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ORIGINAL ARTICLE

Genetic impact of non-consanguineous marriages in Saudi Arabia

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ABSTRACT

Background: Physicians and geneticists face challenges in making accurate diagnoses during clinical evaluations, affecting patients and clinicians. The aim of this study was to estimate the hit rate of the non-consanguineous population. Moreover, the prevalence of the genetic disorder in both the consanguineous and non-consanguineous population of Saudi Arabia at King Abdulaziz Medical City in Riyadh data.

Methods: We reviewed 681 families and 1,563 individuals with 2,565,335 variants in the King Abdullah International Medical Research Center (KAIMRC) Genomic Database (KGD), Riyadh, Saudi Arabia. All the exome sequencing (ES) requests were obtained from the physician and clinical geneticist of KAIMRC, and the test was performed either in-house or in a College of American Pathologists accredited laboratory center for clinical purposes.

Results: A total of 151 non-consanguineous individuals with ES requests in the population KGD of KAIMRC were considered for the study. In total, 27 had disease-causing variants, and the hit rate was 27/151 (18%). Among the 28 different variants in the 27 individuals, 50% were de novo variants and 50% inherited. 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.

Keywords: Saudi Arabia, non-consanguineous, ES, hit rate.

Introduction

Physicians and geneticists face challenges in making accurate diagnoses during clinical evaluations, affecting 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, exome sequencing (ES) is a highly effective and efficient diagnostic tool (1-3). In comparison to more established techniques such as karyotyping, Chromosomal Microarray Analysis, and Sanger sequencing, ES has a diagnostic yield of 25%-45%, with some studies reporting even higher results (4-7). First-cousin marriages, which account for 39.3% of all consanguineous marriages in Saudi Arabia, were the most prevalent (8). The yield of ES in consanguineous marriages is 58% in cases of suspected Mendelian diseases in a heterogeneous phenotypic population, demonstrating the technique's power (2). Additionally, the diagnostic yield of genome sequencing is higher than ES by only 3% to 5% (5). As a result, ES is considered a cost-effective technique and is frequently requested in the clinical setting (1-4).

Previous large ES 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

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(9). This observation is consistent with a study reaching genetic disorders resulting from consanguineous and non-consanguineous marriages (10). Autosomal recessive (AR) pathogenic and likely pathogenic (LP) variants accounted for the majority of the genetic mutations in Saudi Arabia (11). It occurred in 71% of the patients with ES requests, and the majority (97%) of these variations were 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%) (4). 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 AR 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 decrease the prevalence of genetic diseases, particularly in isolated groups (7). 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.

Subjects and Methods

We reviewed 681 families and 1,563 individuals with 2,565,335 variants in the 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 KAIMRC, and the test was performed either in-house or in a College of American Pathologists accredited laboratory center for clinical purposes. ES was performed using Illumina NextSeq, and NovaSeq. For alignment and variant callers, Illumina DRAGEN v3.7 was used. The average coverage depth was ~ 95×. 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 chart note; 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/LP variant identified according to ACMG standards) of ES tests; and finally, (4) the clinical sequence variant that is classified as pathogenic (P), and LP (Figure 1).

Summary of the filtration steps included: Non-consanguinity, WES cases with positive results, index, pathogenic, and LP variants, excluding all cases where zygosity does not match the disease's inheritance patterns. 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's disease, and (2) for the allelic status, we excluded all heterozygous variants that are inherited in an AR pattern (carrier), as well as the Variant of Uncertain Significance, likely benign and benign (B) variants. Additionally, variants that have conflicting interpretations were excluded. Approval for this study was obtained from the Institutional Review Board of KAIMRC, #RC19/315/R.

Results

The KGD database consists of 681 families of consanguineous and non-consanguineous individuals who required ES testing. About 151 ES requests were for non-consanguineous families, 480 consanguineous families, and 50 unknown consanguinities. The number

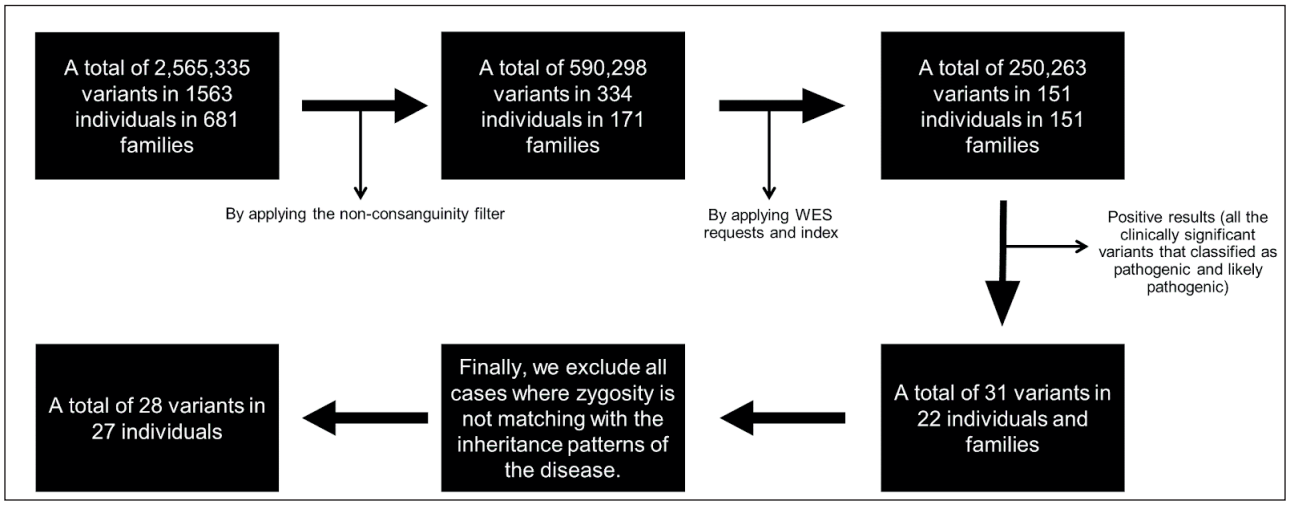

Figure 1. *The summary of the pipeline used in the genomic data filtration.*

of variants that met the criteria was 28 and were found in 27 individuals, one patient had two variants. Of the 27 cases, 15/27 (55.5%) were male, and 12/27 (44.4%) were female. In the 151 non-consanguineous individuals with an ES request, 27/151 (17.8%) positive cases with pathogenic or LP variants were found, negative results in 94/151 individuals (62.2%), and inconclusive findings in 30/151 individuals (19.8%) (Tables 1 and 2).

Solo exome versus extended family testing

Of the 27 positive cases, 17 cases were solo (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 versus loss of function (LoF) variants

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

De novo versus inherited variants

Among the 28 P/LP variants, 14/28 (50%) were de novo, and 14/28 (50%) 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. Regarding 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

Among 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, AR in 12/28 (42.8%) variants, and X-linked (XL) in 3/28 (10.7%) variants (Figure 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. A

Table 1. *Demographic and diagnostic information of the cohort (n = 151).*

	Positive	Inconclusive	Negative	Total
Gender				
Male	15/82 (18%)	19/82 (23%)	48/82 (59%)	82/151 (54%)
Female	12/69 (17%)	11/69 (16%)	46/69 (67%)	69/151 (46%)
Total	27/151 (18%)	30/151 (20%)	94/151 (62%)	151
Age				
Adult	3/15 (20%)	4/15 (27%)	8/15 (53%)	15/151 (9%)
Pediatrics	24/136 (18%)	26/136 (19%)	86/136 (63%)	136/151 (91%)
Total	27/151 (18%)	30/151 (20%)	94/151 (62%)	151
Solo, duo, trio, and trio plus				
Solo	17/66 (26%)	15/66 (23%)	33/66 (50%)	65/151 (43%)
Duo	0/12 (0%)	5/12 (42%)	7/12 (58%)	12/151 (8%)
Trio	9/66 (14%)	9/66 (14%)	48/66 (73%)	66/151 (43%)
Trio plus	1/8 (12.5%)	1/8 (12.5%)	6/8 (75%)	8/151 (5%)
Total	27/151 (18%)	30/151 (20%)	94/151 (62%)	151

Table 2. *Demographic and diagnostic information of the 27 individuals who met the criteria.*

	Positive
Age	
Adult	3/27 (11%)
Pediatrics	24 (89%)
Total	27
Solo, trio, and trio plus	
Solo	17/27 (63%)
Trio	8/27 (30%)
Trio plus	1/27 (3%)
Total	27

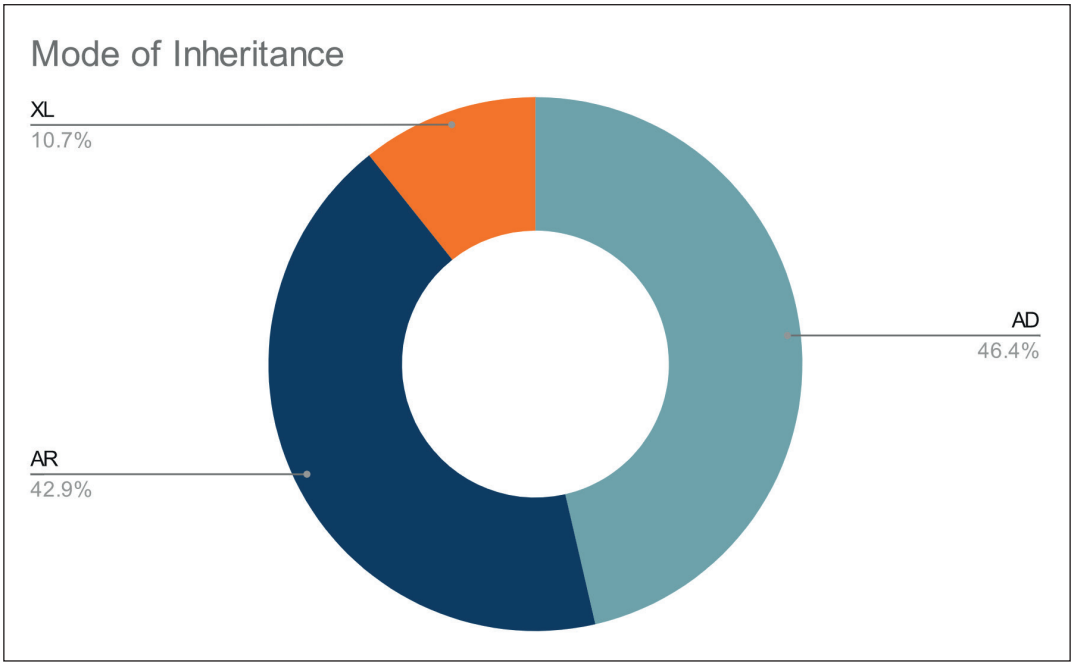

Figure 2. *The mode of inheritance of the 28 variants.*

Table 3. *A comparison of the consanguineous and non-consanguineous individuals between (4) study, and this study regarding the hit rate and mode of inheritance.*

	Alfares et al. (4) study Consanguineous	Alfares et al. (4) study Non-consanguineous	This study consanguineous	This study Non-consanguineous
Overall hit rate	174/327 (53%)	32/82 (39%)	160/480 (33.3%)	27/151 (17.8%)
AR+ Homozygous	147/174 (84%)	20/32 (63%)	142/160 (88.7%)	12/28 (42.8%)
AR+ Compound Heterozygous	4/174 (2%)	1/32 (3%)	6/160 (3.7%)	0/28 (0%)
AD+ Homozygous	1/174 (1%)	0/32 (0%)	0/160 (0%)	0/28 (0%)
AD+ Heterozygous	13/174 (7%)	8/32 (25%)	8/160 (5%)	13/28 (46.4%)
XL	9/174 (6%)	3/32 (9%)	4/160 (2.5%)	3/28 (10.7%)
Total	174 individuals	32 individuals	160 individuals	27 individuals[a]

[a]28 variants were found in 27 individuals, one patient had 2 variants.

small proportion (10.7%, n = 12/28) were hemizygous variants.

Common diseases and phenotypes

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

Discussion

Approximately 50%-60% of Saudi Arabia's marriages are consanguineous, resulting in an increased rate of AR disorders (8,12). Non-consanguineous marriages are a minority. However, in a homogeneous and inbred population, even non-consanguineous marriages are expected to have a genetic impact. This study found that the overall hit rate for established pathogenic and LP 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 essential indicator of 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% (4). 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, 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 inbred, with founder mutations and marriages from the same extended families (Table 3) (4).

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 simultaneously, solo exome with Sanger segregating testing for both parents show a higher hit rate and is more cost-effective. Consanguinity unions have decreased in prevalence due to social and economic factors, such as female education, small family size, and urbanization (8,13). According to this study, avoiding these unions will lead to fewer genetic disorders and rare recessive and dominant Mendelian disorders. Even though 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.

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

Conclusion

The overall hit rate of the non-consanguineous population of Saudi Arabia is 18%, and 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.

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List of Abbreviations

ACMG	American College of Medical Genetics and Genomics
AR	Autosomal recessive
ES	Exome sequencing
HPO	King Abdullah International Medical Research Center
KGD KAIMRC	Genomic database
LOF	Loss of function
LP	Likely pathogenic
XL	X linked

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Declaration of conflicting interests

The authors of this article 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 this manuscript.

Consent to participate

Informed consent was obtained from the patients.

Ethical approval

This study was approved by the Institutional Research Board of the King Abdullah International Medical Research Center #RC19/315/R.

Authors' contribution

MA and Ahmed A designed the study, interpreted the clinical data, and wrote the article. TA, LA, and YA collected samples, genotyped the cases, and helped in statistical analysis. AA, WE, FA, Farouq A, and MA, contributed in samples collection, clinical correlation, and manuscript revision. All authors have read and approved the final manuscript.

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