# Androgen insensitivity syndrome: a review

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## ABSTRACT

Androgenic insensitivity syndrome is the most common cause of disorders of sexual differentiation in 46,XY individuals. It results from alterations in the androgen receptor gene, leading to a frame of hormonal resistance, which may present clinically under 3 phenotypes: complete (CAIS), partial (PAIS) or mild (MAIS). The androgen receptor gene has 8 exons and 3 domains, and allelic variants in this gene occur in all domains and exons, regardless of phenotype, providing a poor genotype – phenotype correlation in this syndrome. Typically, laboratory diagnosis is made through elevated levels of LH and testosterone, with little or no virilization. Treatment depends on the phenotype and social sex of the individual. Open issues in the management of androgen insensitivity syndromes includes decisions on sex assignment, timing of gonadectomy, fertility, physcological outcomes and genetic counseling. Arch Endocrinol Metab. 2018;62(2):227-35

**Keywords**

Androgen insensitivity syndrome; androgen receptor; disorders of sex development; 46,XY DSD

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## INTRODUCTION

Androgen Insensitivity Syndrome (AIS) is an X-linked genetic disease and it is the most common cause of disorders of sex development (DSD) in 46,XY individuals (1). The phenotype ranges from normal female external genitalia in the complete form (CAIS) to normal male external genitalia associated with infertility and/or gynecomastia in the mild form (MAIS). A large spectrum of undervirilized male external genitalia is observed in the partial form (PAIS) (2). Mutations in the androgen receptor gene (*AR*) are found in most individuals with CAIS but in less individuals with PAIS (3).

AIS was first described by Morris, in 1953, with the clinical description of 82 female patients with testes but female phenotype and for this reason Morris named the syndrome as testicular feminization (4). Later, this syndrome was characterized for being a condition resulting from a complete or partial resistance to androgens in 46,XY individuals with normal male gonad development (5).

PAIS should be considered in all individuals with atypical genitalia at birth regardless of the degree of external genitalia virilization and MAIS is a possible diagnosis in males with persistent gynecomastia and or infertility (6).

Role of Androgens in Male Fetal Development: androgens are key elements for appropriate internal and external male sex differentiation. After normal testes development, the Leydig cells produce testosterone, which promotes Wolffian duct differentiation into epididymes, vasa deferentia and seminal vesicles (7). The conversion of testosterone to dihydrotestosterone by the 5α-reductase type 2 enzyme promotes male external genitalia differentiation (8). In humans, the critical period for genitalia virilization occurs between 8 and 14 weeks of gestation and depends on the presence of androgens and of a functioning androgen receptor (9). Impairment of

androgen secretion and defects in the androgen receptor will compromise the virilization process.

## THE HUMAN ANDROGEN RECEPTOR

The *AR* gene is located at chromosome Xq11-12, is encoded by eight exons and codifies a 919 aminoacids protein (Figure 1). The *AR* is a ligand-dependent transcription factor composed by three functional domains as the other nuclear receptors: a large N-terminal domain (NTD) (residues 1-555), a DNA-binding domain (DBD) (556-623 residues), a hinge domain (624-665 residues) and a C-terminal ligand-binding domain (LBD) (666–919 residues) (10). The NTD is encoded by exon 1 and contains a ligand-independent transactivation function 1 (AF1), which contains two distinct transcription activation units: Tau-1 (aminoacids 100-370) and Tau-5 (aminoacids 360-485), that are essential for full *AR* activity. The DBD is composed by two zinc fingers and connects the *AR* to promoter and enhancer regions of *AR* regulated genes by direct nuclear DNA binding allowing the activate functions of NTD and LBD (11). The LBD is encoded by exons 4-8 and contains 11 α-helices associated with two anti-parallel β-sheets in a sandwich-like conformation with a central ligand binding pocket, in which the ligand can bind (12).

## CLINICAL PRESENTATION

CAIS prevalence in 46,XY males is estimated from 1 in 20.400 to 1 in 99.100 (13). Except in cases of familial inheritance, CAIS is diagnosed in three scenarios: in fetal life when prenatal sex determination disclosed a 46,XY karyotype in a fetus with female external genitalia; in childhood in a girl with inguinal hernia or at puberty in females with primary amenorrhea (14). The presence of inguinal hernia in a female child is rare and could indicate a CAIS diagnosis (13). Patients with AIS developed breasts with estradiol levels in normal male range suggesting that the lack of androgen action is the main driver of breast development in these patients, rather than an increased estrogen secretion. Menstrual cycles do not appear since normal production of anti-mullerian hormone (AMH) by the testis impeded uterus, cervix and proximal vagina to development. A shortened blind-ending vagina is observed in almost all patients and the vaginal measurement varied from 2.5 to 8 cm in CAIS and 1.5 – 4 cm in PAIS. Pubic and axillary hair are sparse or absent (1,14).

Final height in CAIS is above normal mean female height, probably due to the action of the growth-controlling gene (GCY) located at the Y chromosome (15). Interestingly, newborns with CAIS have the same size of male newborns, suggesting that postnatal factors are involved in the final height in these individuals (16). In our cohort, the final height of CAIS individuals (165.7 ± 8.9 cm) was taller than described for Brazilian females, but lower than expected for Brazilian males (15).

Differential diagnosis of CAIS includes complete gonadal dysgenesis, Mayer-Rokitanski-Kuster-Hauser syndrome and Mullerian ducts anomalies (1). Biosynthetic enzyme deficiencies are rarely a differential diagnosis for CAIS (8,17).

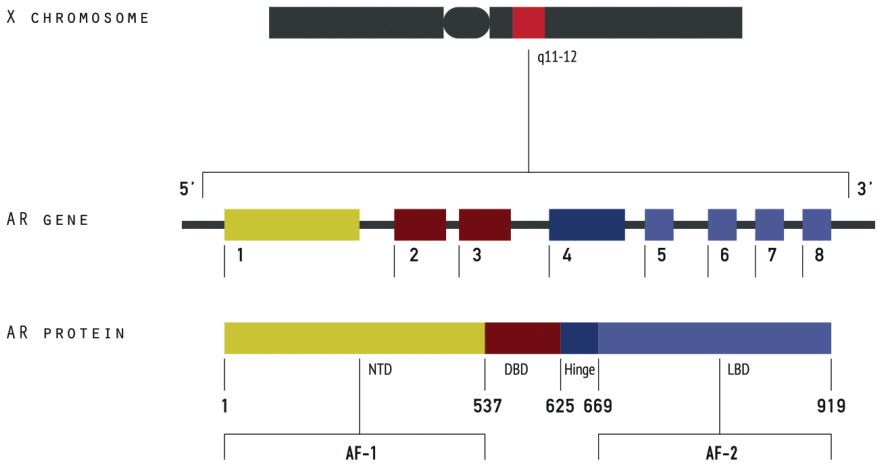


**Figure 1.** A schematic representation of androgen receptor gene and androgen receptor protein.

The PAIS clinical phenotype varies according to the degree of *AR* residual function and ranges from proximal hypospadias to micropenis (18). Hypospadias are a common finding with an estimated prevalence of 1:8000 male births and *AR* sequencing is necessary to exclude PAIS diagnosis (19). Gynecomastia observed at puberty time in patients with atypical genitalia can be indicative of PAIS (2,20). Differential diagnosis of PAIS includes all causes resulting in a undervirilized male external genitalia such as chromosomal defects (Klinefelter syndrome), genetic diseases (Smith-Lemli-Opitz syndrome, Denys-Drash syndrome, Frasier syndrome), partial gonadal dysgenesis, LH receptor defects, biosynthetic enzyme deficiencies (17,20-lyase deficiency, P450 oxidoreductase deficiency, 17β-hydroxysteroid dehydrogenase deficiency type 3, 5α-reductase 2 deficiency and hypospadias in small for gestation age boys (8,17).

MAIS is associated with *AR* mutations but without external genitalia abnormalities (6). This diagnosis could be suspected in the investigation of male infertility or in pubertal gynecomastia (14,18). There are few *AR* mutations associated exclusively with MAIS, but this condition is probably underdiagnosed (3,6).

MAIS can also manifest in a patient with neurological disorder characterized by bulbar and muscular atrophy (Kennedy's disease). This condition is due to the hyperexpansion of the CAG repeats (> 38), present in *AR* exon 1 (21). These patients present with normal male external genitalia, but testosterone resistance will develop with disease progression. For MAIS, the differential diagnosis includes other causes of male infertility.

## ENDOCRINE FEATURES

In AIS the endocrine profile is consistent with androgen resistance characterized by elevated or normal basal serum testosterone levels associated with high serum LH levels (22). Elevated serum AMH and testosterone levels in a newborn suggest the diagnosis of androgen insensitivity and also exclude the diagnosis of complete gonadal dysgenesis (23). In postpuberal patients estradiol levels are normal or slightly elevated for a male individual (22). This pattern is seen at mini-puberty or after puberty. During childhood when gonadotropin axis is not activated, a hCG stimulation is necessary to evaluate testosterone secretion by Leydig cells (24). In MAIS, hormone concentrations are usually normal, but elevated serum LH and testosterone levels could be found in these patients (19).

Typically in AIS, basal testosterone and LH levels are elevated demonstrating the impairment of androgen negative feedback on the anterior pituitary (22). In contrast, FSH levels are usually normal in AIS. This is explained by the fact that FSH is mainly regulated by gonadal inhibin (25). Although there are differences in the *AR* residual function among the mutated receptors between CAIS and PAIS phenotypes, no difference are observed in hormonal levels (20,22). Serum LH, FSH estradiol, DHT were not different in subjects with CAIS and PAIS (Table 1).

## MOLECULAR DEFECTS IN THE ANDROGEN RECEPTOR GENE

The AIS diagnosis is confirmed by the presence of allelic variants in the *AR* gene (1,26). About 30% of *AR* mutations in AIS are *de novo* and sequencing of the entire *AR* gene is recommended for all 46,XY DSD newborns, regardless of a familial history of DSD or AIS (26). In the absence of allelic variants in *AR* a multiplex ligation-dependent probe amplification (MLPA) can be helpful in order to detect deletions, insertions and duplications in the *AR* gene (26). There are more than 1000 *AR* mutations described in a website database

**Table 1.** Basal hormone levels in patients with AIS

| Phenotype | LH (U/L) | FSH (U/L) | Testosterone ng/dL | Estradiol pg/mL | Reference |
|---|---|---|---|---|---|
| CAIS | 14 – 43* | 3.5 – 16* | 186 – 1033* | 10 – 40* | (22) |
| n = 11 | 26** | 7.4** | 342** | 27** | |
| PAIS | 9 – 32* | – 34* | 157 – 1592* | 20 – 109* | (22) |
| n = 14 | 26** | 5.0** | 1032 | 49 | |
| CAIS | 5.5 – 51 | 0.4 – 16** | 173 – 1497* | 4.8 – 70* | (60) |
| n = 42 | 18.5 | 3.5* | 576** | 30.7** | |

* Range; ** Median.

associated with AIS and prostate cancer (http://www.mcgill.ca/androgendb) and around 600 of them were described in AIS (3). Mutations are found along the *AR* gene, being more frequent in exon 1 (the largest *AR* exon, which encodes the NTD). Defects in the NTD domain are more frequent in CAIS's patients and variants in exons 5 and 6 (that encode LBD) are more frequent in PAIS's patients (3). Almost all *AR* mutations in MAIS were found in the NTD, but there is a low number of *AR* mutations related to this phenotype.

The most common *AR* allelic variants in all AIS phenotypes are non-synonymous point mutations. Insertions and deletions causing a frameshift leading to a premature stop codon downstream are more frequently reported in CAIS's patients. Allelic variants affecting mRNA splicing are reported in CAIS and PAIS phenotypes. Rarely, synonymous allelic variants affecting splicing sites has been described in PAIS (27) and in CAIS individuals (28).

Large structural mutations (exon 1 deletion, exon 2 duplication, exon 3 deletion, exon 4-8 (LBD domain) deletion and deletion of entire *AR* gene) have been described but are very rare in AIS (3). Interesting, a deletion of an entire exon (exon 4) was previously described in a phenotypic male with azoospermia (29).

Postzygotic *AR* allelic variants resulting in somatic mosaicism are rarely described in AIS (30). In this situation the variant appears in heterozygote instead of hemizygote state. *AR* allelic variants in heterozygosis was also identified in some individuals with 47,XXY karyotype causing AIS (31).

There is not a perfect correlation between genotype and phenotype in AIS. In the *AR* mutation database, there are some *AR* allelic variants that can cause different phenotypes (Table 2). The explanation for this is not completely understood. It is hypothesized that *AR* co-regulators (activators and repressors) are implicated with this phenomenon. Other possibilities are variations in the level of 5α-reductase type 2 activity resulting in different DHT availability, and the presence of germ-line *AR* allelic variants at a post zygote stage conferring somatic mosaicism (31).

## CLINICAL MANAGEMENT OF AIS

AIS patients have complex issues including functional, sexual and psychosocial aspects. Sex assignment, external genitalia adequacy for social sex, hormonal replacement, psychosexual outcome, ideal time for gonadectomy, infertility and genetic counseling are issues that need attention in AIS care. All of them demand flexible, sensible and individualized procedures to achieve good results.

## CLINICAL MANAGEMENT OF CAIS

After diagnosis, the first aspect to be considered is the time for bilateral gonadectomy. In a girl, maintenance of the gonads will allow spontaneous breast development, though breast development is similar with estrogen replacement in gonadectomized females. So far, gonadectomy is performed at early age, in order to avoid the risk of malignancies and the psychosocial difficulties in submitting an adolescent female to gonadectomy (24). When gonadectomy is performed before puberty, estrogen replacement is necessary to induce puberty. In general, hormonal replacement is started at the age of 11-12 years with oral or transdermal estrogen. Both ways are adequate and the patient and family can choose the route in which the compliance will be better (18). Due to the absence of uterus, progesterone replacement is not necessary.

Genitoplasty is not necessary in CAIS and vaginal dilation promotes an adequate vaginal length vaginal dilation should occur after puberty or when the patient refers to desire to initiate sexual activity (32). Most of the individuals (80%) who were submitted to vaginal dilation referred satisfactory and some of them reported dyspareunia (33). There are many vaginoplasty techniques (34), but non-surgical dilation is effective, safe, non expensive and normalizes vaginal length and

**Table 2.** *AR* allelic variants identified in more than one AIS phenotype (3)

| Allelic variants | Phenotype |
|---|---|
| p.Leu174, p.Arg616Pro, p.Asn693del, p.Asn706Ser,p.Gly744Val, p.Met746Phe, p.Met750Val, p.Trp752*, p.Ala766Thr, p.Pro767Ser, p.Arg775His, p.Arg841His, p.Ile843Thr, p.Val867Met, p.Val890Met, p.Ser704Gly | CAIS, PAIS |
| p.Pro392Ser, p.Leu548Phe, p.Arg616His, p.Asp696Asn, p.Met781Ile, p.Arg856His, p.Ala646Asp | CAIS, PAIS, MAIS |
| p.Tyr572His, p.Arg608Gly, p.Asn757Ser, p.Arg789Ser, p.Gln799Glu, p.Thr801Ile, p.Ser815Asn, p.Leu822Val, p.Ala871Gly, p.Gly216Arg, p.Arg608Gly | PAIS, MAIS |

sex intercourse (32). Because of that, surgical creation of a vagina should be avoid regardless of the surgical technique (32).

## CLINICAL MANAGEMENT OF PAIS

PAIS diagnosis is usually suspected in a newborn with atypical genitalia and palpable gonads. Most of the patients are raised as male. The degree of external genitalia virilization is related to the residual AR function and can be predictive of androgen response at puberty. In male patients, correction of cryptorchidism and hypospadias are recommended as soon as possible, preferably before two years of age (35).

PAIS males frequently develop gynecomastia at puberty and surgical correction is generally necessary (22). High testosterone or DHT trials (intramuscular or topic testosterone esters or topic DHT) can be use to increase penile length and to improve other virilization signs (18,30). The results are unpredictable but are usually limited. Maximum virilization effect is observed after 6 months of high androgen usage treatment, subsequently, androgen therapy can be withdrawn in the patients with normal testes and preserved testosterone secretion.

For individuals raised as females, bilateral gonadectomy is recommended in childhood to avoid virilization and to eliminate the risk of testicular tumors (36). Genitoplasty is usually necessary in PAIS females and estrogen replacement is mandatory at pubertal time, with similar recommendation as describe for CAIS patients (15).

For MAIS, there is little information about clinical outcomes. Gynecomastia and infertility are the usual clinical presentation of this phenotype (6) and mastectomy is recommended for gynecomastia correction. This phenotype is observed in individuals with Kennedy's disease, which is more commonly known as spinal and bulbar muscular atrophy (SBMA). This syndrome is caused by an excessive number of CAG repeats in the *AR* exon 1 and a number of patients also have testicular atrophy, gynecomastia, oligospermia and erectile dysfunction (37).

**Table 3.** Types of androgen receptor allelic variants related to AIS reported in the androgen receptor mutations database

| Type of defect | CAIS | PAIS | MAIS |
|---|---|---|---|
| Non-synonymous | 155 | 125 | 41 |
| Stop codon | 57 | 2 | 0 |
| Indel | 41 | 4 | 2 |
| Duplication | 6 | 0 | 0 |
| Total | 259 | 131 | 43 |

## HORMONAL REPLACEMENT IN AIS

Hormonal replacement is mandatory for all gonadectomized individuals. In females, the purpose is the development of secondary sexual characteristics and an adequate and bone mass (2). Estrogen can be introduced in low doses (one quarter of the adult dose), at 9 – 11 years of age, with titration of this dosage every 6 months (20). The time for complete feminization is expected to be about 2 years. Oral or transdermic estrogen are alternative ways for estrogen replacement. The initial dose is 0.25 mg/day of 17β-estradiol increasing the dose each 6 months considering the progression of breast development. After complete breast development, a regular dose can be introduced (1-2 mg/day of 17β-estradiol continuously) (9).

In male individuals, the testes are able to produce testosterone. In male AIS, at pubertal age, high testosterone doses (200–500 mg twice a week) can be used, in order to increase the penile size and to promote virilization (1). Maximum penile length is obtained after six months of treatment with high testosterone doses. After this period, the dose of testosterone when necessary should return to the maintenance dose. The use of DHT in male PAIS has been tested (0.3 mg/kg of androstanolone gel 2.5% for 4 months) and mixed results were obtained following DHT therapy (38).

## GONADAL TUMOR RISK IN AIS

Disorders of sex development are recognized as a risk factor for type II germ cell tumors (GCTs). These tumors are classified as seminomatous and non-seminomatous types (39). The seminomatous tumors referred to seminoma (testis) and to dysgerminoma (ovary and dysgenetic gonads). In the non-seminomatous group, many differentiated variants can be identified according to the cellular origin, being the teratomas from somatic differentiation, yolk sac tumor and choriocarcinoma from extra-embryonic differentiation, and embryonal carcinoma from stem cells (27). These tumors derivate from a non-invasive precursor named carcinoma *in situ* – CIS – or Intrabular germ cell neoplasia unclassified – IGCNU). In 2016, the World Health Organization suggested to change the nomenclature of

this initial germinative neoplastic lesion from CIS or IGCNU to germ cell neoplasia *in situ* (GCNIS) (40). GCNIS are always non-invasive, but 50% of GCNIS progress to invasive GCTs within 5 years. The risk of GCTs development is related to the presence of a Y chromosome, but is not the same for the different etiologies of 46,XY DSD. So far, some factors, as chronological age and gonadal location can influence GCTs development (41).

In CAIS, the risk of GCTs is considered low and related to age (36). The estimated risk of gonadal tumors in CAIS gonads was about 0.8% - 22% (42). However, most old series included patients without confirmed AR mutation or without description of age at gonadectomy. The reports of malignant GCTs before puberty in CAIS are very rare (43). There is only one documented report of an invasive yolk-sac tumor in a CAIS individual before puberty. This occurred in a 17-months-old CAIS girl with abdominal gonads (44). After puberty, the risk is low, but not negligible. In a study, including 133 patients with CAIS, the gonads' histological and immunohistochemical findings showed a prevalence of 1.5% (2/133) for malignancies (45). The low incidence of GCTs in CAIS individuals can be explain by the rapid decline of germ cells after the first year of life (46).

PAIS individuals may maintain their germ cells because of the presence of residual androgen receptor responsiveness, differently of CAIS (46). Therefore, the incidence of GCTs in PAIS (15%) is higher than in CAIS (42). In cases of PAIS with untreated undescended testes the GCTs risk may be as high as 50% (47). Therefore, laparoscopic bilateral gonadectomy is indicated in all PAIS females and orquidopexy in scrotum in the male patients (48).

In patients who maintained the gonads, a careful monitoring including ultrasonography (US) or MRI has been suggested (43). Due to easy access and low cost, US remain the first choice for monitoring retained gonads. MRI has demonstrated adequate sensitivity to detect benign gonadal lesions, such as cysts or Sertoli cell adenomas, but failed to detect GCNIS (49). Annual US follow-up of labioscrotal and/or inguinal gonads is recommended. For abdominal gonads monitoring MRI is more helpful (50).

## FERTILITY IN AIS

A normal androgen receptor is necessary for normal male reproduction, because testosterone and FSH, are essential factors for male spermatogenesis. Therefore, mutations in the androgen receptor gene have been searched in order to identify possible causes for male infertility. As previously described, infertility may be the only clinical manifestation of undervirilization in MAIS phenotype (6,51).

The strategy to obtain fertility in AIS individuals has not been defined yet (52). In CAIS, there is absence of uterus and testes histology reveals incomplete spermatogenesis, increased fibrosis, Leydig cell hyperplasia and low frequency of spermatogonia conferring a very low potential to fertility. In addition, the viability of male germ cells in CAIS is restricted to the first two years of life and for fertility in adult life germ cells should be preserved before this age (46). In PAIS individuals, some residual androgen receptor function is preserved, but not usually enough to promote fertility (46). Indeed, infertility is the rule in AIS (22).

Probably, fertility is the most sensitive outcome which depends of an intact androgen receptor. For it, MAIS individuals can present only infertility (6,51). However, the p.G824K and p.R840C *AR* variant allelics, were found in male individuals with preserved fertility (51,53).

A successful fertility was recently described in a PAIS individual harboring the p.V686A *AR* variant, after prolonged high-dose testosterone therapy (250 mg of testosterone enanthate weekly by four years) causing improvement in sperm count. The gonadotropin concentrations remained unaffected and intracytoplasmic sperm injection with a single sperm directly into an egg resulted in proved fertility (54).

In general, infertility in AIS is the rule. The evidence of sperm count improvement after high doses of testosterone (as described above) can be an indicative of fertility success, but should be tested in further studies as well as the use of aromatase inhibitors and clomiphene citrate to obtain fertility in these patients

## PSYCHOLOGICAL OUTCOMES

Psychological support is essential for AIS individuals and their parents, in general (55). Dialogue about fertility, sexuality and karyotype are delicated issues to be approached with AIS individuals.

The gender identity, gender role and sexual orientation show a female pattern in CAIS individuals. In PAIS patients, in general, gender identity aligned with both sex of rearing male or female (56).

Gender change is very rarely described in CAIS and there are just four cases of gender change in individuals with CAIS (57). Therefore, gender dysphoria in CAIS is considered truly transgenderism. However, sexual functioning and sexual quality of life demonstrated less-positive outcome in CAIS patients in comparison with normal woman (58).

Although there is no inconsistency in gender identity, male PAIS individuals show disappointment with undervirilization signs. The absence or paucity of facial and body hair, the high-pitched voice compromised their self-perception of manhood (59). In female individuals, low scores in feminility scales have been reported (58). An impairment of sexual functioning is reported in male and female PAIS individuals (58).

## CONCLUSION

AIS is the most common molecular diagnosis in newborns with 46,XY DSD and results of an *AR* defect. It has an X-linked inheritance and affects 50% of the male offspring. In CAIS, the diagnosis can be done intrauterus, at birth, childhood or after puberty. In PAIS, the diagnosis is usually at birth due to the atypical external genitalia. In MAIS, the diagnosis should be considered in cases of pubertal gynecomastia and male infertility. *AR* defects are found along *AR* gene in all AIS phenotypes. Non-synonymous point mutations are the commonest *AR* defects reported in AIS. Molecular diagnosis is achieved in almost all patients with CAIS and in a lower frequency in PAIS individuals. AIS is characterized by elevated serum LH and testosterone. In CAIS, there is a low risk of GCTs before puberty and postponing surgery to after puberty may allow the development of spontaneous puberty. In PAIS there is a risk of GCTs in 15% of the patients, and bilateral gonadectomy is recommended at childhood in all individuals raised in the female social sex. For males with PAIS, the testis should be placed in the scrotum and regularly monitored. Fertility was described in one PAIS individuals, and therapeutic strategy for successful fertility could be experienced in PAIS and MAIS individuals. In AIS, gender identity usually follows the sex of rearing, but quality of sexual life, sexual functioning and quality of life can be slightly compromised and are important issues for keeping patients in psychological care.

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Review



# Oculocutaneous albinism

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## Abstract

Oculocutaneous albinism (OCA) is a group of inherited disorders of melanin biosynthesis characterized by a generalized reduction in pigmentation of hair, skin and eyes. The prevalence of all forms of albinism varies considerably worldwide and has been estimated at approximately 1/17,000, suggesting that about 1 in 70 people carry a gene for OCA. The clinical spectrum of OCA ranges, with OCA1A being the most severe type with a complete lack of melanin production throughout life, while the milder forms OCA1B, OCA2, OCA3 and OCA4 show some pigment accumulation over time. Clinical manifestations include various degrees of congenital nystagmus, iris hypopigmentation and translucency, reduced pigmentation of the retinal pigment epithelium, foveal hypoplasia, reduced visual acuity usually (20/60 to 20/400) and refractive errors, color vision impairment and prominent photophobia. Misrouting of the optic nerves is a characteristic finding, resulting in strabismus and reduced stereoscopic vision. The degree of skin and hair hypopigmentation varies with the type of OCA. The incidence of skin cancer may be increased. All four types of OCA are inherited as autosomal recessive disorders. At least four genes are responsible for the different types of the disease (*TYR*, *OCA2*, *TYRP1* and *MATP*). Diagnosis is based on clinical findings of hypopigmentation of the skin and hair, in addition to the characteristic ocular symptoms. Due to the clinical overlap between the OCA forms, molecular diagnosis is necessary to establish the gene defect and OCA subtype. Molecular genetic testing of *TYR* and *OCA2* is available on a clinical basis, while, at present, analysis of *TYRP1* and *MATP* is on research basis only. Differential diagnosis includes ocular albinism, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, Griscelli syndrome, and Waardenburg syndrome type II. Carrier detection and prenatal diagnosis are possible when the disease causing mutations have been identified in the family. Glasses (possibly bifocals) and dark glasses or photocromic lenses may offer sufficient help for reduced visual activity and photophobia. Correction of strabismus and nystagmus is necessary and sunscreens are recommended. Regular skin checks for early detection of skin cancer should be offered. Persons with OCA have normal lifespan, development, intelligence and fertility.

## Disease name

Oculocutaneous albinism

## Definition

Oculocutaneous albinism (OCA) is a group of four autosomal recessive disorders caused by either a complete lack or a reduction of melanin biosynthesis in the melanocytes

resulting in hypopigmentation of the hair, skin and eyes. Reduction of melanin in the eyes results in reduced visual acuity caused by foveal hypoplasia and misrouting of the optic nerve fibres. The clinical spectrum of OCA varies, with OCA1A being the most severe type characterized by a complete lack of melanin production throughout life, while the milder forms OCA1B, OCA2, OCA3 and OCA4 show some pigment accumulation over time. The different types of OCA are caused by mutations in different genes but the clinical phenotype is not always distinguishable, making molecular diagnosis a useful tool and essential for genetic counseling.

## Epidemiology

Albinism can affect people of all ethnic backgrounds and has been extensively studied. Approximately one in 17,000 people have one of the types of albinism [1]. This suggests that about 1 in 70 people carry a gene for OCA. Prevalence of the different forms of albinism varies considerably worldwide, partly explained by the different founder mutations in different genes and the fact that it can be difficult clinically to distinguish between the different subtypes of albinism among the large normal spectrum of pigmentation. OCA2 is the most prevalent form worldwide [2] (Table 1).

• OCA1 has a prevalence of approximately 1 per 40,000 [3] in most populations but is very uncommon among African-Americans.

• In contrast, OCA2 is the most common type of albinism in African Black OCA patients. The overall prevalence of OCA2 is estimated to be 1:36,000 in the USA, but is about 1:10,000 among African Americans [4]. It affects 1 in 3,900 of the population in some parts of the southern part of Africa [5].

• OCA3 or Rufous oculocutaneous albinism has been reported to affect 1:8,500 individuals in Africa, whereas it is very rare in Caucasians and Asiatic populations [6].

• Recently, mutations in a fourth gene were shown to be the cause of albinism, OCA4, [7] and were reported to explain the disease in approximately 5–8% of German patients with albinism [8] but 18% of Japanese patients [9].

## Clinical description

All types of OCA and ocular albinism (OA) have similar ocular findings, including various degrees of congenital nystagmus, hypopigmentation of iris leading to iris translucency, reduced pigmentation of the retinal pigment epithelium, foveal hypoplasia, reduced visual acuity usually in the range 20/60 to 20/400 and refractive errors, and sometimes a degree of color vision impairment [1,10] (Figure 1). Photophobia may be prominent. Iris translucency is demonstrable by slit lamp examination. A characteristic finding is misrouting of the optic nerves, consisting in an excessive crossing of the fibres in the optic chiasma, which can result in strabismus and reduced stereoscopic vision [11]. The abnormal crossing of fibres can be demonstrated by monocular visual evoked potential [12]. Absence of misrouting excludes the diagnosis of albinism.

The degree of skin and hair hypopigmentation varies with the type of albinism but is in general reduced [10] (Table 1).

• In OCA1A the hair, eyelashes and eyebrows are white, and the skin is white and does not tan. Irises are light blue to almost pink, and fully translucent (Figure 2). Pigment does not develop and amelanotic nevi may be present. The symptoms do not vary with age or race. Visual acuity is 1/10 or less, and photophobia is intense.

• In OCA1B, the hair and skin may develop some pigment with time (after 1 to 3 years), and blue irises may change to green/brown. Temperature-sensitive variants manifest as having depigmented body hairs, and pigmented hairs on hands and feet due to lower temperatures. Visual acu-

**Table 1: The four known types of OCA**

| *Gene* | *Gene product* | Chr. localization | Size | Disease name | Prevalence |
|---|---|---|---|---|---|
| ***TYR*** | Tyrosinase (TYR) | 11q14.3 | 65 kb (529aa) | OCA1<br>OCA1A<br>OCA1B *(Yellow alb.)* | 1:40,000 |
| ***OCA2 (p gene)*** | OCA2 | 15q11.2-q12 | 345 kb (838aa) | OCA2 *(Brown OCA in Africans)* | 1:36,000 (white Europeans)<br>1:3,900–10.000 (Africans) |
| ***TYRP1*** | Tyrosinase-related protein 1 (TYRP1) | 9p23 | 17 kb (536aa) | OCA3 (*Rufous OCA*) | Rare (white Europeans, Asians)<br>1:8,500 (Africans) |
| ***MATP*** | Membrane-associated transporter protein (MATP) | 5p13.3 | 40 kb (530aa) | OCA4 | Rare (white Europeans) 1:85,000 (Japanese) |

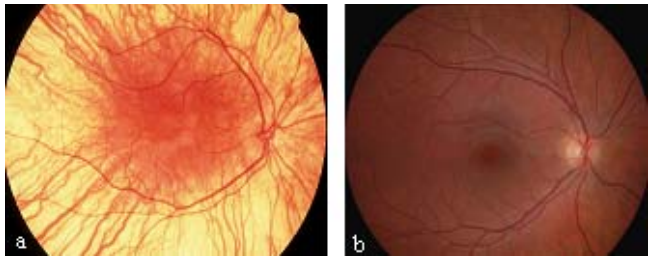


**Figure 1**
Fundus picture of a patient with albinism (a) and fundus picture of a normal eye (b).

ity is 2/10. This phenotype was previously known as yellow albinism.

• In OCA2, the amount of cutaneous pigment may vary, and newborn nearly always have pigmented hair. Nevi and ephelids are common. Iris color varies and the pink eyes seen in OCA1A are usually absent. Visual acuity is usually better than in OCA1, and can reach 3/10. In Africans, brown OCA is associated with light brown hair and skin, and gray irises. Visual acuity may reach 3/10.

• OCA3 results in Rufous or red OCA in African individuals, who have red hair and reddish brown skin (xanthism). Visual anomalies are not always detectable, maybe because the hypopigmentation is not sufficient to alter the development.

• OCA4 cannot be distinguished from OCA2 on clinical findings.

## Etiology

OCA is a group of congenital heterogeneous disorders of melanin biosynthesis in the melanocytes (Figure 3). At least four genes are responsible for the different types of OCA (OCA1-4) (Table 1). Most patients are compound heterozygotes, *i.e.* harbouring two different mutations in one of the genes.

• OCA1 (MIM 203100) is caused by mutations in the tyrosinase gene (*TYR*, MIM 606933) on chromosome 11q14.3 [13]. The gene consists of 5 exons spanning about 65 kb of genomic DNA and encoding a protein of 529 amino acids [14]. TYR (EC 1.14.18.1) is a copper-containing enzyme catalysing the first two steps in the melanin biosynthesis pathway, converting tyrosine to L-dihydroxy-phenylalanine (DOPA) and subsequently to DOPAquinone [15]. Mutations completely abolishing tyrosinase activity result in OCA1A, while mutations rendering some enzyme activity result in OCA1B allowing some accumulation of melanin pigment over time. Almost 200 mutations in *TYR* are known [16]. As with all recessive disorders, the "mildest" mutation is determining for the phenotype. It has been shown that mutations in the mouse *Tyr* gene cause the Tyr protein to be retained in the endoplasmic reticulum, with subsequently early degradation [17] (Figure 3).

• Mutations in the *OCA2* gene (formerly known as the P-gene) (MIM 203200) cause the OCA2 phenotype (MIM 203200) [18]. The gene consists of 24 exons (23 coding), spanning almost 345 kb of genomic DNA in the region 15q11.2-q12, and encoding a protein of 838 amino acids [19]. The OCA2 protein is a 110 kDa integral melanosomal protein with 12 predicted transmembrane domains [18,20]. OCA2 protein is important for normal biogenesis of melanosomes [21,22], and for normal processing and transport of melanosomal proteins such as TYR and TYRP1 [23-26] (Figure 3). TYR stably expressed in a human cell line is retained in perinuclear compartments; this mislocalization can be reverted if OCA2 is co-expressed [27]. It seems that OCA2 exerts at least some of its effects by maintaining an acidic pH in melanosomes [27]. In the Human Gene Mutation Database (HGMD) [16], 72 mutations in *OCA2* are listed to cause OCA.

• OCA3 (MIM 203290) is caused by mutations in tyrosinase-related protein 1 (*TYRP1*, MIM 115501, 9p23) [28]. *TYRP1* spans almost 17 kb genomic DNA, and consists of 8 exons encoding a protein of 536 amino acids [29]. TYRP1 is an enzyme in the melanin biosynthesis pathway, catalysing the oxidation of 5,6-dihydroxyindole-2-carboxylic acid (DHICA) monomers into melanin (Figure 3). Studies of mouse melanocytes showed that Tyrp1 functions to stabilize Tyr, and that mutations in *Tyrp1* cause a

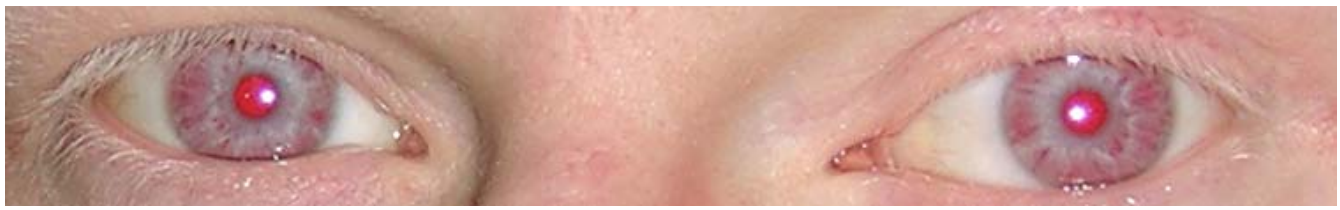

**Figure 2**
Eyes from a patient with OCA1A. Note that the irises are almost pink, and fully translucent.

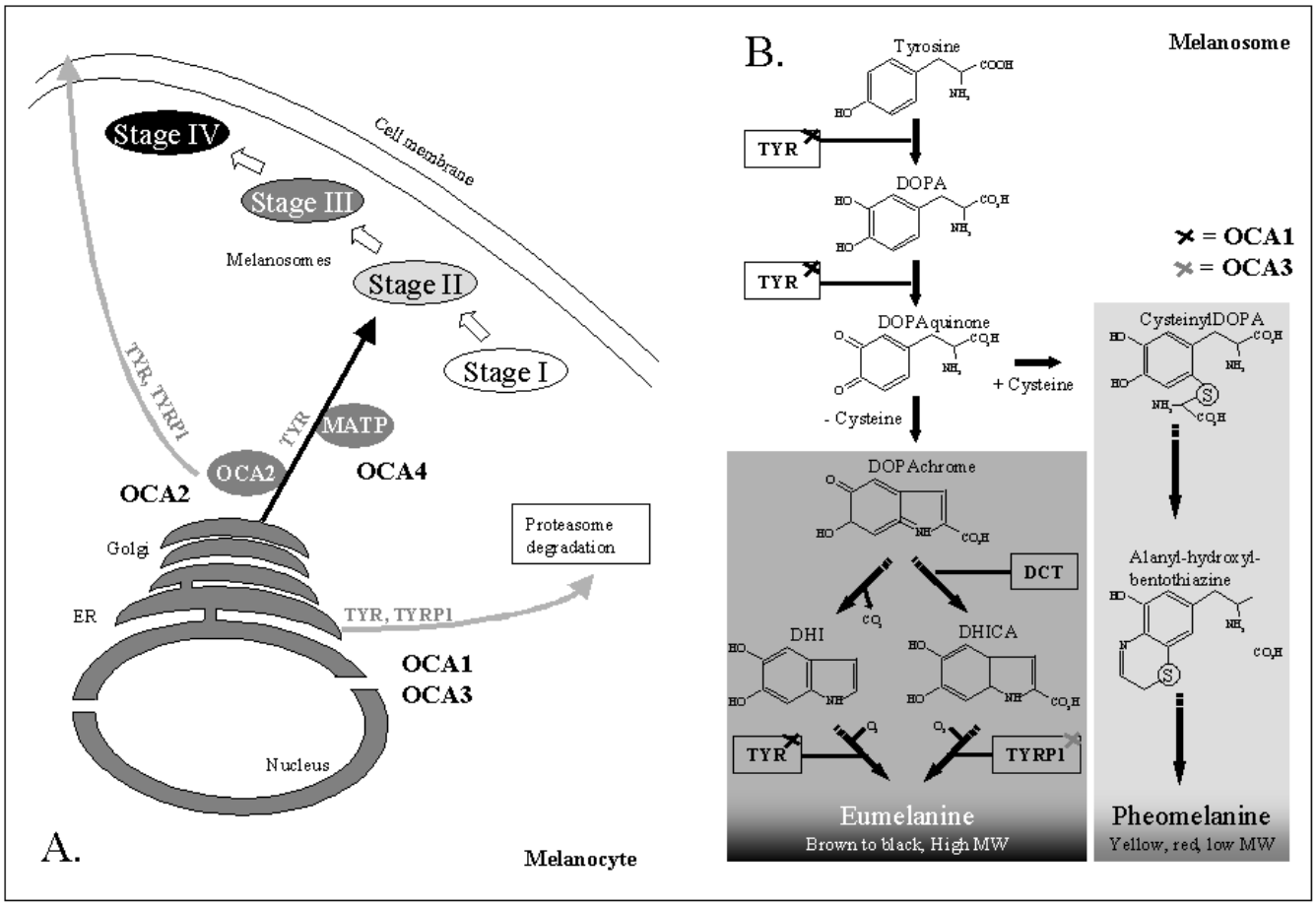


**Figure 3**
Tyrosinase (TYR) and Tyrosinase-related protein 1 (TYRP1) processing and the melanin biosynthetic pathway in the melanocyte and in the melanosome, respectively. **A**) Schematic representation of melanosome biogenesis in the melanocyte and trafficking of TYR and TYRP1 from the endoplasmatic reticulum (ER) via Golgi apparatus to the developing melanosome. Places are indicated where the transport or sorting of TYR and TYRP1 from the synthesis in the ER to the melanosomes is abolished caused by mutations in the four genes found to be responsible for OCA (OCA1 to OCA4, respectively) (adapted from [49]). **B**) Illustration of the melanin (eumelanin/pheomelanin) biosynthesis pathway in the melanosome. DHI: 5,6-Dihydroxyindole, DHICA: 5,6-Dihydroxyindole-2-carboxylic acid, TYR: tyrosinase, TYRP1: Tyrosinase-related protein 1 (DHICA oxidase), DCT: Dopachrome tautomerase.

delayed maturation and an early degradation of Tyr [17] (Figure 3). Until recently, OCA3 was only known in individuals of African descent, however currently mutations in *TYRP1* have been identified in both a large Pakistani family [30] and in a Caucasian patient [6].

• Mutations in the membrane-associated transporter protein gene (*MATP*, also known as *SLC45A2*, MIM 606202) cause OCA4 (MIM 606574) [7]. *MATP* consists of 7 exons spanning approximately 40 kb of genomic DNA, mapping to chromosomal position 5p13.3. The MATP protein of 530 amino acids contains 12 putative transmembrane domains and shows sequence and structural similarity to plant sucrose transporters; it is expressed in melanosomal cell lines [31,32]. The function of MATP is still unknown, but studies from Medaka fish show that the MATP protein plays an important role in pigmentation and probably functions as a membrane transporter in melanosomes [31] (Figure 3). Mutations in *MATP* were found for the first time in a Turkish OCA patient [7], and have since been found in German, Japanese and Korean OCA patients [8,9,33,34].

## Diagnostic methods

The diagnosis of OCA is based on clinical findings of hypopigmentation of the skin and hair, in addition to the characteristic ocular symptoms (Figure 1). However, due to the clinical overlap between the OCA subtypes, molecular diagnosis is necessary in order to establish the gene defect and thus the OCA subtype. Molecular genetic test-

ing of *TYR* and *OCA2* are available on a clinical basis, while at present, analysis of *TYRP1* and *MATP* is on research basis only. Molecular genetic testing is based on mutational analysis of the genes, by standard screening methods such as denaturing high performance liquid chromatography (DHPLC) or single stranded conformational polymorphism (SSCP), followed by DNA sequencing.

Mutational analysis of *TYR* is complicated by the presence of a pseudogene harbouring sequences highly similar to exon 4 and 5 of *TYR*. This can be overcome either by digestion of pseudogene sequences with restriction enzymes prior to PCR amplification or by use of specific primers only amplifying *TYR* sequences [35].

Due to the presence of numerous polymorphisms, mutational analysis of *OCA2* is difficult and until a functional assay is available, investigation of control chromosomes in addition to *in silico* analyses of amino acid substitutions are necessary in order to substantiate the probable deleterious effect of a (missense) mutation.

## Genetic counseling and antenatal diagnosis

All four types of OCA are inherited as autosomal recessive disorders. Thus, the parents of an affected child are obligate carriers, the recurrence risk for another affected child is 25%, and healthy sibs are at 67% risk of being carriers. Offspring of an affected person are obligate carriers. Carriers are asymptomatic.

In most cases, there is no previous family history of albinism but the condition does occur in individuals of two generations of a family, so called pseudodominance, and is due to an affected person having children with a person who is a carrier.

In African populations, there is a high frequency of *OCA2* mutant alleles, hence affected patients in several generations may be seen.

Carrier detection and prenatal diagnosis are possible when the disease causing mutations have been identified in the family. Both disease causing mutations in an affected person have to be identified and established to be on the paternal and maternal chromosome, respectively, before prenatal diagnosis can be performed in pregnancies at 25% risk for an affected child. The testing can be done on DNA extracted from chorion villus sampling (CVS) at 10–12 weeks gestation or on DNA extracted from cultured amniocytes. Preimplantation diagnosis using molecular genetic analysis is also possible in principle, but to our knowledge, this has not been carried out.

Previously, prenatal diagnosis has been performed on skin biopsies from the fetus [36,37]. Requests for prenatal diagnosis for OCA are not common, and may reflect the nature of the condition (not affecting intellectual functions or general health). However, many centers including ours would consider prenatal testing after careful genetic counseling of the parents.

## Management

### *Management of eye problems*

Reduced visual acuity can be helped in various ways. Clinics specialized in low vision will provide the expertise. Glasses, possibly bifocals, may often be of sufficient help. Photophobia can be helped with dark glasses or photocromic lenses that darken with exposure to bright light. Nystagmus may be helped with contact lenses or surgery of the eye muscles. Certain positions of the head may dampen nystagmus. For strabismus it may be necessary to patch one eye in children to force the non-preferred eye to be used.

Children should be given special attention at school, for instance with high contrast written material, large type textbooks, various optic devices as enlargement machines (closed circuit TV), and the use of computers.

### *Skin*

Most people with severe forms of OCA do not tan and easily get sunburned. Those forms with a little pigment developing with age may not be very bothered by the sun. Sunscreens are recommended with at least a sun protection factor of 15. Ultraviolet rays can penetrate light T-shirts especially when wet. Now, T-shirts have been developed which protect against the sun even when wet. The incidence of skin cancer is increased in patients with OCA [3]. Since the prevalence of OCA2 is high in Africa, this may pose a serious health problem.

## Differential diagnosis

It has become evident that heterogeneity exists within oculocutaneous albinism, and several disorders with characteristic of OCA in addition to other symptoms have been identified. On the contrary, in Ocular Albinism (OA) the hypopigmentation is limited to the eyes resulting in irides that are blue to brown, nystagmus, strabismus, foveal hypoplasia, abnormal crossing of the optic fibres and reduced visual acuity [38]. The gene *OA1* is localized on the X chromosome and only fibersboys are affected [39]. In young boys with light complexion, of *e.g.* Scandinavian extraction, some difficulty in the differential diagnosis of OCA versus OA is not uncommon.

Among disorders where albinism is part of a larger syndrome are Hermansky-Pudlak syndrome (HPS), Chediak-Higashi syndrome (CHS), Griscelli Syndrome, and

Waardenburg Syndrome type II (WS2). All, except WS2, are inherited as autosomal recessive traits and can be distinguished on the basis of clinical and biochemical criteria. Several subtypes exist within the different diagnoses. Further, an association of hypopigmentation in Prader Willi syndrome and Angelman disease with a deletion on 15q11 has been found, presumable caused by mutations in *OCA2* [40].

• The Hermansky-Pudlak syndrome is characterized by hypopigmentation and the accumulation of a material called ceroid in tissues throughout the body [41]. Further, patients exhibit severe immunologic deficiency with neutropenia and lack of killer cells [42]. HPS is very rare, except in Puerto Rico where it affects approximately 1 in 1,800 individuals [43]. The most important medical problems in HPS are related to interstitial lung fibrosis, granulomatous colitis and mild bleeding problems due to a deficiency of granules in the platelets [44].

• The Chediak-Higashi syndrome is a rare condition that includes an increased susceptibility to bacterial infections, hypopigmentation, prolonged bleeding time, easy bruisability, and peripheral neuropathy. The skin, hair, and eye pigment is reduced or diluted in CHS [45,46].

• The Griscelli syndrome is a rare disorder with immune impairment or neurological deficit and hypopigmentation of skin and hair, and the presence of large clumps of pigment in hair shafts [47].

• A syndrome of sensory deafness and partial albinism is referred to as the albinism-deafness syndrome or the Waardenburg syndrome [48].

## Prognosis

Lifespan in patients with OCA is not limited, and medical problems are generally not increased compared to those in the general population. As mentioned, skin cancers may occur and regular skin checks should be offered. Development and intelligence are normal. Persons with OCA have normal fertility.

## Unresolved questions

We and others have identified mutations in two alleles in approximately 50% of the patients investigated with genetic screening of the four known OCA genes (*OCA1-4*) (unpublished results). Further, some individuals classified with OCA1 or OCA2 have only one mutation identified. This means that a fraction of patients with albinism still need to be genetically solved. Therefore, more work is needed to establish whether subtle genetic changes in regions not traditionally covered by genetic screening, *i.e.* introns or regulatory domains are the cause of the disease in cases with only one mutation identified. Further, large genomic deletions or single exon deletions not identified by traditional screening methods may explain the disease in a fraction of the patients. In addition, a percentage of genetically unresolved cases might be explained by mutations in not yet identified OCA genes. Finally, the biological function of the gene products of the genes identified as the cause of albinism is not clarified and further elucidation of these mechanisms may give clues to further candidate genes where mutations are the cause of new subtypes of OCA.

## Abbreviations

CHS : Chediak-Higashi syndrome

CVS : Chorion villus biopsy

DOPA : L-dihydroxy-phenylalanine

HPS : Hermansky-Pudlak syndrome

OA : Ocular albinism

OCA : Oculocutaneous albinism

WS2 : Waardenburg Syndrome type II

## Competing interests

The author(s) declare that they have no competing interests.

## Authors' contributions

All authors contributed to a draft of the manuscript and were subsequently involved in revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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# Rare disease emerging as a global public health priority

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The genomics revolution over the past three decades has led to great strides in rare disease (RD) research, which presents a major shift in global policy landscape. While RDs are individually rare, there are common challenges and unmet medical and social needs experienced by the RD population globally. The various disabilities arising from RDs as well as diagnostic and treatment uncertainty were demonstrated to have detrimental influence on the health, psychosocial, and economic aspects of RD families. Despite the collective large number of patients and families affected by RDs internationally, the general lack of public awareness and expertise constraints have neglected and marginalized the RD population in health systems and in health- and social-care policies. The current Coronavirus Disease of 2019 (COVID-19) pandemic has exposed the long-standing and fundamental challenges of the RD population, and has reminded us of the critical need of addressing the systemic inequalities and widespread disparities across populations and jurisdictions. Owing to the commonality in goals between RD movements and universal health coverage targets, the United Nations (UN) has highlighted the importance of recognizing RDs in policies, and has recently adopted the UN Resolution to promote greater integration of RDs in the UN agenda, advancing UN's commitment in achieving the 2030 Sustainable Development Goals of "leav[ing] no one behind." Governments have also started to launch Genome Projects in their respective jurisdictions, aiming to integrate genomic medicine into mainstream healthcare. In this paper, we review the challenges experienced by the RD population, the establishment and adoption of RD policies, and the state of evidence in addressing these challenges from a global perspective. The Hong Kong Genome Project was illustrated as a case study to highlight the role of Genome Projects in enhancing clinical application of genomic medicine for personalized medicine and in improving equity of access and return in global genomics. Through reviewing what has been achieved to date, this paper will provide future directions as RD emerges as a global public health priority, in hopes of moving a step toward a more equitable and inclusive community for the RD population in times of pandemics and beyond.

KEYWORDS

**rare disease, genomic equity, diversity, public health priority, inclusiveness, Hong Kong Genome Project**

## Introduction

Rare diseases (RDs) are an emerging public health priority. RD refers to a disease that affects a small number of people in a population (1). There are 6,000–8,000 unique RDs identified, with approximately 80% being genetic in origin, and 50–75% being pediatric onset (1–3). They are often chronic, progressive, and debilitating, and can lead to significant morbidity and mortality (4). With RDs' nature being heterogeneous, complex, and individually rare, they are difficult to be diagnosed, and are challenging to be assessed in aggregate. Currently there is no universal definition for RDs, with differing prevalence among different parts of the world. The European Union Regulation on orphan medicinal products defined RDs as conditions affecting <50 per 100,000 individuals in the European population (5), whereas the American Orphan Drug Act defined RDs as conditions affecting <200,000 individuals in the United States (6, 7). Other definitions have been proposed by different jurisdictions, ranging from five per 100,000 to 76 per 100,000 individuals, with the global average being 40 per 100,000 individuals (Figure 1) (8–10).

Although individually rare, the collective number of people affected by RDs was equivalent to the population of the world's third largest country (11). A recent global RD prevalence based on 3,585 RDs was estimated to be 3.5–5.9% of the world's population, which corresponds to 263 to 446 million people worldwide (10). When the impact of RDs extends to family members and carers of the RD patient, it was expected that RDs affect approximately 1.05–1.4 billion people globally (12).

Long diagnostic odyssey, lifelong disabilities, lack of compensatory support, and few but costly effective treatments are some of the unmet needs that plagues the lives of RD patients (13, 14). The various disabilities arising from the disease as well as diagnostic and treatment uncertainty have been demonstrated to have detrimental influence on the health, psychosocial, and economic aspects of the lives of the RD families (15, 16). In 2019, Rare Diseases International released a position paper emphasizing the need for universal health coverage (UHC) policies to account for RDs, owing to the commonality in goals between RD movements and the UHC targets (17). The United Nations (UN) political declaration on UHC has recognized the RD population as a marginalized group that should be considered during healthcare planning, claiming that UHC "shall never be fully attained nor realized if persons living with RDs are left behind and their needs left unmet" (17). Despite the significant challenges faced, under allocation of resources and inadequate healthcare planning for the RD population remains prevalent (13).

Abbreviations: NHGRI, National Human Genome Research Institute; NIH, National Institutes of Health; RD, rare disease; RNA Seq, RNA sequencing; WES, whole-exome sequencing; WGS, whole-genome sequencing.

## Challenges experienced by the RD population

While RDs are individually rare, there are common features across the range of RDs and common challenges experienced by the RD population. Unmet medical and social needs of RD patients, families, and carers exist globally. Approximately half of the individuals with suspected RDs are undiagnosed, while RD patients who have received a diagnosis encounter fundamental myriad challenges due to delays or incorrect diagnoses, treatment, care, and social acceptance (18).

From the individual's perspective, long diagnostic odyssey often plagues the lives of RD patients. In Europe, 25% of the RD patients had to wait between 5 and 30 years from disease onset to receiving a genetic diagnosis for their condition, and 40% had initially received multiple misdiagnoses, leading to ineffective and unnecessary medical management (19). In another survey of RD families from the United Kingdom and United States, patients typically visit eight physicians and receive two to three misdiagnoses prior to receiving a correct genetic diagnosis, which spanned over a period of 5.6–7.6 years (2, 20). Not only do the individuals endure years of diagnostic odyssey, but it is also expensive for the health systems to undergo a succession of unnecessary medical follow-ups and conventional diagnostic approaches.

Undeniably, a genetic diagnosis offers the potential for personalized medicine, yet opens another door of challenges in treatment availability, accessibility, and affordability. With RDs being heterogeneous and individually rare, interventions and therapies, including orphan drugs, are seldom available due to the lack of market incentives and small market opportunity for the biopharmaceutical industry (21, 22). Currently, <3% of diagnosed RDs have a suitable drug treatment (21, 23); it was estimated that fewer than one-tenth of RD patients have received disease-specific treatment globally (24). Where a treatment has been approved for a RD, cost of the drug is generally extremely costly, with RD drugs reported to be as high as 13.8 times more than conventional drugs (21, 23). This can be financially overwhelming for many, especially when RD drugs usually require out-of-pocket (OOP) cost-sharing by the patient. Consequently, RD patients may need to bear the catastrophically high OOP expenditure on health services and resources, posing a higher risk of financial hardship. For patients who are not able to afford the extremely costly therapies, they will continue to be managed with conventional approaches, adding to the never-ending socio-economic costs of RDs. Accessibility also remains to be a problem, with access and reimbursement recommendations on the same intervention varying vastly across jurisdictions.

From a wider socio-economic perspective, both patients and carers have highlighted the challenges in maintaining

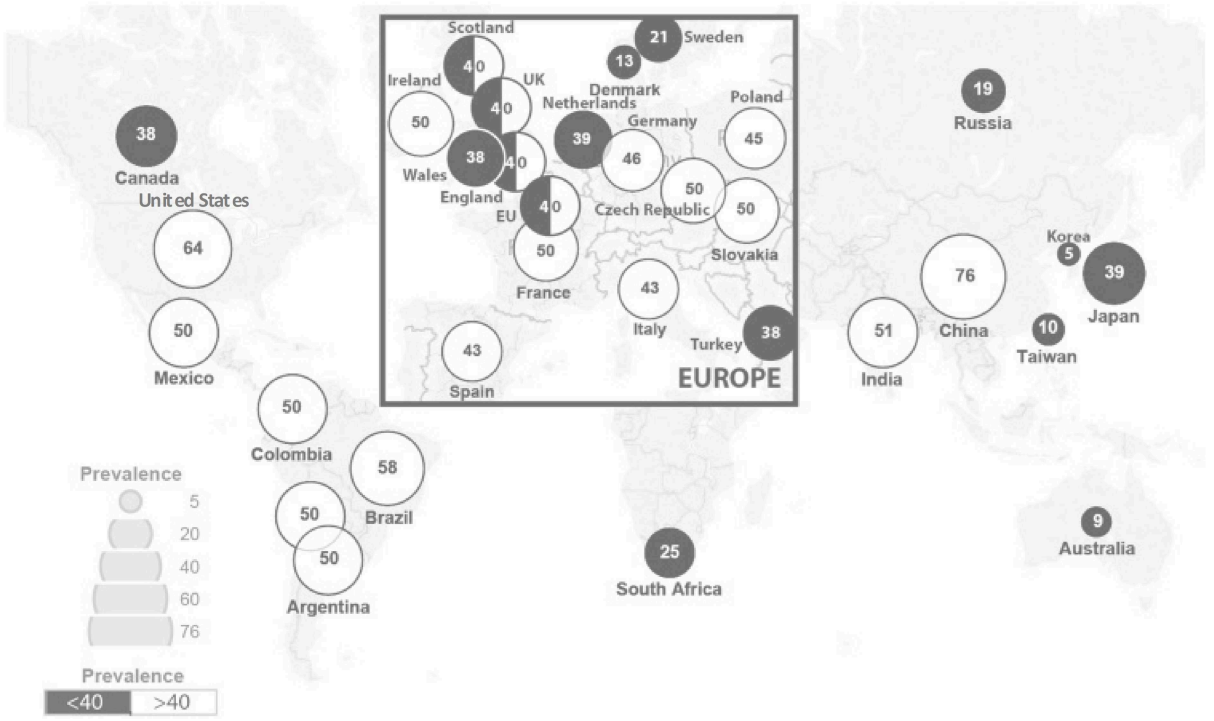


FIGURE 1
RD prevalence per 100,000 across jurisdictions [adapted from Richter et al. (9)].

employment and education due to frequent medical follow-ups and the unprecedented and uncertainty nature of their condition (25–28). In the United Kingdom, 66% of the RD patients and carers indicated that their ability to hold paid employment was affected, with many of them being forced to retire early or reduce working hours due to the condition or the related caring responsibilities (25). Importantly, a significant number of RD patients and carers were forced to reduce working days or quit their job completely by their employer because they were considered as "unreliable." These ultimately manifest as significant opportunities and productivity loss, and can be a burden for the RD patients, families, and the society as a whole. Due to social discrimination and stigmatization, low social awareness, and lack of knowledge and understanding from the general public, both RD patients and carers often feel isolated and excluded from the society (29). As such, the RD population experience extraordinary healthcare, psychosocial, and economic burden, contributing to the decreased wellbeing and quality of life.

Despite the collective large number of patients and families affected by RDs internationally, the general lack of public awareness and expertise constraints have neglected and marginalized the RD population in healthcare systems and in health- and social-care policies.

## Challenges in funding treatments and therapies for RDs

In the era of resource and budget constraints, health economic evidence plays a critical role in guiding decision makers to prioritize and allocate resources efficiently and effectively. Although cost-effectiveness and cost-utility analyses are often considered to be more useful in informing health and social care decisions, as they take account into both costs and outcomes simultaneously as compared to other option alternatives, such types of analyses are relatively difficult to be conducted within the RD population. This is due to the limited intervention alternatives that are available in the market, the small number of patients that can be recruited into clinical studies, and the conflicting ethical considerations for funding RD treatment (21, 22, 30, 31). Orphan drugs and RD interventions are often considered to be cost-ineffective against standard cost-effectiveness thresholds, such as the £20k – £30k (US$26k–$39k) per quality-adjusted life year (QALY) threshold proposed by National Institute for Health and Care Excellence (NICE), due to treatment's epidemiological and economic specifics (31, 32). Future health technology assessments concerning epidemiological, clinical, and economic evidence are warranted for assessing and appraising RD treatment and medications at a territory-wide or national level (31).

Genomic medicine challenges conventional health economic evaluation paradigms, which fails to capture the multi-dimensional outcomes that genomic medicine generates. Some health economists and ethicists have argued for an adjusted threshold for the RD population, such as the £78.3k (US$102.4k) per QALY threshold at the RD mid-point population and £937.1k (US$1,225.9k) per QALY for ultra-rare orphan drugs, based on the principles of equity and "veil of ignorance" (22, 33–35). Nevertheless, the adjusted threshold does not fully encompass the challenges associated with rarity. While the QALY can be a useful measure to evaluate health-related quality of life and survival, its simplicity in methodological calculation does not capture multi-dimensional patient benefits. The QALY is only one of the many elements of value in the "value flower" proposed by Lakdawalla et al., which could all contribute to how a healthcare intervention is valued (36). Elements such as the severity of disease, insurance value, real option value, and equity, are particularly relevant and important for RD therapies and should also be considered (37). Others have proposed that efficiency assessments such as cost per QALY should not be employed when the alternative choice is between an only treatment and no treatment (35). On the other hand, the multi-criteria decision analysis approach is proposed to provide more transparent and inclusive evidence in identifying and combining the relative importance of different criteria and stakeholder perspectives in a single health technology assessment for RD therapies, with the aim of balancing evidence among different stakeholders. More recently, the new NICE methods and processes for technology appraisals have been adopted in February 2022, with some of the changes made of particular relevance to determining the value of RD therapies. These include consideration of disease severity, different types of evidence including qualitative and expert elicitation, flexibility to accept uncertainty in specific situations, and commercial and managed access. It is recommended that NICE appraisals should consider the degree of need and desirability to promote innovation in addition to the clinical effectiveness and value for money. Health system's obligations for equality and human rights must also be considered. Flexibilities should be adopted rather than strictly following the cost-effectiveness threshold. These provide an innovative and sustainable framework to assess and appraise RD interventions. In the future, decision makers and health authorities should take account into the spill over effect, the broader social value of RD treatment and intervention, and their potential and innovativeness for other non-rare cases (31).

## RDs under the COVID-19 pandemic

The current Coronavirus Disease of 2019 (COVID-19) pandemic remains to be an unprecedented global health challenge due to its persistent spread and unpredictable clinical course. As of August 23, 2022, over 595.1 million cases were confirmed and over 6.4 million deaths were reported across 222 jurisdictions since the outbreak of COVID-19 in December 2019 in Wuhan China (38). The pandemic has reminded us of the critical need of addressing the systemic inequalities in the determinants of health and illnesses, including genomic, social, and environmental factors, which has resulted in widespread disparities across populations and jurisdictions. This highlights the paramount importance of engaging a more diverse and inclusive research workforce, including the RD population.

The COVID-19 pandemic has further perpetuated and exacerbated the unmet needs and challenges experienced by the RD community, regardless of whether they were infected with COVID-19.

First, RD has been identified as a risk factor for COVID-19 related mortality. While RD patients had a similar rate of COVID-19 infection as the general population, Chung et al. reported that RD patients were associated with an adjusted 3.4 times odds of COVID-19 related hospital mortality compared to the general population in Hong Kong (95% CI 1.24–9.41; $p = 0.017$) (39). Similar findings were observed in a retrospective cohort study in Genomics England 100k Genomes participants, in which RD patients were found to have a 3.5 times odds of COVID-19-related deaths compared to the unaffected relatives (95% CI 1.21–12.2), although the effect was insignificant after adjusting for age and number of comorbidities (OR 1.94; 95% CI 0.65–5.80) (40). COVID-19-related mortality was not confined to one specific group of RD patients, as suggested by both studies. Results from these studies suggested that RD as a group is a pre-existing comorbidity that is associated with COVID-19-related mortality, and should be considered in healthcare prioritization (39, 40).

In addition to RD patients who were infected with COVID-19, patients without infection had also experienced enormous and multifaceted challenges during the pandemic. Interruptions of care, particularly delays and cessation of diagnostic workups, therapies, rehabilitation, surgeries, and medications, pose substantial impact on the health and social wellbeing of the RD patients. Genetic laboratories and hospitals were required to provide urgent services only, to focus manpower and resources on combating COVID-19. In the United Kingdom, referrals to Clinical Genetics Service fell over 50% during April to June 2020 as compared to the same period in 2019 (41). Request for genetic testing such as microarrays, which is often the first line genetic diagnostic test for patients with suspected undiagnosed genetic disease, was markedly reduced (41). There was also substantial decrease in the number of other diagnostic tests performed, including echocardiograms, radiological investigation, and gastroscopies (41). The pandemic has disproportionately exacerbated the problem of diagnostic delay for RDs, affecting all points on the path to diagnosis, from initial engagement with health services, referral for investigation or specialist assessment, to the availability of definitive testing and registering with patient advocacy groups for support. In addition to the significant drop

in RD diagnosis, health service utilization was also substantially affected. In Hong Kong, over 70% of the RD patients had reduce health service utilization during the pandemic (42). Importantly, health status was affected in 46% of the patients due to reduced service provision. Psychological health and rehabilitation were affected in 79% and 78% of the patients respectively, especially among patients who are severely or totally dependent according to the Barthel Index for Activities of Daily Living (42). Moreover, patients' social life, daily living, and financial status were also severely impacted by the COVID-19 pandemic, affecting 92%, 89%, and 81%, respectively (42). Almost 60% of the patients reported increased expenditure during the pandemic, while 56% of the patients experienced reduction in household income, indicating the magnified financial burden on the RD population (42). Similar patterns were also identified in other cohorts in the West, all highlighting the significant repercussion of the pandemic on regular healthcare service, physical and psychological health, and financial status of the RD population (43–47). The COVID-19 pandemic has inspired and accelerated the adoption of telemedicine and telehealth in some parts of the world (43, 48). Future implementation of telemedicine into the healthcare systems may serve as a sustainable healthcare delivery model beyond the COVID-19 pandemic.

For carers of the RD patients, lifelong caring has posed substantial psychological and financial burden in the best of times, and these challenges have been further exacerbated during the COVID-19 pandemic. In a study by Fuerboeter et al. to assess the mental health and overall quality of life in parents of children with rare congenital surgical diseases in Germany, the parents, especially mothers, reported severe psychosocial impairment during the pandemic (49). Parents of the RD patients had a significantly lower quality of life than parents in the control group, potentially due to the lockdown measures imposed, daily care for the patient, work-from-home measures, and the concerns of their children being at a higher risk of infection after surgeries (49). This study highlighted the need to provide support and raise awareness for parents in addition to the RD patient *via* a family-centered approach, especially during difficult periods such as the era of COVID-19 pandemic.

Besides RD patients and carers, the pandemic has also brought unprecedented challenges to RD patient organizations internationally. A multinational cross-sectional study was conducted to evaluate the impact of the COVID-19 pandemic on 80 RD organizations across 10 jurisdictions in the Asia Pacific region, namely Australia, Hong Kong, India, Japan, mainland China, Malaysia, New Zealand, the Philippines, Singapore and Taiwan (48). The study found that almost 90% of the patient organization representatives were concerned about the pandemic's impact on their organizations. In particular, over 60% and over 40% of the participants have highlighted reduction in organization capacity and funding as their biggest challenges during the pandemic respectively (48). They have also experienced difficulties in supporting their members as physical interactions were restricted. Importantly, patient group representatives underpinned the need to move toward a digitalised era, both in organization operation and healthcare, especially amidst confinement measures. In particular, operation of RD patient organizations in Australia and New Zealand were not impacted or were less affected by the pandemic as they had greater digital capacities and have digitalised their operations prior to the pandemic (48). The pandemic has brought myriad challenges to the RD patients and organizations, yet has also created opportunities by accelerating the adaption of tele-operation and telehealth, complementing face-to-face visits and consultations.

The current COVID-19 pandemic has highlighted and exposed the long-standing and fundamental challenges and healthcare needs of the RD population. The healthcare, social care, economic, and organizational challenges experienced by the RD community indicate the importance of ensuring adequate and continuity of diagnostic and priority management strategies for RDs during pandemics and beyond.

## RDs: A global public health priority

The challenges arising from the nature of RDs have led RDs to emerge as a global public health priority. Unprecedented global integration of RD research is crucial to raise awareness, enhance understanding, accelerate diagnosis, and improve treatment for RDs. Recognizing its importance, the International Rare Diseases Research Consortium (IRDiRC) was established in 2011 to facilitate international collaboration between public and private sectors, and among stakeholders active in RDs research across government research funding bodies, companies, academia, and patient advocacy organizations around the world (50, 51). The IRDiRC have set out three 10-year goals for 2017 to 2027, with the vision to enable RD patients to achieve an accurate diagnosis, and to receive appropriate care and available therapy within 1 year of seeking medical attention (50). The three IRDiRC goals are:

- To provide all individuals with suspected RDs who have seek medical attention with a diagnosis within 1 year if the RD is reported in medical literature; and to put those who remain undiagnosed in an international coordinated diagnostic and research pipeline;
- To approve a thousand new therapies for RDs, with the majority focusing on RDs without approved options; and
- To develop new methodologies for assessing the impact of RD diagnoses and therapies.

The three IRDiRC goals mainly target the healthcare challenges of RDs, with the overarching aim being to galvanize the broad RD community to enable universal diagnosis and treatment, to ensure that the programmes and interventions can reach RD patients and families, and to pose the intended

positive impact on the health and wellbeing of the RD population (50, 51).

Recognizing the importance of promoting inclusion and protecting the human rights of the RD population, EURORDIS, Rare Disease International, and the Committee on Non-Governmental Organizations (NGOs) for RDs, together called for a UN Resolution for RDs in 2019, urging the 193 UN Member States of the General Assembly to adopt the Resolution by the end of 2021. This campaign targets the RD patients and families by recognizing and addressing their needs and challenges, which aims to promote greater integration of RDs in the agenda of the UN, and advances UN's commitment in achieving the Sustainable Development Goals (SDGs) of the 2030 Agenda, with the endeavor to "leave no one behind." The UN resolution has five key asks:

- Social inclusion and participation of RD patients and families;
- Universal and equitable access of quality healthcare without having to experience financial hardship;
- Promotion of RD strategies and actions at a national level;
- Integration of RDs into UN programmes, agencies, and priorities; and
- Routine publication of UN reports for resolution progress monitoring.

The Call for UN Resolution has promoted research and global coalition to tackle the socio-economic challenges of the RD population. The UN resolution was subsequently adopted on December 16, 2021 (52); this is an important milestone toward greater awareness and recognition for the RD community, allowing implementation of international policies to address the needs and challenges of the RD population.

## The state of evidence in addressing the challenges of the RD population

National and international stakeholders across academia, health systems, governments, funding bodies, NGOs, and patient advocacy organizations have set out research projects and programmes to tackle the challenges experienced by the RD population, contributing to achieving the three IRDiRC goals and the five UN Resolution key asks. There has been tremendous progress in RD research over the past decade, especially in RD diagnoses and gene discoveries, achieved by the advancement in genomic technologies. Positive trend in RD-related therapeutic development was also observed, with the IRDiRC's 2020 goal for 200 new therapies being achieved in early 2017, three years ahead of the agenda (50). The socio-economic burden of RDs is harder to gauge and is rather limited in literature, given the collective number of unique RDs identified and the lack of standardized methodologies to collect related data.

### Improving RD diagnoses and its implications

Traditionally, making a diagnosis is particularly challenging due to the heterogeneity and the rarity of each of the 6,000–8,000 RDs, multisystemic involvement, and pleiotropic manifestations (53–55). In the era of genomic medicine, our understanding on RDs has been transformed by the rapid expansion and translational application of next-generation sequencing (NGS) technologies in the past decade. NGS technology utilizes massively parallel sequencing methods to simultaneously and comprehensively sequence multiple genes, the entire protein-coding region of the genome (the "exome"), or the entire human genome (56). The diagnostic capacity of whole-exome sequencing (WES) and whole-genome sequencing (WGS), both NGS approaches, were shown to be effective over conventional diagnostic approaches across multiple studies in different populations. In a meta-analysis including 37 studies and comprising 20,068 children, the pooled diagnostic rates among WES and WGS were found to be 0.36 (95% CI 0.33–0.40, $I^2 = 83\%$) and 0.41 (95% CI 0.34–0.48, $I^2 = 44\%$), respectively, higher than the conventional diagnostic method of chromosomal microarray (0.10, 95% CI 0.08–0.12, $I^2 = 81\%$) (57). In critically ill patients with urgent needs, previous clinical studies have illustrated the vast amount of potential of rapid WES (rWES) and rapid WGS (rWGS) in diagnostic capacity, speed, and clinical utility in acute care (53, 58–60). The diagnostic capacity of rWES and rWGS was corroborated by findings from 18 studies comprising 1,049 patients from different countries, combined as part of a meta-analysis, with the pooled diagnostic yield being 0.43 (95% CI 0.36–0.50, $I^2 = 80.7\%$) (61). The successful application of WES and WGS in diagnosing patients with RDs in different settings has also allowed new gene discoveries over the years since its introduction in 2010 (Figure 2) (62, 63). The speed of new gene discoveries has been increasing substantially, with discoveries made by WES and WGS almost tripled the discoveries made by conventional methods since 2013 (62).

More importantly, WES and WGS offer the potential for the development of pragmatic, phenotype-driven management with genotype-differentiated personalized treatment (64). Personalized medicine, according to the National Human Genome Research Institute (NHGRI), was defined as an emerging practice of medicine that utilizes an individual's genetic profile to guide clinical decision-making in disease prevention, diagnosis, and treatment (65). WES and WGS have the potential to impact diagnosis-predicated clinical management, often referred as clinical utility, which includes but not limited to referral to specialists, surveillance for potential future complications, lifestyle changes, and indication or contraindication of investigations, procedures, surgeries, and medications (61, 66). In the meta-analysis by Clark et al. that included four WGS studies and 12 WES studies with

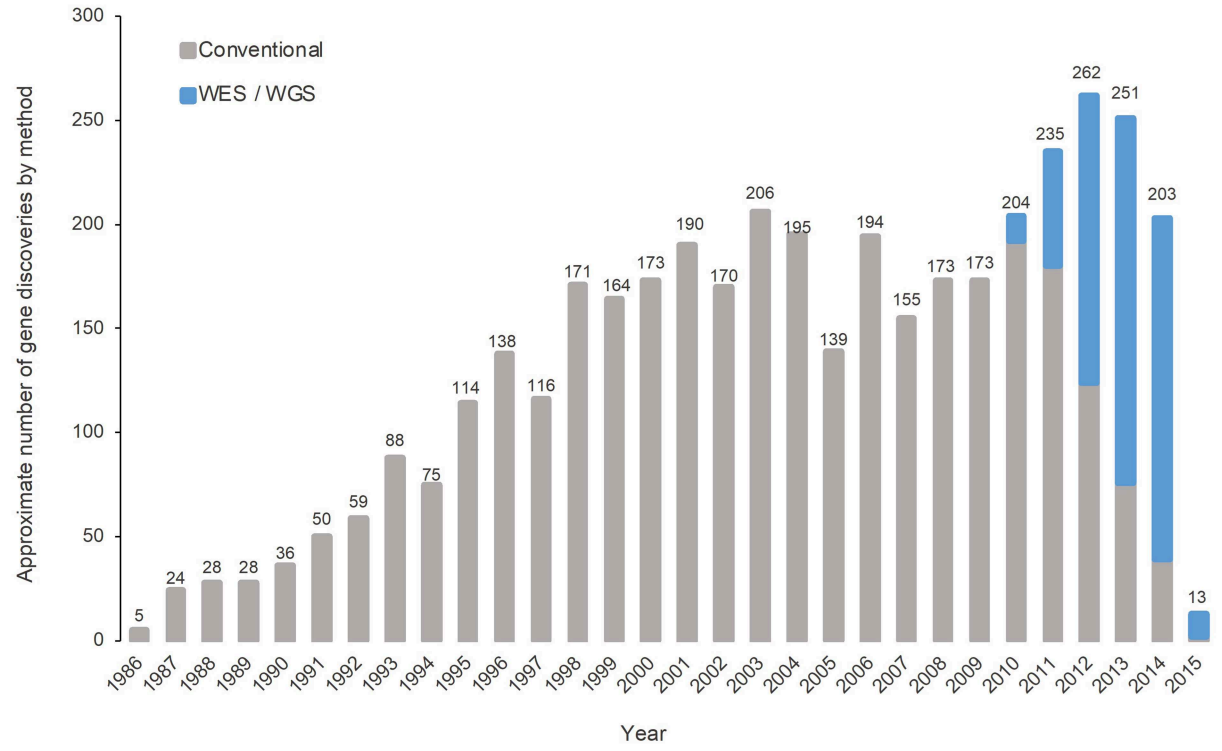


FIGURE 2
Number of gene discoveries made by WES/WGS compared with conventional diagnostic methods [adapted from Chong et al. (62)].

data on clinical utility, 27% (95% CI 17–40%, $I^2 = 54\%$) and 17% (95% CI 12–24%, $I^2 = 76\%$) of children with genetic diagnoses had subsequent changes in their clinical management respectively (57). Early and rapid adoption of rWES or rWGS within a median of two to three weeks of results turnaround time could potentially impact clinical management promptly and profoundly, thus improving patient's clinical outcome and quality of life, and reducing morbidity and mortality (58–60, 67). In the intensive care setting of the National Health Service (NHS) of the United Kingdom, the use of rWGS led to changes in clinical management in 65% of the diagnosed patients (60). Chung et al. investigated the diagnostic utility of rWES and rWGS as a meta-analysis, and illustrated that genetic diagnoses could impact clinical management in up to 100% of the diagnosed patients in some cohorts (61). A rapid and timely genetic diagnosis is particularly important among critically ill patients with urgent needs, as it is potentially lifesaving.

The implication of RD diagnoses is beyond that on patients. In the era of resource and budget constraints, the evaluation of economic implications of providing WES and WGS within clinical settings has a principal role in informing efficient and effective healthcare resource allocation. Despite the high unit costs of WES and WGS, studies have demonstrated the cost-effectiveness of WES and WGS across clinical settings (68–72). On the other hand, health-economic evidence of rWES and rWGS is rather limited, with the fact that parallel comparison of rWES/rWGS and conventional diagnostic methods is more challenging due to the critical and urgent clinical setting that requires immediate clinical management decisions. Studies however illustrated the potential of rWES and rWGS to reduce healthcare costs, with costs being saved in the avoidance of unnecessary investigations, procedures, hospitalisations, and medications (58, 59, 61). In particular, Stark et al. reported a cost-saving of AU$543,178 (US$408,090) from avoidance of planned procedures and hospital days using rWES in Australia (59). In Hong Kong, Chung et al. demonstrated a reduction of 566 hospital days and a cost-saving of HK$8 million (US$1.03 million) from clinical management changes using rWES (61). In the United States, Farnaes et al. illustrated a net cost-saving of US$128,555 from reduced inpatient days using rWGS (58). Available evidence shed light on the consideration of integrating WES/WGS into clinical workflows to enable precision medicine and reduce healthcare costs.

The importance of an early genetic diagnosis for RD patients was demonstrated and highlighted in many of the previous studies, contributing to and reinforcing the 10-year

| Benefits of a diagnosis | Details |
|---|---|
| Certainty | The power of ending the diagnostic odyssey by identifying the underlying cause of a condition, including improved prognostication. |
| Change in clinical management | Initiation or contraindication of investigations, procedures, surgeries, and medications, with the potential to save time, resources, and cost. |
| Targeted follow-up and surveillance | Access to improved or best practice medical care, with the potential for early identification of potential future complications. |
| Clarify recurrence risk | To increase certainty and restore reproductive confidence. |
| Reproductive choices | Provides additional reproductive options for prenatal or pre-implementation genetic diagnosis. |
| Reduced isolation | Offers the possibility of connecting to other patients and families with the same diagnosis for shared experience. |
| Access to social and educational services | Access to special social and educational services and allowances targeting specific groups of RDs. |
| Better understanding of RD epidemiology | Provides a more comprehensive picture of the epidemiology of RDs in a jurisdictions, thereby aiding RD policies and service planning. |
| Targeting health disparities | Potential to identify health disparities by comparing service and resource utilisation patterns across different RDs. |

FIGURE 3
Benefits of an early genetic diagnosis [adapted from Tan et al. (73)].

goal of IRDiRC to provide an early definitive molecular diagnosis within 1 year of medical attention (50, 63). An accurate genetic diagnosis is the first step in managing the RD properly, allowing the identification of useful resources and treatment for the best possible clinical outcome for patients. The diagnosis-predicated changes in management not only improved clinical outcomes for patients, but could also lead to net cost-savings, stressing its multi-level significance. In addition to the immediate clinical changes and associated cost-savings from a rapid genetic diagnosis, an early genetic diagnosis has the power to aid better understanding in RD epidemiology and target health disparities, which all act as strong advocacies for the RD population (Figure 3) (73). It also contributes to existing literature and provides empirical evidence for better health- and social-care planning, such as implementation of population-wide sequencing and prevention strategies (74).

## Socio-economic costs of RDs

The societal impact of RDs has an economic dimension. In literature, majority of the economic evidence was based on individual RDs that are relatively "common," while recent studies accounting for a wider range of RDs often quantify direct healthcare costs from a health system perspective due to the lack of standardized methodologies to collect cost-related data beyond health administrative dataset for the RD population (15, 75).

The largest study to date, estimated healthcare utilization and related costs across 1,600 RDs from a health system perspective in the United States. The study highlighted the disproportionately higher number of inpatient stays, readmissions, emergency visits, and the related costs of the RD population as compared to other common conditions (76). Similarly, the direct immediate healthcare burden of RDs was also estimated in studies conducted in Australia, Hong Kong, Shanghai, and Taiwan (77–81), suggesting the high direct healthcare costs in the RD population.

Although often neglected and rather challenging to estimate, it is also extremely important to evaluate and estimate the direct non-healthcare and indirect economic consequences for healthcare and related planning, especially in a chronic disease population. With RDs often being medically devastating and life-threatening, unpaid informal carers, usually a family member or a friend of the patient, play an extremely important role in supporting and assisting the patient's daily healthcare and social needs. This harbors a unique set of challenges and burden in RD carers, which encompasses coordination of care as well as helping with daily activities, both of which have spill over effects onto the carers' own personal lives, especially work responsibilities. The nature of RDs thus potentially inhibits patient's and carer's participation and integration into society, resulting in significant productivity loss, posing financial constraints for the RD family in addition to the substantial medical costs that often requires cost-sharing by the patient (82). On the other hand, many of these carers, usually both parents of the patients with RDs, have to sustain family's financial income by staying in the workforce. Therefore, paid carers, such as live-in domestic helpers, are commonly hired as an alternative to provide formal care support. This is particularly prevalent in Asia, such as the case in Hong Kong. In fact, previous evidence has demonstrated that direct non-healthcare and indirect costs of RDs (including paid and unpaid carers) are higher than direct healthcare costs of RDs, reflecting the importance to consider the broader socio-economic consequences of RDs in health- and social-care policies (16).

As highlighted by a meta-analysis published in 2021 that identified 19 studies in literature, economic evidence from a wider societal perspective has been very limited, with majority of the evidence focusing on individual RDs (75). Almost all of the identified studies were conducted in European populations, with many of them collected as part of the "Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe" (BURQOL-RD) project series, which estimated the costs of 10 relatively "common" RDs across eight jurisdictions in Europe (15, 83–92). The results undoubtedly aided understanding on the patterns of resource use and areas that require prioritization, supporting appropriate healthcare planning for these 10 RDs. Nevertheless, the 10

selected RDs may be insufficient to encompass the heterogeneity and differential impacts of the 6,000–8,000 known RDs. It is important to note that the economic impact of RDs that are relatively "rare" was never reported in literature, due to the challenges in patient recruitment. Recently, the EverydayLife Foundation has published a report that estimated the costs of 379 RDs in the United States from a societal perspective, which was found to be US$62,141 per patient per year (16). In 2019, the national cost of RDs in the United States totalled US$966 billion (non-healthcare and indirect costs accounting for 56.7%), significantly higher than the costs estimated for some of the most expensive chronic illnesses, including cancer, diabetes, and heart disease as indicated by the Centers for Disease Control and Prevention (CDC) (16). Although only 379 of the 6,000–8,000 RDs were included for estimation, to the best of knowledge, this represents the only and the most comprehensive study to evaluate the socio-economic burden of RDs as a collective group.

In addition to the high societal costs of RDs, it was anticipated that the disproportionately high service and resource needs, and the RD-related productivity loss might pose significant financial burden on the RD families, putting them at a higher risk of experiencing financial hardship. Only two studies have attempted to evaluate the proportion of financial hardship brought about by extremely high OOP health expenditure in the RD population to date, one being in China where the authors have estimated the rate of catastrophic health expenditure (CHE) across seven RD groups (93), and another study being in Turkey where the authors estimated the CHE incidence mainly in patients with metabolic and neuromuscular diseases (94). These two studies have reported very different rates of CHE at different thresholds (0.0015–0.1670% vs. 47.35%), reflecting the differences in healthcare and social care contexts, and the availability and accessibility of resources across jurisdictions.

## Health-related quality of life of the RD population

The impact of RDs can also be determined by quantifying patient's health-related quality of life (HRQoL). HRQoL is defined as "an individual's perception of his/her living quality, encompassing physical, mental, and social wellbeing" (95). Most RDs are typically chronic, progressive, degenerative, and life-threatening, with effective drugs being costly and scarce. Social exclusion and discrimination based on RD health conditions further depletes available resources for coping with RDs (27). It is therefore crucial to identify and understand the impact of disease and social related difficulties on the quality of life of RD patients. Previous studies have attempted to investigate the HRQoL of the RD population in more than one RD group, and have highlighted the significantly lowered HRQoL as compared to the general population (15, 28, 95, 96). In particular, the meta-analysis by Ng et al. included four studies comprising 2,079 RD patients and demonstrated a pooled utility score of 0.57 (95% CI 0.48–0.66), consistently lower than that of the general public (95). Importantly, Ng et al. has also demonstrated the "spill over effects" on carers' HRQoL in Hong Kong. Lifelong caring, high dependency of patient, and economic strain are all factors that contribute to the decreased wellbeing of patient family members and carers. In Hong Kong, both RD patients (mean utility score of 0.53) and their carers (mean utility score of 0.78) reported lower utility scores than the general population (mean utility score of 0.92) (95). More strikingly, they reported utility scores even lower than that of patients with other chronic illnesses, including patients with heart disease (0.88), hypertension (0.88), diabetes (0.87), and cancer (0.87), reflecting the disproportionate impact of RDs on healthcare and social wellbeing (95, 97, 98).

## The role of Genome Projects in advancing genomic medicine

The importance of generating greater representation and diversity across genomic datasets is becoming more widely recognized. Initially, genetic research and genomic databases were biased toward data from Caucasians, particularly of European ancestry. In 2009, 96% of genome-wide association studies were of European descent (99). Groups of other ancestries were very poorly represented. The lack of ethnic diversity in genomics was limiting the usefulness of genomic technologies and widening inequalities across different populations. To address this, contribution of genomic data of other ethnicities has increased over the past few years, increasing from 4% in 2009 to 19% in 2016 (99).

Besides research, governments have also started to launch Genome Projects in their respective jurisdictions to apply WGS to the study of RDs, and to a lesser extent, cancers and common disorders, at a much bigger population size, or even at a nationwide level, to integrate genomic medicine into mainstream healthcare and to improve global genomic diversity and equity (100).

The government of the United Kingdom has launched the 100,000 Genomes Project in 2013, and it has been a huge success in providing grounds for the NHS Genomic Medicine Service to be the first national health care system to offer WGS as part of routine clinical care for patients with undiagnosed RDs and cancers (101, 102). This has inspired governments worldwide, even in middle-income countries, to launch Genome Projects in their respective jurisdictions, aiming to enhance clinical application of genomic medicine for personalized medicine (Figure 4) (100, 103). In the upcoming years, results from Genome Projects worldwide would potentially enhance our capability to better diagnose and manage RDs, and would provide empirical evidence for implementation of

| Country/Region | Project/Program Name | Expected Sample Size | Project years | NGS technology |
|---|---|---|---|---|
| Australia | Australian Genomics Health Alliance[i] | >25,000 | 2016 – ongoing | Depending on the flagship projects |
| Australia | Genomics Health Future Mission[ii] | 200,000 | 2018 – ongoing (targeted completion in 2028) | Depending on the projects |
| Canada | Canadian Genomics Partnership for Rare Diseases[iii] | Nationwide | 2019 – ongoing | Depending on the projects |
| China | Precision Medicine Initiative[iv] | 100,000–100 million | 2015 – ongoing (targeted completion in 2030) | WGS |
| Denmark | Danish National Genome Center[v] | 60,000 | 2021 – ongoing (targeted completion in 2024) | WGS |
| France | Genomic Medicine France 2025[vi] | 235,000 per year | 2015 – ongoing (targeted completion in 2025) | WGS / WES / RNA seq |
| Hong Kong | Hong Kong Genome Project[vii] | 50,000 | 2021 – ongoing (targeted completion in 2026) | WGS |
| Japan | GEnome Medical alliance Japan[viii] | Nationwide | 2018 – ongoing | WGS |
| Saudi Arabia | Saudi Human Genome Program[ix] | 100,000 | 2018 – ongoing (targeted completion in 2030) | WGS / WES / panel |
| Thailand | Genomics Thailand[x] | 50,000 | 2019 – ongoing (targeted completion in 2024) | WGS / WES / Microarray |
| Turkey | Turkish Genome Project[xi] | 100,000–1,000,000 | 2017 – ongoing (targeted completion in 2023) | WGS |
| United Kingdom | 100,000 Genomes Project[xii] | 100,000 | 2013 – 2018 (completed) | WGS |
| United Kingdom | Our Future Health[xiii] | 5,000,000 | 2020 – ongoing | Depending on the projects |
| United States | NHGRI Genomic Medicine[xiv] | Nationwide | 2011 – ongoing | Depending on the projects |
| United States | NIH Undiagnosed Diseases Program[xv] | Nationwide | 2008 – ongoing | WES / Microarray |

FIGURE 4
Large-scale Genome Projects targeting RDs and undiagnosed diseases (>20,000 subject genomes) (i) (104, 105); (ii) (106); (iii) (107); (iv) (108, 109); (v) (110); (vi) (111); (vii) (112); (viii) (113, 114); (ix) (115); (x) (116, 117); (xi) (118, 119); (xii)(101, 120); (xiii) (121, 122); (xiv) (123); (xv) (124). [adapted from Chung et al. (100) and Chu et al. (103)].

WES/WGS in health systems. More importantly, genomic data across populations, especially those beyond Europe and North America, will together contribute to improving equity of access and return in global genomics.

## Case study: The Hong Kong Genome Project

As discussed above, genomic data of non-European ancestries has been increasing over the years. Genome Projects in Asia for example, are playing a major role in contributing genomic data of Asian ancestry to improve global genomic diversity. In Asia, Hong Kong has a relatively homogeneous Chinese population. The case study of the Hong Kong Genome Project (HKGP) was selected to illustrate the contribution of Chinese genomic data.

In the 7.5 million population in Hong Kong with 94% of the population being Chinese (ethnically speaking, Han Chinese), one in 67 individuals is living with one or more RDs, with 35% being pediatric patients (78, 125). As of 2018, over 470 RDs have been identified in Hong Kong, affecting approximately 1.5% of the population (78). In order to enhance clinical application of WGS to benefit patients and families, particularly the RD population, and to strive for excellence and adherence to international standards, the Hong Kong Genome Institute (HKGI) was established in May 2020 by the former Food and Health Bureau (currently the Health Bureau), Hong Kong Special Administrative Region, to implement the HKGP, with the vision being "to avail genomic medicine to all for better health and wellbeing" (126).

The HKGP, which is implemented in two phases, the pilot phase and the main phase, is the first large-scale genome sequencing project in Hong Kong. It is set to conduct WGS for 20,000 cases with the aim to enhance clinical application of genomic medicine to benefit patients and their families with more precise diagnoses and personalized treatment (126). The pilot phase of the HKGP was launched in July 2021, focusing on undiagnosed diseases and hereditary cancers. Lessons learnt during the pilot phase of HKGP would guide the directions of the Project's main phase, which is set out to be rolled out in July 2022, expanding eligibility to cover other hereditary diseases and research cohorts related to "genomics and precision health."

With WGS being offered as part of the HKGP, it could potentially lead to diagnosis-predicated precision medicine for patients and families, thereby improving patient outcomes whilst minimizing healthcare expenditure and related financial hardships, achieving diagnostic, clinical, and economic utility. In addition to the clinical benefits, the HKGP also aims to advance research, establish infrastructure and protocols, nurture talents, enhance public genomic literacy and engagement, and drive health- and social- care policy measures to pioneer the development of genomic medicine in Hong Kong (126). The potentials and prospects that have emerged in the launching of the HKGP pilot phase were highlighted by Chu et al., providing insights to prepare for the launching of the main phase (103). With HKGP being the first and the largest local clinical genomic database, it creates novel research opportunities for studying various diseases, including RDs, contributing to improving genomic equity in healthcare. With a relatively homogenous population, genomic data generated from the HKGP would contribute to global genomic diversity in the foreseeable future.

## Future directions of RDs

With the three 10-year goals laid out by IRDiRC and the adoption of the UN Resolution in December 2021 to stress the importance of including RD population in the UN 2030 Agenda, great strides have been made in RD research over the past decade, presenting a major shift in the global policy landscape. In particular, previous studies have highlighted the importance of an early diagnosis and the significant consequences of RDs on the living quality and socio-economic burden of patients. It should be recognized that the health, social, and economic implications of RDs are inherently the results of insufficient social support, limited medical expertise, and the lack of public awareness on RDs. As RD emerges as a global public health priority, RD policies and strategies in the sectors of healthcare, social care, insurance, education, and many more, are required to foster a more equitable and inclusive community for the RD population. Progress in RD research and analysis will likely improve all disease understanding in the future. Here, we recommend future action plans for RDs through a patient-centered and multidisciplinary approach, focusing on the implementation of education and training programmes, elimination of discrimination and stigmatization, and global coalition among multi-disciplinary stakeholders.

Firstly, providing education and training to clinicians at the primary, secondary, and tertiary care level is the first step to an accurate genetic diagnosis. Despite the technological advancement and increased data sharing, many RD patients still experience extensive diagnostic odysseys, and some remain undiagnosed. One of the major barriers to obtaining a diagnosis is the lack of knowledge and insufficient training on RDs. According to the National Organization for Rare Disorders (NORD) survey 2019, almost half of the patients and carers identified limited medical specialization to be a major barrier to delays in RD diagnosis (127). Previous studies have shown that many primary care physicians profess low confidence in their skillsets in managing patients with genetic-related issues and in using genetic information to make clinical decisions (128–131). Primary care physicians have identified lack of knowledge and training opportunities to be the major barriers to genomic medicine in primary care (128, 131, 132). Emphasis on further education and training in genomic medicine among medical specialists should be prioritized in order to improve RD diagnosis and management. Continuous technological and technical advancement in genomics is also required to diagnose patients and to transform sequencing information into diagnostic knowledge, such as the application of bioinformatics, analytic algorithm, functional analysis, health informatics, data linkage capability, data sharing, etc. (74, 133). Global network involving full participation by clinicians, researchers, and patients and carers should be formed to tackle the undiagnosed cases (74). International efforts have been made over the years to investigate and diagnose patients who had long sought one without success, such as the initiation of the Undiagnosed Disease Program by the National Institutes of Health (NIH) and the Undiagnosed Diseases Network International (134, 135). The establishment of these programmes and networks have supported global improvements in diagnosis of RDs *via* core principles and implementation methods (74).

Secondly, in addressing the significant socio-economic burden and the lowered HRQoL of the RD population, the government and healthcare system should work together to provide affordable and accessible resources, thereby improving the HRQoL of patients and carers. Previous cost-of-illness studies highlighted the unique and complex challenges the RD population face, providing strong evidence that management of these challenges should be treated differently to other common disease (15, 16, 77–79, 83–92). With RD patients requiring services and care across multi-disciplines, patients often experience frustration in service fragmentation. The implementation of "one-stop" clinics may improve coordination of care through providing various services at a single location, tackling multiple and complex problems simultaneously (29). In France and the United Kingdom, the integration of "one-stop" clinics was shown to improve coordination between services,

providing timely and informed care to the RD population (136). Overall, the utilization of such "one-stop" clinics have yielded better patient outcomes and are more cost-effective and thus, are a possible solution to the high socio-economic burden and the lowered HRQoL of RDs (137). In addition, implementation of reimbursement regulations would improve affordability and accessibility of treatments, potentially reducing the risk of financial hardship of the RD population (138). Other action plans in Australia and New Zealand have also been put forward to support the RD population (139). These aim to reduce the healthcare, social care, and economic burden through empowering, improving diagnosis and intervention, coordinating care and increasing research for RDs.

Thirdly, the government plays a pivotal role in raising awareness and in mitigating discrimination and stigmatization of the RD population. Efforts have been made in different parts of the world to implement Genome Projects to integrate genomic medicine in mainstream healthcare. In order to enhance understanding and mitigate genetic discrimination, unprecedented global coalition is of paramount importance to improve inclusivity of the RD population. Previous studies have demonstrated participants' concerns on genetic discrimination in the context of employment and insurance (140–142). In particular, undergraduates in Hong Kong were found to be pessimistic toward unfavorable genetic testing results, with almost 60% of the respondents claiming that they would feel "inadequate or different," 56% would feel helpless, and nearly 60% perceived that they would be disadvantaged in job seeking in case of unfavorable genetic testing results (140). It is of utmost importance to eliminate the root causes of stigmatization and discrimination of the RD population in order to improve social inclusion and reduce opportunities and productivity loss. This can be done through the implementation of anti-discrimination policies such as Genetic Information Nondiscrimination Act (GINA) in the United States to aid assimilation of the RD population into society (143, 144). Legislations in Japan and Taiwan have also incorporated social care services into their RD framework, thereby facilitating the inclusion and integration of the RD population into the society in addition to providing quality healthcare (145). Additional education and awareness for the public on the RDs should also be implemented to increase acceptance and reduce stigma. Both these strategies in conjunction will work toward improving social integration of the RD population, thereby improving their HRQoL and reducing socio-economic burden.

Fourthly, a more widespread utilization of telehealth or telemedicine constitutes a sustainable and alternate model amidst the COVID-19 pandemic and beyond. Telemedicine has the potential to revolutionize patient access to clinical specialists around the world without geographical boundaries. The COVID-19 pandemic has accelerated the digitalisation of healthcare across the world and have inspired healthcare professional licensing agencies to address this in various nations and states. This improves access for all patients in both urban and rural areas, and in both developed and developing countries regardless of their economic status. Adoption of telemedicine into routine clinical care would require innovative approaches to increase capacity and the strengthening of health systems. In the long run, greater reliance on telemedicine is undeniably the way forward, which constitutes a sustainable healthcare delivery model in times of and beyond pandemics.

Finally, RD patient organizations have the power to drive forward the adoption of necessary policies and help to coordinate care (146). Governments should strive to strengthen the public's awareness on the needs of RD populations through in-depth conversations and focus group meetings with patient representatives. On one hand, RD patient groups have important roles in advocating for patients' rights and research opportunity. On the other hand, patient groups are the pillar of psychologic support for patients and their families. The recently adopted ground-breaking UN Resolution led by Rare Disease International, EURORDIS, and the Committee on NGOs for RDs serves as a strong example. It represents a major shift in the global policy landscape, by promoting greater integration and prioritization of the RD population in the UN agenda. Through this global campaign, the needs of the RD community are brought to light, allowing for the development of necessary strategies and plans to provide affordable and accessible care. Acting as the voice of the RD population, RD patient organizations can empower patients and carers alike while raising awareness to educate the community.

Taken collectively, there is a scientific, social, ethical, and political imperative to promote greater integration and inclusiveness of RDs in research and policies, contributing to the goal of the UN Resolution, to "leave no one behind."

## Author contributions

CC and BC contributed to the conception of the review. CC performed the literature review and drafted the manuscript. Hong Kong Genome Project, AC, and BC critically reviewed and revised the manuscript for important intellectual content. AC and BC oversaw and supervised the review. All authors contributed to the overall interpretation, reviewed, and approved the final draft for submission.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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