Genetic impact of non-consanguineous marriages in Saudi Arabia

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Abstract

**Aim:** The aim of this study was to determine the prevalence of genetic disorders in the non-consanguineous population of Saudi Arabia.

**Methods:** We assessed all the exome sequencing requests associated with pathogenic or likely pathogenic variants at King Abdulaziz Medical City in Riyadh.

**Results:** In total, there were 151 non-consanguineous individuals with exome sequencing requests in the population genomic database of King Abdullah International Medical Research Center. In total, 27 had disease-causing variants, and the hit rate was 27/151 (18%). The 27 people had 28 different variants. There were 14/28 (50%) de novo variants and 14/28 (50%) inherited variants in the 28 variants. The hit rate of the variants causing autosomal recessive disorders was 12/28 (42.8%), autosomal dominant disorders 13/28 (46.4%), and X-linked disorders 3/28 (10.7%).

**Conclusion:** Non-consanguineous marriages have a lower risk of genetic disorders, and reducing consanguinity reduces the risk of genetic disorders by two to three times.

Introduction:

Physicians and geneticists face challenges in making accurate diagnoses during clinical evaluations, which affect both patients and clinicians. A detailed family history and pedigree are required, as is a detailed description of the observed phenotypes, which are frequently difficult to express in terms of the Human Phenotype Ontology (HPO). According to numerous scientific studies, ES is a highly effective and efficient diagnostic tool (Gao, 2019; Dillon et al., 2018; Shendure, 2011). In comparison to more established techniques such as karyotyping, CMA, and Sanger sequencing, ES has a diagnostic yield of 25–45%, with some studies reporting even higher yields (Alfares et al., 2017; Alfares et al., 2020; Han and Lee, 2020; Mu et al., 2019). The yield of ES in consanguineous marriages is 58%, in cases of suspected Mendelian diseases in a heterogeneous phenotypic population, demonstrating the power of the technique (Dillon et al., 2018). Additionally, the diagnostic yield of GS is higher than ES by only 3–5% (Alfares et al., 2020). As a result, ES is considered as a cost-effective technique and is frequently requested in the clinical setting (Alfares et al., 2017; Gao, 2019; Dillon et al., 2018).

Previous large exome sequencing studies in inbred populations with a high rate of consanguinity, demonstrated an increased rate of recessive conditions as the etiological cause of genetic diseases, compared to the dominant diseases (Gilissen et al., 2011). This observation is consistent with a study that compared the genetic diseases resulting from consanguineous and non-consanguineous marriages (Alfares, 2018). According to Monies et al. (2017) AR pathogenic and likely pathogenic variants accounted for the majority of the genetic mutations in Saudi Arabia. It occurred in 71% of the patients with ES requests, and the majority (97%) of these variations was homozygous. In another study with the Saudi population 454 ES cases had a higher diagnostic rate with a family history (49%) and higher in the consanguineous population (53%) (Alfares et al., 2017). In addition, in 192 ES cases with intellectual
disability from Iranian and Pakistani ancestry, the diagnostic yield of ES in the consanguineous population was 58%. These studies demonstrate the burden of consanguinity and its contributions to the proportion of autosomal recessive disorders. Among other preventive measures to reduce genetic disorders in any population, such as expanded premarital screening and prenatal interventions, lowering the rate of consanguinity is expected to result in a decrease in the prevalence of genetic diseases, particularly in isolated groups (Mu et al., 2019).

This study investigated the hit rate and mode of inheritance of disorders present in the non-consanguineous population of Saudi Arabia, which is a population that has a high rate of consanguinity compared to other populations.

**Materials And Methods:**

We reviewed 681 families, 1563 individuals with 2,565,335 variants in the genomic database of King Abdullah International Medical Research Center (KAIMRC) Genomic Database (KGD), Riyadh, Saudi Arabia. All the ES requests were obtained from the physician and clinical geneticist of KAMC, and the test was performed either in-house or in a College of American Pathologists (CAP) accredited laboratory center for clinical purposes. ES was performed using Illumina NextSeq, NovaSeq. For alignment and variant callers, Illumina DRAGEN v3.7 was used. The average coverage depth was ~ 95X. Several tools were used for variant classification, including Alamut Visual (http://www.interactive-biosoftware.com/alamut-visual/), Varsome (https://varsome.com/), Mastermind (https://mastermind.genomenon.com), and gnomAD (https://gnomad.broadinstitute.org/). All the variants are classified according to the American College of Medical Genetics and Genomics (ACMG) classification guidelines. The final candidate list of the filtered data was checked with the hospital’s electronic health records to confirm the variant for each index and the HPO. The criteria of inclusion were: (1) ES requests in non-consanguineous individuals are defined as the union of unrelated individuals up to the second degree of consanguinity; consanguinity is determined by the treating physicians using a requisition form, electronic health records, or chartnote; all cases are evaluated, reviewed, and manually entered into the KGD following verification of the results by a genetics counselor. (2) inclusion of only the index from each family, (3) positive cases (meaning a pathogenic/likely pathogenic variant identified according to ACMG standards) of ES tests, and finally (4) the clinical sequence variant that classified as pathogenic (P), and likely pathogenic (LP) (Fig. 1).

The exclusion criteria were: (1) Diseases associated or risk factors variant (checked with database i.e OMIM and others), such as GIGYF2 as a risk factor for Parkinson disease, and (2) for the allelic status, we excluded all heterozygous variants that are inherited in an autosomal recessive pattern (carrier), as well as the Variant of Uncertain Significance (VUS), Likely Benign (LB) and Benign (B) variants. Additionally, variants that have a conflicting interpretation were excluded. Approval for this study was obtained from the Institutional Review Board of King Abdullah International Medical Research Center, #RC19/315/R.

**Results:**
The KGD database consists of 681 families of consanguineous and non-consanguineous individuals who required ES testing. In total, 151 ES requests were for non-consanguineous families, 480 consanguineous families, and 50 unknown consanguinity. The number of variants that met the criteria were 28 variants and found in 27 individuals, one patient had 2 variants. Of the 27 cases, 15/27 (55.5%) cases were male, and 12/27 (44.4%) cases female. In the 151 non-consanguineous individuals with an ES request, 27/151 (17.8%) positive cases with pathogenic or likely pathogenic variants were found, negative results in 94/151 individuals (62.2%) and inconclusive findings in 30/151 individuals (19.8%) (Table 1 and 2).

- Solo exome vs extended family testing:

Of the 27 positive cases, 17 cases were solo cases (62.9%), trios in 9 cases (one patient had 2 variants) (33.3%), and only one trio plus case (index and parents with additional family members) (3.7%) (The detailed table is available in Supplementary Table 1).

- Missense vs Loss of Function (LoF) variants:

Of the 28 P/LP variants, missense variations were responsible for 22/28 (78.6%), and Loss of Function (LoF) variants for 6/28 (21.4%).

- De novo vs inherited variants:

Of the 28 P/LP variants, 14/28 (50%) variants were de novo and 14/28 (50%) variants were inherited. In the solo exome cases, 7/18 (38.8%) variants were inherited and 10/18 (55.5%) were de novo. However, in trio exome cases, 6/9 (66.6%) variants were inherited (one patient had 2 inherited variants) and 4/9 (44.4%) were de novo. One trio plus case had 1 (100%) inherited variant. In terms of the type of DNA variations, there were 22 missense variants (12/22 inherited 54.5%, 10/22 de novo 45.45%), and 6 LoF variants (3/6 inherited 50%, 3/6 de novo 50%).

- Mode of inheritance and zygosity:

Of the 27 positive cases and the one case with two P/LP variants, the mode of inheritance was autosomal dominant (AD) in 13/28 (46.4%) variants, autosomal recessive (AR) in 12/28 (42.8%) variants and X-linked XL in 3/28 (10.7%) variants (Fig. 2). For the allele state and zygosity in the P/LP variants, 13/28 (46.4%) were heterozygous variants and 12/28 cases (42.8%) were homozygous variants, and a small proportion (10.7%, n=12/28) were hemizygous variants.

- Common diseases and phenotypes:

There were no common disorders frequently observed in the non-consanguineous group in this study (Supplementary Table 1).

Discussion
Approximately 50-60% (Al Husain, Al Bunyan. 1997; Almazroua, A. M., Alsughayer et al., 2020) of the marriages in Saudi Arabia are consanguineous marriages, resulting in an increased rate of AR disorders. Non-consanguineous marriages are a minority. However, in a population that is homogeneous and inbred, even non-consanguineous marriages are expected to have a genetic impact. In this study, we found that the overall hit rate for established pathogenic and likely pathogenic variants in non-consanguineous marriages was 18%, compared to 40%-50% in consanguineous families. This reality indicates that the consanguinity rate in a population could be an important indicator for the incidence of genetic disorders.

In the non-consanguineous population of Saudi Arabia, the incidence rates of AD, AR, and XL cases were 46.4%, 42.9%, and 10.7%, respectively, compared to a previous study that estimated the hit rate of AR in consanguineous marriages in the same population to be 80% (Alfares et al., 2017). In contrast to the consanguineous cohort, the non-consanguineous cohort had a higher hit rate of AD cases (46.4%) than the consanguineous cohort (7%). However, and interestingly, homozygous variants in AR disorders account for 42.8% of the diseases detected in non-consanguineous marriages and 50% of the disease causing variants are inherited. This is explained by the fact that the population is an inbred population, with founder mutations, and marriages from same extended families (Table 3) (Alfares et al., 2017).

As a testing strategy, even in cases with de novo variants, where trio exome may have an advantage in detecting and confirming non-inherited variants when both parents are tested at the same time, solo exome with Sanger segregating testing for both parents shows a higher hit rate and is more cost effective. Consanguinity unions have been decreasing in prevalence due to social and economic factors, such as female education, small family size, and urbanization (Al-Abdulkareem et al., 1998; Mahboub et al., 2020). According to this study, avoiding these unions will lead to fewer genetic disorders, as well as rare recessive and dominant Mendelian disorders. Despite the fact that the etiology of these rare variants is unknown, this study predicts that reducing consanguinity will result in a two to threefold reduction in the incidence of genetic disorders.

**Conclusion:**

The overall hit rate of the non-consanguineous population of Saudi Arabia is 18% and for the rates of AD, AR and XL disorders were 46.4%, 42.9%, and 10.7% respectively. Reduced consanguinity results in a decrease in the prevalence of genetic disorders.

**Limitations:**

The limited size of the cohort, genetic heterogeneity, and a lower number of publications that focused on the non-consanguineous population, not only in the Saudi population, but also in the Middle Eastern population.

**Declarations:**
Authors contributions:

M.A and Ahmed.A designed the study, interpreted the clinical data, and wrote the article. T.A, L.A and Y.A collected samples, genotyped the cases and helped in statistical analysis. A.A, W.E, F.A, Farouq.A, and M.A, contributed in samples collection, clinical correlation and manuscript revision. All authors have read and approved the final manuscripts.

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Conflict of interest:

The authors have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in the manuscript.

Statement of Ethics:

This study was approved by the Institutional Research Board of the King Abdullah International Medical Research Center #RC19/315/R. All patients have been consented to be enrolled in this study, a written consent form was obtained from all subjects and/or their parents or legal guardians in the case of minors aged 18 years old or younger.

Data Availability Statement:

All the data that presented in this article are included in this published article. All enquiries should be directed to Ahmed A Alfares: fars@qu.edu.sa

References:

family analysis in consanguineous populations. BMC Med Genom 13(1).
https://doi.org/10.1186/s12920-020-00743-8


https://doi.org/10.3345/kjp.2019.00808


https://doi.org/10.1186/gb-2011-12-9-408

Tables:
Tables 1 to 3 are available in the Supplementary Files section

Figures
Figure 1

The summary of the pipeline that has been used in the genomic data filtration.
Figure 2

The mode of inheritance of the 28 variants.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- Table2.xlsx
- Table3.xlsx
- SupplementaryTable1.xlsx