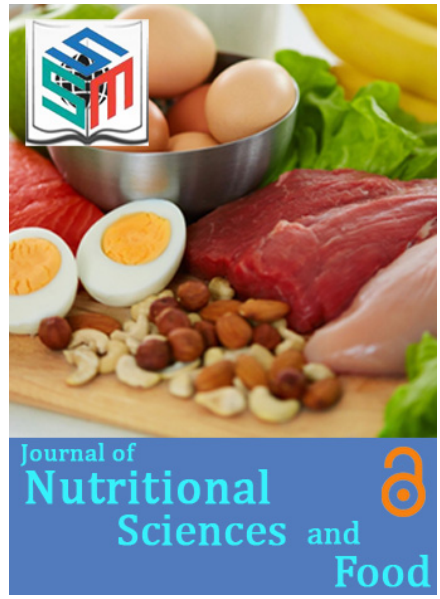
Short Review

Complications of Marriage of Celiac Individuals and Risk of Developing Celiac Disease in Their Progeny



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Abstract

Celiac Disease (CD) is a multifactorial disorder occurs due to the indigestion of immune-potent gluten peptides found in wheat and related grains in genetically predisposed individuals. More than 1% of the world population is affected with CD. A life-long strict Gluten-Free Diet (GFD) is the only acceptable treatment for CD till date. Susceptibility to CD is inherited in the family members. Class-II Human Leukocyte Antigen (HLA) DQ alleles are strongly associated with CD susceptibility. High prevalence (up to 20 %) of CD in First-Degree Family members (FDRs) of CD patients has been reported. Due to this, CD affected individuals face a challenges for their marriage. There is a misconception in society that marrying a CD affected person will inherit the disease in their child. However, this is not always true, and it can be answered scientifically to some extent by genetic testing (HLA-DQ characterization).

So far no article has discussed this issue in detail. In this article, we raised this issue and provided scientific justifications. Our justifications are based on the previous documented information that investigated the family risk of CD. Our literature-based information concluded that except for some certain situations, marriage between a healthy individual (HLA-DQ negative) with a celiac affected individual will not inherit CD to their progeny. Hence, a healthy individual may decide to marry to a CD patient. There are only some probabilities that a celiac patient's child would develop CD. However, there are certain preventive measures that CD parents should follow. Moreover, CD genetic test (HLA-DQ characterization) is very important to determine the risk of developing CD in the child.

Keyword: Celiac Disease; Genetic; Gluten Free Diet; HLA-DQ Allele; Marriage

Introduction

Celiac Disease (CD) is an immune-mediated inflammation of the small intestine. It occurs due to the ingestion of a particular protein 'gluten' found in wheat, barley, and rye in genetically predisposed individuals [1]. CD can develop at any age and stage of life. More than 1% of the world population is affected by CD [1]. Recent studies showed an increasing trend in the prevalence of CD [1,2]. A lifelong strict Gluten-Free Diet (GFD) is the only accepted treatment to date for CD [3]. As gluten is used in diverse food industries it is challenging to follow a gluten-free diet. CD is an interplay between environmental (gluten), and genetic factors Human Leukocyte Antigen (HLA). Probably some other factors also involved (microbiota). However, the class II HLA-DQ molecule located on chromosome 6p21 is strongly associated with CD development. About 95% CD patients display HLA (Human Leukocyte Antigen)-DQ2 (HLA DQA1*05 and DQB1*02) and the rest 5% displays HLA-DQ8 alleles (HLA-DQA1*03 and HLA-DQB1*03:02) [4]. Due to close genetic repertoire, a certain group of patients remain at risk of developing a CD, like patients with specific chromosomal disorders, autoimmune disorders (type 1 diabetes), and the family members (first and second-degree relatives) of celiac patients [5,6]. Therefore, several landmark studies have recommended CD screening for all at-risk individuals [4-7]. Diagnosis of CD is made on the basis of the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines that consist of serology (anti transglutaminase ab test, anti-gliadin antibody test, and anti endomysial antibody test) and histology test (duodenal biopsy) [8]. HLA-DQ characterization is considered as an additional test for the screening of CD however due to its high negative predictive value (about 100%) HLA-DQ characterization test is recognized as a test of exclusion and recommended for the screening of at-risk population

[9]. If a person does not display HLA-DQ genes there will not be any chance developing CD ever in life. HLA-testing sets free to the suspected individuals for future surveillance of CD i.e., repetitive serology and biopsy tests. Hence genetic test (HLA-DQ typing) is very important [4].

CD has a strong social impact on the quality-of-life of CD individuals [10]. Marriage is one of the social responsibilities that become a challenge for the CD individuals as there is a high concordance rate of CD in the FDRs [6,9,11]. Marriage is not just a legal commitment between two individuals, but it is more of a family festival and is done with the mutual agreement not only between two people but also between their families. Especially in most Asian countries where different stages to be followed to fix a marriage and diverse rituals have to be fulfilled during these stages. Family members organize the marriage formalities and their agreement and blessings are needed. However, there are several myths spread out about the marriage of CD individuals. People have a perception that marrying a CD affected individual would lead to developing CD to the healthy partner. There are numerous illusions and due to this healthy people (non-celiacs) fear to marry with a celiac affected individual. As CD runs in the family, another perception is the child of the celiac individual would have CD since birth. However, all these perceptions do not have a strong scientific basis. So far multiple articles estimated the celiac and HLA-DQ prevalence in the celiac family members that however provide an indirect answer to such unanswered questions. To the best of our knowledge, till date there is no article available that has discussed celiac and marriage issues [5,6,9,11-13]. In this short review article, we have raised this issue and provided scientific justifications in a lucid form about celiac and marriage issues based on the knowledge of previously published articles.

Celiac Disease: A Small Introduction

CD is a heritable, inflammatory condition of the small intestine, that develop due to ingestion of immune-dominant dietary peptide (gliadin in wheat, hordein in barley, and secalin in rye) in the predisposed individuals Ingestion of these peptides causes an intense immune reaction and ultimately CD [1,9].

The principal toxic component of wheat gluten belongs to a family of closely related proline and glutamine-rich proteins called gliadins. *In-vitro* and *in-vivo* studies (rats and human) confirmed that CD is triggered by the presence of 33-mer peptides that develops due to the partial digestion of gliadins because the gliadin remains stable toward breakdown by all gastric, pancreatic, and intestinal brush border membrane endoproteases [14,15]. This peptide was identified as the primary initiator of the inflammatory response to gluten in CD patients. When a celiac individual ingests gliadin in any form, due to the lack of the proly-endopeptidase among gastric, pancreatic, and brush border enzyme relatively large gluten peptide are formed that is rich in proline and glutamine remain after initial digestion [12]. Tissue transglutaminase-2 (tTG) when interacts with this larger size partially digested gluten proteins it deamidates glutamine into glutamic acid that is recognized by the HLA-DQ2/-DQ8 molecules. Once bound to the HLA-DQ2/8 molecule, the gluten peptides HLA-DQ complex can activate CD4 T-helper (Th1) cells in the mucosa of the small intestine that recognizes this complex. Th1 cells then release IFN-γ that eventually causes the flattening of villi. Due to this, celiac affected individuals face several clinical manifestations related to CD, such as classical signs and symptoms of malabsorption (diarrhea, steatorrhea, weight loss & growth failure) or non-classical and symptomatic (with evident GI and/or extra-intestinal symptoms) or asymptomatic symptoms [14-16].

Treatment

Currently, the only effective treatment for CD is a strict lifelong GFD. GFD is a diet that results in clinical, serological, and histological improvement [3]. GFD is based on the complete elimination of gluten , related grains and their derivatives, i.e., complete elimination of wheat, rye, barley, oats, Kamut, or their hybridized varieties such as Khorasan wheat (Kamut®), spelt (sometimes called Farro), and triticale (a combination of wheat and rye) from the diet [17]. As, it is essential to avoid gluten-containing cereals, however naturally gluten-free foods like vegetables, milk, meat, and fish are allowed in GFD. As a substitute for gluten-containing grains such as rice, maize and potatoes, and pseudocereals such as buckwheat, quinoas are widely used [18]. It has been calculated that gluten-free products with <20 mg/kg (or parts per million = ppm) of gluten contamination are safe over a wide range of daily consumption. Codex Alimentarius regulation, also endorses that gluten-free food should contain < 20 ppm of gluten in total [15,19].

Celiac Disease Risk in the Family Members

Celiac disease is a multifactorial disorder it hence, it does not depend on specific mutations of a single gene, multiple or a combination of genes in response to the interaction with environmental factors that could be responsible for the development of CD [7]. The HLA region alone accounts for approximately 40% of the disease heritability meaning that other genes are involved in CD susceptibility [9]. Numerous studies confirmed that DQB1*02 homozygosity usually associated with increased risk and more aggressive forms of CD [4].

The risk of developing CD in relatives is based on the assumption (empiric risk data). However, high prevalence of CD and celiac associated predisposing genes (HLA-DQ alleles) have been estimated in the first degree relatives (FDRs) of CD patient (up to 10-20%) with a high concordance rate in monozygotic twins (up to 86%) [5]. That shows that the relatives especially the FDRs to CD patients are at high risk of developing CD.

In an interesting study, *Fasano* et al. showed 1: 22 ratio of prevalence of CD in FDRs while in second-degree relatives (SDRs) it was 1:30 [20]. In a recent study, *Sdepanian V.L.* et al. found 67% FDRs with at least one copy of HLA-DQB1*02 alleles in Brazilian population. They calculated the risk percentage in FDRs as 9.1% whereas the risk percentage of HLA-DQB1*02 homozygous in FDRs was 23.1% [11]. Means, out of 100 CD FDRs, 23 would develop CD. *Singla S.* et al. identified 96.7% positivity of HLA DQ2/8 in Indian celiac FDRs [6]. All such studies strongly recommend genetic testing (HLA-DQ characterization) for every celiac family member especially for celiac FDRs and SDRs.

Celiac Disease Risk in the Child of Celiac Parents

In the case of CD, the susceptibility to CD is inherited but the disease itself does not. Although CD runs in the families, it does not follow a Mendelian inheritance pattern [21]. Therefore, it is quite tough to determine if CD will occur in a particular individual. If one partner displays predisposing alleles (may or may not be a celiac patient) and the other does not (HLA-DQ negative individual), there will not be any possibility of developing CD to the healthy (HLA-DQ negative) partner as CD is not an infectious disease.

If this is the situation, marriage between such individuals will have the least risk probability to develop CD in their child however genetic testing is needed to determine the risk level. In both cases, If an individual shows HLA-DQ alleles, there will be 3-5% probability to develop CD in his/her progeny as in healthy individuals with HLA-DQ alleles only 3-5% individuals develop CD [4]. However, if one of such couples has confirmed CD the chances of developing CD in their child will be a little higher, genetic testing has to be done to reach any decision. Nonetheless, there is a 50% chance if a parent has CD the progeny will have susceptible genes [4,7].

Nevertheless, if status of genetic testing is known, the risk assessment will be easy. Numerous studies confirmed that DQB1*02 homozygosity is usually associated with increased risk and more aggressive forms of celiac disease [4,7,11,12]. So, if both the partners are affected with a CD with the double dose of DQB1*02 homozygosity, risk of developing CD in their progeny will be higher, and if the parents will have DQB1*03:02 the chances will be less. In case, only one of the partners presents the DQB1*03:02 allele the risk will be even reduced [4,12]. Table 1 shows the intensity of susceptibility due to the celiac associated alleles.

DQA1 allele	DQB1 allele	Susceptibility
DQA1*05	DQB1*02	Higher
DQA1*0201	DQB1*02	Lower
DQA1*03	DQB1*02	Lower
DQA1*05	DQB1*0301/0304	Lower
DQX_a	DQX_b	Extremely low

Table 1: HLA-DQ allele combination and susceptibility risk.

X_a: DQA1 alleles other than *05; X_b: DQB1 alleles other than **02 or *03:02

On the other hand *Megiorni* et al. assessed the risk gradient to develop CD based on HLA-DQ characterization in Italian pediatric population. The authors confirmed that DQ2 and DQ8-positive subjects remain at the highest risk value followed by DQ2, B1*02/*02, DQ8, B1*02, and B1*02/*02 positive individuals. However, individuals with a single dose of the B1*02 allele remain at a lower risk. A child, whose parents display DQ2 positivity, has 50% chance to inherit the susceptible allele however, having such a gene does not guarantee to develop CD [4].

However, at the time of pregnancy, some preventive measures have been described by Prof. Guandalini. According to him, a mother can take if she or the father is celiac and expecting a baby [22]. A pregnant woman must adhere to a strict GFD. Gluten exposure during pregnancy can activate the gluten-specific T-cell mediated immune reaction enough to cause malabsorption to nutrients to the women along with the child. However, genetic testing is recommended for the child as well (after >3 years of the age), and if it comes negative the chance of CD will be eliminated. If the baby detected with celiac susceptible alleles (HLA-DQ 2/8) the parents must watch for the symptoms. A serology test must be performed after a certain age (preferably after 3 years of age). A delayed celiac-specific symptoms have been observed in the babies if they breast fed for 6 months and before exposure of the first introduction of grain.

In a recent study of Swedish children, researchers showed that first gluten exposure during the breast-feeding phase reduces the risk of developing CD even breastfeed after gluten exposure protects the children [23]. The amount and the quality of wheat also a determining factor. A smaller amount of wheat was found a safer option in comparison to the large amount [17]. If a baby responds well to gluten exposure (not showing celiac related symptoms) the parents should choose to feed the baby a normal diet. However, parents must not choose to give GFD their own. A recent systematic review and meta-analysis documented a higher CD sero-prevalence in women with overall infertility, unexplained infertility, and recurrent spontaneous abortions.

For this reason, CD screening would be useful in women with reproductive problems and if the CD diagnosis is confirmed in those women, it would be important to assess if a strict GFD has a role in decreasing the risk factor of infertility or other reproductive problems [24].

Conclusion

Except for some certain situations, marriage between a healthy individual (HLA-DQ negative) with a celiac affected individual will not inherit CD to their progeny. However, marriage between CD affected individuals has a little higher risk that their child may develop CD in the later stage of life, but there are several preventive measures available to delay the symptoms. However, in all the cases, a genetic testing (HLA-DQ characterization) must be performed to all CD cases and their family member to assess the CD risk and to eliminate the doubt to develop celiac disease.

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Conflict of Interest

Authors declare no conflict of interest.

Author's Contribution

Yeliz Serin and Anil K Verma: wrote and drafted the manuscript.

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