The approach can also be used with one affected family member and an unaffected parent to perform a 'trio' to triangulate down to candidate variants seen in the affected individuals and absent in the unaffected individual. With MVP this can be used for cases where MVP and arrhythmia are frequent as recently identified in a family with MVP and a novel truncating variant in the *FLNC* gene which cosegregated with the disease [28].

When WES does not yield a candidate variant, WGS approaches can be used. Although WES implies all of the exome is sequenced, this is not the case, as enrichment steps target approximately 96–98% of the WES. Thus, WGS will cover the entire exonic regions and intronic regions that may be involved with exonic splicing. However, WGS has lower depth of coverage (this refers to the number of times a genomic region is read or sequenced). For WES the minimum standard, 30x, which refers to the number of times a nucleotide is read during sequencing to avoid sequencing errors. The coverage varies between laboratories and the platform used.

Utilizing WES or WGS can lead to large amounts of VUS being identified which are not clinically meaningful without functional validation, which becomes near impossible for a single case with hundreds of VUSs. Analysing the entire WES or WGS can also increase the likelihood of incidental findings, some of which are

actionable. The ACMG updated a policy on reporting of incidental findings in 2016, which includes 59 actionable genes, many of which are related to cardiomyopathies and Aortopathies [29]. These scenarios emphasize the importance of thorough pre-test evaluation, counselling, and informed consent, so that potential scenarios, outcomes, and impact on management to the individual and family have been thoroughly prepared for.

Conclusions

The vast majority of MVP cases are multi-factorially inherited and no indications for clinical genetic testing exist. Patients may undergo direct-to-consumer tests, which may identify some recognized SNPs associated with MVP. It is important to note that the yield is highly dependent on the type of GWAS testing chip used. Given MVP is associated with aortopathies and connective tissue diseases, this is the most likely way that patients with MVP will be referred for genetic testing. In some familial cases with an arrhythmia component and/or SCD history, these may have dual pathologies of MVP with a form of non-ischaemic cardiomyopathy and propensity for arrhythmia. These cases either as survivors of SCD events, or family members with a relative with MVP and SCD, may seek out genetic testing. The evaluation of these cases should be at specialist centres with expertise in deep phenotype. The selection of genetic tests available should then be carefully considered, with pre-test genetic counselling, explaining the complexities, potential results, implications for management to the probands and family members. Ideally the process should be delivered with the assistance of genetic counsellors; however, where this is unavailable, this can be provided by clinicians competent and experienced with inherited cardiovascular conditions.

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