

# V Genetic Disorders in Saudi Arabia: A CTGA Perspective

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## نبذة مختصرة

أطلق المركز العربي للدراسات الجينية «فهرس الأمراض الوراثية عند العرب» المعروف أيضاً بقاعدة بيانات CTGA في عام ٢٠١٤ بهدف تشكيل مرجع شامل عام لتوثيق الأمراض الوراثية والطفرات الجينية عند المرضى العرب. بعد جمع وأرشفة البيانات من دولة الإمارات العربية المتحدة والبحرين وعمان وقطر في قاعدة بيانات CTGA وتلخيصها في مجلدات سابقة من هذه السلسلة، بدأت عملية جمع البيانات الوراثية من المملكة العربية السعودية وتنظيمها في ٢٠١٥. شمل المسح بيانات سريرية والجزيئية تم تجميعها من المقالات المنشورة والمفهرسة عن سكان المملكة العربية السعودية، وأسفر هذا المسح عن إضافة ٦٨٢ سجلاً للإضطرابات الوراثية و٥٧٥ سجلاً للمورثات الجينية إلى قاعدة بيانات CTGA. نعرض في هذا الفصل قائمة كاملة بسجلات الأمراض الوراثية والمورثات المرتبطة بالمملكة العربية السعودية الموثقة في CTGA قاعدة بيانات ، ونقدم تحليلاً موجزاً لهذه البيانات بحسب معايير معينة بما فيه الأنماط الوراثية للأمراض.

## Abstract

The Centre for Arab Genomic Studies launched the Catalogue of Transmission Genetics in Arabs (CTGA) in 2004 in the aim of developing a public comprehensive reference database that documents genetic disorders and gene variants in Arab patients. Following the incorporation of data from the UAE, Bahrain, Oman, and Qatar in the CTGA database (summarized in previous volumes of this series), a data collection and curation process began in 2015 to review genetic disorders from the Kingdom of Saudi Arabia. The survey spanned clinical and molecular data from the Saudi population collated from articles published in indexed databases, and resulted in the association of 682 genetic disorders and 575 gene loci in the CTGA database. In this chapter, we provide the complete list of disease and gene records associated with KSA which are currently hosted in CTGA, and briefly analyze this data according to certain criteria including exclusivity, distribution of the modes of inheritance, and distribution between disease group classifications.

## Introduction

The high prevalence of genetic disorders in the Arab World (AW) contributes to a significant proportion of infant mortality and morbidity in the region. The Centre for Arab Genomic Studies (CAGS) initiated an effort to develop a comprehensive open-access database of genetic disorders and gene variants in the AW, leading to the public release of the Catalogue of Transmission Genetics in Arabs (CTGA) in 2004.

Similar to the data collected for UAE, Bahrain, Oman, Qatar, and Kuwait from 2004-2014, an extensive data collection process for the Kingdom of Saudi Arabia (KSA) was launched in 2015. The

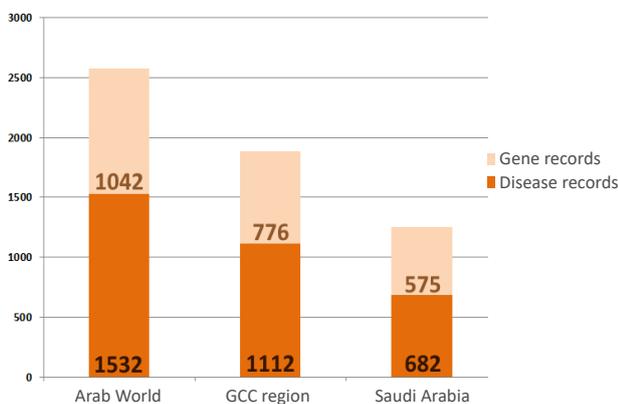
criteria set for the data included research articles (original articles, clinical reports, reviews, letters, and communications) involving familial case reports or patient cohorts with clear clinical and/or molecular diagnosis of genetic disorders, as well as disease prevalence studies, from the Saudi population. CAGS part-time researchers, based in KSA, were responsible for data collection and curation. An intricate search of relevant studies was performed for journal articles published in internationally and locally indexed databases, namely PubMed (US National Library of Medicine; National Institutes of Health (1)) and IMEM (Index Medicus of the Eastern Mediterranean; World Health Organization (2)).

The search term involved a basic search of “Saudi\*” in PubMed with the “\*” filter used for pulling data from all variations of the word “Saudi”. Additionally, a sensitive query search of articles associated with Saudi-related affiliations such as doctors and hospitals involved the following search: “‘Saudi Arabia’[affiliation] OR ‘KSA’[affiliation]” (3). Abstracts of the compiled articles were examined and those fitting the inclusion criteria were obtained in full-text online through open-access links, library subscriptions, or author communications. The full-text articles were then studied for material suitable for the CTGA database. Data analysis, curation, editing, and review were completed in approximately three years. Data in CTGA is presented as disease and gene records with summaries of published clinical and molecular data divided based on geographical location and article references.

## Number of KSA Disease and Gene Records in CTGA

The survey uncovered 2,290 articles relating to genetic disorders in the Saudi population. After data filtration, 682 genetic disorders and 575 associated gene loci were incorporated as records associated with KSA in the CTGA database. The complete list of disease and gene records can be found in appendix 1 and 2 respectively. The CTGA database currently hosts 1532 genetic diseases and 1042 genes. Compared to all other Arab countries, records from KSA contribute to the largest proportion of disease and gene records (approximately 49% of total records) in the database (Figure 1).

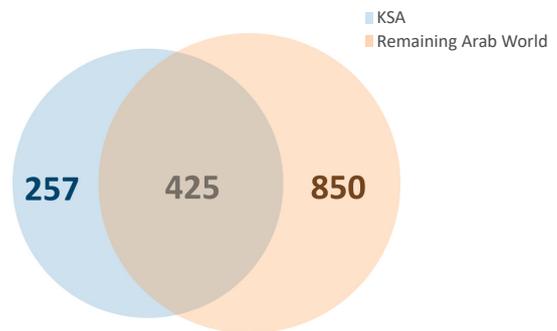
Despite the neighboring proximity and shared political, religious, and historical relations of KSA with the GCC and AW countries, a large portion (~17%) of total CTGA disease records are



**Figure 1:** Number of genetic disorders and associated gene loci indexed in the CTGA database (November 2018).

exclusive to clinical data from the Kingdom (~37% of KSA disease records; Figure 2). This could be attributed to the presence of founder mutations in genes restricted to the region, in combination with factors that result in the more frequent occurrence of rare mutations, such as high rates of consanguinity (discussed in chapter 3). KSA is, however, the largest country in the Middle East and exhibits one of the largest health workforces in the AW in terms of raw numbers, despite a somewhat low physician-patient ratio with roughly 1 physician per 332 individuals reported in 2017 (4-6). It follows that research output in the clinical genetics field from KSA is also among the highest. This is indicated by the number of entries in the Online Mendelian Inheritance in Man (OMIM) database (retrieved from the basic search ‘Saudi or ‘Saudi Arabian’) which pulled the highest number of results compared to other Arab countries (550 disease and gene records); similar results are seen from the number of published articles in indexed databases (PubMed) relative to other Arab countries.

The KSA-exclusive CTGA records most commonly involve diseases describing congenital



**Figure 2:** Proportion of total CTGA disease records exclusive to KSA (November 2018).

malformations, metabolic syndromes, eye and nervous system disorders, heart disease and digestive system disorders, as well as blood disorders and cancers (Appendix 1; Records marked with a \*). Over half (~55%) of these records involve diseases that are rare subtypes of genetically heterogeneous disorders. Prominent examples include subtypes of primary microcephaly, spinocerebellar ataxia, spastic paraplegia, retinitis pigmentosa, microphthalmia, cataracts, congenital disorders of glycosylation, as well as ciliopathies like Joubert syndrome and Meckel syndrome.

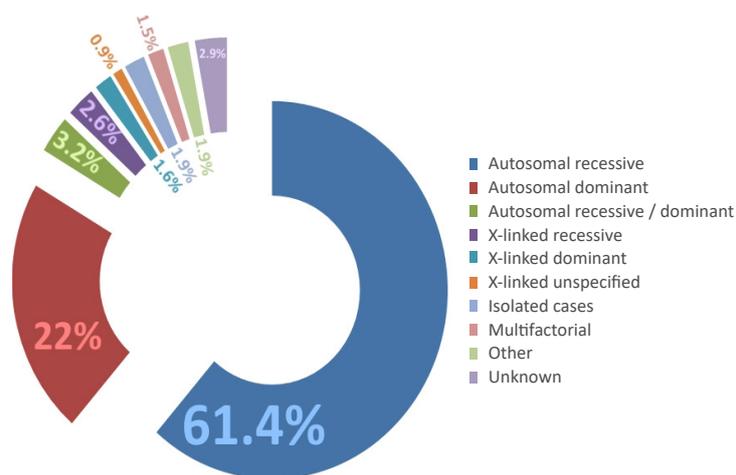
In contrast, only 18 CTGA disease records describe genetic disorders that have been reported in KSA

and all other GCC countries. These encompass common blood disorders including thalassaemia, sickle cell disease, and other hemolytic anaemias including glucose-6-phosphate dehydrogenase deficiency; neoplasms including lung, breast, and ovarian cancers; metabolic disorders including cystic fibrosis, phenylketonuria, maple syrup disease, primary hyperoxaluria, and propionic acidemia; multigenic disorders such as diabetes mellitus, systemic lupus erythematosus, essential hypertension, and thrombophilia; chromosomal disorders including down syndrome; and X-linked glomerulonephritis. Although these disorders are penetrant in the AW, certain pathogenic variants, variants particularly associated with common autosomal recessive disorders such as cystic fibrosis and beta-thalassaemia were described as founder mutations with high local frequencies in KSA (7).

### Distribution of the Modes of Inheritance of KSA-CTGA Disease Records

Genetic disorders in KSA follow the expected trend of a predominantly recessive disease transmission ascribed to Arab populations (8). This is especially the case in KSA as two of the largest exome studies ever performed on unselected Saudi patients revealed 71-83% of recessive mutations in cases positive for genetic disorder (9, 10). The high prevalence of consanguineous marriages, common practice of endogamy, and high parity in the Saudi population are thought to be significant factors behind this observation (7). Approximately 67.3% of KSA-CTGA disease records involve disorders transmitted through recessive inheritance. These include autosomal and X-linked disorders as well as disorders classified with other relatively rarely reported forms of inheritance (sporadic, mosaic, Y-linked, mitochondrial, multifactorial, digenic inheritance, and different descriptions of transmission modes of the same disease reported between affected families). The exact distribution of types of disease transmission in KSA disease records is shown in Figure 3. The complete list of KSA disease records are filtered according to modes of inheritance (Appendix Table 1) with records highlighted in color denoting additional specific modes of inheritance. KSA records exhibit the highest proportion of recessive disorders compared to other Arab countries in the database, whose proportions of recessive disorders mainly range between 50-60%. This could be due to the fact that KSA has one of the highest average rates

and ranged regional rates of consanguinity (42.1-67.2%) in the AW (11) (see Chapter 1 Figure 1). Consanguinity rates from specific KSA regions such as the rural area of Tabouk (80.4%) are among the highest ever reported (12). Other countries such as Bahrain and Qatar reflect a relatively more equal distribution of recessive and dominant disorders in the database. However, a significant limitation to this observation includes a difference in the number of disease records.



**Figure 3:** Distribution of the modes of inheritance of KSA disease records in CTGA (November 2018).

A small minority of KSA disease records encompass the relatively rare modes of disease inheritance described earlier. These include Y-linked and mitochondrial disorders; only one disorder, testicular torsion, reported in multiple Saudi cases was described as a possible Y-linked disorder although the exact genetic component is unknown (13). Among the mitochondrial disorders added as KSA records are Leigh Syndrome identified in multiple Saudi patients, patients with medullary thyroid cancer and Leber Optic Atrophy with mutations identified in the subunit ND1 Complex, and one case of MELAS (Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like Episodes) syndrome (14-17). Another disorder, found as separate (non-familial) cases, is Proteus Syndrome (a rare complex disorder characterized by asymmetrical overgrowth of bones, skin, and other tissues and organs), caused by de novo mutations in the early stages of development, resulting in cases with somatic mosaicism (18, 19). Other records characterized by mosaicism include the X-linked inborn error of metabolism, Congenital Disorder of Glycosylation Type 2m described in a single Saudi patient, as well as the immune system disorder, Severe Combined Immunodeficiency caused by Adenosine Deaminase Deficiency (ADA-

SCID) described in four Saudi families (20-22). Notably, the incidence of SCID was found to be very high (roughly 20 times that reported in the West) in a recent study in Saudi Arabia (23). Highly sporadic genetic disorders that have been reported in KSA include Myasthenia Gravis, for which a clinical review as well as Human Leukocyte Antigen gene association studies have been performed with large cohorts of Saudi patients (24, 25).

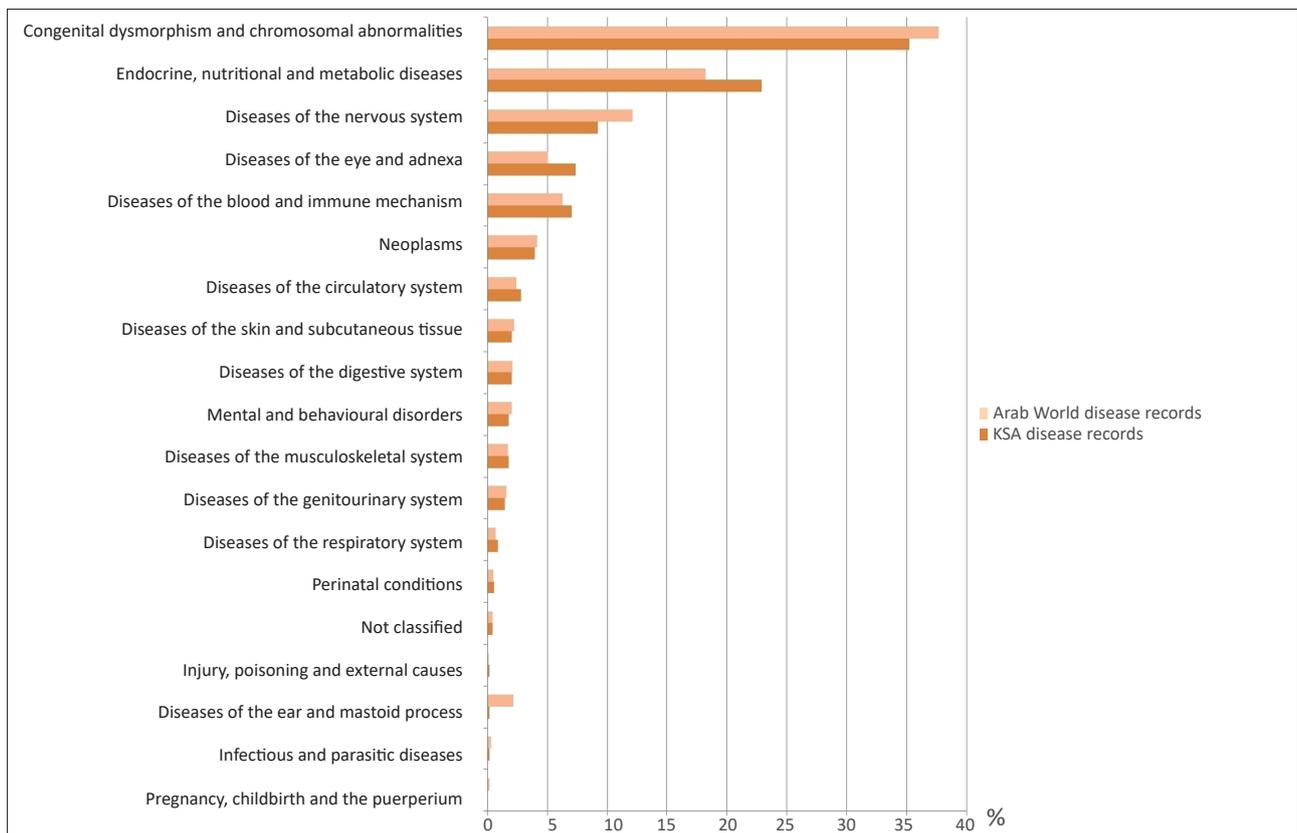
Multiple disorders with complex inheritance patterns were reported in KSA, including the common autoimmune intestinal disorder, Celiac Disease, of which prevalence rates in the Arab World are similar to the West (26). In a consanguineous Saudi family, a rare homozygous variant in the AK5 gene thought to be causative of Celiac Disease, was instead found to be remarkably penetrant in the Saudi population, and to significantly modify risk against development of the disorder (27). Disorders reported with digenic inheritance include the recessive hyperbilirubinaemia disorder, Rotor Syndrome. Three Saudi families were described with homozygous deletion and splice-site mutations in *SLC01B3* and *SLC01B1* respectively (28). Various reported disorders are characterized by multiple types of inheritance. One example is Congenital Nephrogenic Diabetes Insipidus (CNDI), which was reported in five Saudi families, with separate cases involving X-linked or autosomal recessive inheritance (29); autosomal

CNDI was described to be dominantly inherited in non-Arab patients (30). Additional forms of genetic disorders include chromosomal disorders such as Down's syndrome. A 10-year retrospective study described a higher than average incidence rate (1 in 554 live births) of the disorder in KSA, with the majority of cases involving trisomy 21 caused by nondisjunction (31).

The rarest reports of genetic disorders include instances of comorbidity, such as the case of a Saudi patient with Down's syndrome, Atrial Septal Defect, and Prune-Belly Syndrome, as well as a patient described with Sickle cell anemia and glycogen storage disease(32, 33). Approximately 2.9% of KSA disorders incorporated into CTGA currently exhibit an unknown mode of inheritance; although the genetic component may be known in some cases, further supporting evidence is required before classification.

## Distribution of Disease Groups and Affected Systems of KSA-CTGA Disease Records

The KSA disease records have been classified according to the 10<sup>th</sup> World Health Organization International Classification of Diseases (WHO ICD-10).



**Figure 4:** Classification of CTGA genetic disorders in KSA and the overall Arab World (November 2018).

The main WHO ICD-10 disease groups of the KSA records as well as total records are presented in Figure 4. Although CTGA mainly focuses on Mendelian disorders, frequency studies with large cohorts of patients with chromosomal abnormality disorders such as Down's Syndrome and Fragile X syndrome are also included in the database.

The most prominent disease category in KSA and AW, representing over 30% of disorders, includes congenital deformations and malformations. KSA records describe congenital deformities and abnormalities across many systems, most commonly the musculoskeletal and nervous systems. The second most prominent disease group involves disorders falling under the 'Endocrine, Nutritional, and Metabolic diseases' classification. These records, particularly those involving inborn errors of metabolism, appear to be significantly overrepresented in KSA compared to the Arab average population. This is likely a reflection of the incorporation of newborn screening using tandem mass spectrometry in KSA since 1995 (34). Published data of over a decade of screening with a focus on metabolic and endocrine disorders across all regions of KSA revealed high incidence rates of metabolic and endocrine disorders (35, 36); discussed in Chapter 3. The high heterogeneity of inborn errors of metabolism also factors into the number of metabolic disease records included in the CTGA. Apart from inborn errors of metabolism, these records prominently feature endocrine gland disorders, thyroid gland disorders, multiple forms of diabetes mellitus, as well as hyperalimentation disorders.

Disease groups representing <10% of KSA records include nervous system, ocular, and blood disorders. The reported nervous system disorders most commonly involve systemic atrophies and demyelinating diseases affecting the central nervous system, as well as disorders involving the myoneural junction and muscle. This is followed by episodic and paroxysmal (seizure) disorders, as well as extrapyramidal and movement system disorders, neurodegenerative disorders, and more rarely, nerve root and plexus disorders, such as Progressive Hemifacial Atrophy. Diseases of the eyes and adnexa commonly involve disorders of the choroid and retina, as well as ocular muscles, and are followed by disorders affecting the optic nerve and vision, and disorders affecting eye tissue. Eye disorders similarly appear overrepresented in KSA; a multitude of publications focusing on genetic studies of various ophthalmological disorders in

large cohorts of Saudi patients have been reported (discussed in Chapter 3). Diseases of the blood and immune mechanism are also represented more prominently in KSA compared to the overall Arab average population. Haemorrhagic conditions, disorders affecting the immune mechanism, and haemolytic anaemias represent the majority of these disorders; aplastic anaemias such as Fanconi anaemia and nutritional anaemias including the B12 deficiency disorder, Megaloblastic anaemia 1, are also included.

Among the disease groups representing <5% of KSA disorders are neoplasms, mainly involving malignant cancers. Benign tumors involved in disorders such as retinoblastoma and hemangioma-thrombocytopenia syndrome have also been described. Reported circulatory system disorders mainly include ischemic heart and cerebrovascular diseases, followed by artery and vein disorders, as well as other forms including cardiomyopathies, ventricular tachycardia, and lymphatic disorder. Reported digestive system disorders include multiple oral cavity disorders, mainly involving subtypes of tooth agenesis and failure of eruption; liver, gallbladder, and bile duct diseases including Inflammatory Bowel Disease, cholangitis as well as bile duct cyst formation, bile acid synthesis, and multiple subtypes of bile flow (cholestasis) disorders. Various skin disorders were reported involving bullous, papulosquamous, and eczemic disorders, and extending to disorders affecting the skin appendages including alopecia and hypotrichosis, as well as unique disorders such as Vitiligo, Keloid formation and Papillon-Lefevre syndrome. Reported musculoskeletal disorders include osteopathies such as osteoporosis and Hajdu-Cheney syndrome, and arthropathies including juvenile systemic arthritis and Bruck Syndrome. Mental disorders in KSA spanned psychological development disorders including Autism and Rett syndrome, behavioural disorders such as OCD, Tourettes Syndrome, ADHD, and schizophrenia, as well as subtypes of autosomal recessive mental retardation syndromes. Reported genitourinary disorders mainly involved glomerular disorders including multiple subtypes of nephrotic syndrome, glomerulonephritis, as well as renal disorders including renal tubular acidosis and urine reflux disorder. Respiratory disorders in KSA mainly feature chronic lower respiratory diseases such as asthma, as well as allergic disorders (rhinitis) and pulmonary surfactant disorders (including X-linked alveolar proteinosis and pulmonary fibrosis caused by lung iron deposits). Three perinatal disorders

were described in KSA including idiopathic hydrops fetalis, congenital diarrhea, and neonatal diabetes mellitus.

Disease groups rarely represented in the KSA records include infectious diseases, and disorders related to injury and poisoning; one record represented in each including susceptibility to herpes simplex encephalitis and susceptibility to malignant hyperthermia respectively.

## Concluding Remarks

The clinical and molecular data from KSA represents the largest dataset in CTGA to date. The unique representation of the Saudi demographic in relation to the prevalence and heterogeneity of genetic disorders, and the recent influx of large numbers of novel mutations, genes, and clinical phenotypes, serve as prime examples of the need to maintain a free resource of indexed genetic disorders in Arabs. This purpose is hoped to be fulfilled by the CTGA which continues to collate and adequately present genetic data to doctors, clinicians, and researchers worldwide. Data from the CTGA is significant in that it is structured geographically, includes data from indexed journals as well as non-indexed local sources, and also includes available studies on incidence and prevalence rates of genetic disorders. The database also serves as a resource for forming collaborations between regional and international researchers working in the same field or on particular disorders.

The CTGA is a good example of the amount of information that can be retrieved and analyzed from just a few basic searches. Despite this, the curation of articles has met some drawbacks as the search process is not foolproof; this, in addition to human error can result in a significant information gap even from missing a single article. The search and incorporation of missed and newly published data remains part of the ongoing process of maintaining the database. CTGA data is estimated to increase greatly in the current era of big data. The Saudi Human Genome Program is one example that continues to output molecular data and prevalence studies of large cohorts of patients on a wide range of genetic disorders (37).

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