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CGT Bank v5.4.10

Patient Information

Unique pat id.:	0260201
Patient name:	
Patient DOB:	
Ethnic group:	Caucasian
Indication:	No family history

Sample Information

Sample type:	Blood
Date of draw:	15/07/2025
Date of receipt:	23/07/2025
Report date/time:	05/03/2026

Clinic Information

Clinic:	WeFIV
Doctor:	CAROLINA BOUTEILLER

TEST RESULTS

POSITIVE

The individual is carrier of:

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency

Gene :	CYP21A2	**Allele:**	Het
DNA Change:	NM_000500.9:c.955C>T + CYP21A2 gene duplication	**Inheritance:**	AR
Protein change:		**OMIM phenotype:**	201910
Variant classification:	Pathogenic		

INTERPRETATION OF TEST RESULTS

Typically, a positive result does not have direct clinical consequences for the carrier individual. There is another normal gene copy for all positive autosomal recessive (AR) genes indicated in the table which provides normal biological information. The likelihood of transmission of the variant(s) to offspring is 50%, independent for each variant. If the partner, or gamete donor, screens negative for the pathogenic or likely pathogenic variants in the gene(s) included in the table for this patient, the reproductive risk would be reduced. Please note that family members may also carry the variant(s) reported here, and this information may be significant for them and their offspring.

If a patient and partner, or gamete donor, are both carriers of variants in the same gene associated with AR inheritance, there is a 25% chance that any child they have together would be affected. If a female patient is a carrier for an X-linked condition, there is a 50% chance that each of the reproductive couple's children would also be a carrier. Males would typically express symptoms of the condition, and females are typically unaffected or may display milder symptoms.

For genes with a negative test result, the risk of having children affected by the associated disorders decreases significantly compared to the general population. This also the case for a negative personal result when a reproductive partner or a gamete donor is a carrier for a pathogenic or likely pathogenic variant in one or more of the tested genes. However, due to test limitations associated with any genetic test, this low risk is not zero (see limitations section and informed consent form)

In this individual, we detected two variants in the CYP21A2 gene, located in chromosome 6: (i) three CYP21A2 gene copies are detected during CNV analysis, i.e., presence of gene duplication in one allele; (ii) during sequence analysis, the variant c.955C>T (p.Q318*) is detected. Nevertheless, according to the literature (Pajares et al., 2008), risk of being CAH carrier is low since in about 85% of the cases both variants (c.955C>T and gene duplication) are in cis configuration (in the same chromosome) and then there is still one functional CYP21A2 gene copy in that chromosome 6. Remarkably, having both DNA changes in different chromosomes (trans configuration) will represent a true CAH carrier. Conclusion: most probably this individual is not carrier of CAH. In order to determine if the individual is a true positive (carrier), a separate family analysis must be performed to study both variant's segregation. If the p.Q318X variant and the duplicated gene were inherited from different parent (less than 15% of the times), the c.955C>T (p.Q318*) will represent a true CAH-allele, ie., the individual will be CAH carrier.

TEST DESCRIPTION

The Carrier Genetic Test (CGT) is a preconception DNA screening test that aims to identify individuals and couples at increased risk of conceiving children affected by a monogenic disease. Knowledge of this risk may influence a couple's decision to conceive or encourage the couple to adopt preventive measures, including preimplantation genetic testing for the at risk disease (PGT-M) prenatal genetic testing, or to use donated gametes. The multigene CGT interrogates thousands of DNA variants using a high-throughput technology (Next Generation Sequencing, NGS).

COMMENTS

Report's language has been updated by clinic's request.

TEST METHODOLOGY

DNA is isolated from the sample, usually blood or saliva, and analyzed by whole exome sequencing by NGS. This includes capture and sequence of all human exons and other gene regions of interest where known disease-causing variants are located. Sequencing raw data is then analyzed using bioinformatics (bioinformatic pipeline v3.0), which includes sequence alignment against the GRCh37 human genome reference, variant calling, annotation, and real-time interpretation of variants. QC parameters include, all reported samples that will have a minimum of 7Gb of data, with minimal mean coverage greater than 75x, and a specific depth analysis for more than 68,000 DNA positions where known pathogenic variants are located. In addition, complementary tests (non-NGS techniques) are performed for the following genes, if included, CFTR gene intronic variant/s; SMN1 gene exon 7-deletion; CYP21A2 gene frequent mutations; HBA1 and HBA2 genes frequent deletions; FXN gene GAA repeat sizing; FMR1gene CGG repeat sizing (females only); DMD gene frequent deletions/duplications; F8 gene intron 22 inversion (females only). When requested, CNV analysis by MLPA is performed for CFTR, HBB and HBA1/HBA2. Based on our validations studies, reported samples will have analytical detection rate for SNV variants as per the control sample NA12878 (Control positive); PASS value: NA12878 Sensitivity SNV ≥0.97000).

TEST LIMITATIONS

In the general population, there is a 3-5% risk for birth defects caused by genetic and/or non-genetic factors not detected by this type of test.

Analytically, the CGT test does not cover all known monogenic diseases nor all disease-causing variants for each tested gene. The test does not include the analysis of conditions associated with mitochondrial DNA nor multifactorial nor digenic inheritance. The test does not detect large rearrangements (inversions, deletions and duplications more than 15 nucleotides), variants located in regulatory regions or intronic regions outside the +/-3bp cut off (except if otherwise indicated), or in low sequence coverage areas (<7x). DNA changes caused by trinucleotide repeat expansions are not detected, except those indicated in the methodology section. For copy number variation analysis, when a normal result is obtained (2 copies detected), it is not possible to confirm that one copy is present in each of the two alleles (non-carrier) or if both copies are present in cis on the same allele, with no copies in the other allele (silent carrier). Clinical sensitivity varies among conditions. In particular, the sensitivity for SMN1 is approximately 96% because it is not possible to identify silent carriers among patients with 2 SMN1 copies detected and because point mutations or small indels are not analyzed. The CYP21A2 gene analysis presents unique challenges due to its high sequence homology (~98%) with the pseudogene CYP21A1P, which leads to frequent gene rearrangements and complex mutations. These challenges can cause difficulties in distinguishing CYP21A2 from CYP21A1P, increasing the risk of misdiagnosis. Different testing methods have specific limitations, requiring a combination of techniques such as long-range PCR, Sanger sequencing, next-generation sequencing (NGS), MLPA, and qPCR to achieve accurate results. These challenges and limitations may lead to false or inconclusive results. Therefore, genetic counselling is strongly recommended to evaluate the findings, discuss potential implications, and determine whether additional testing (such as MLPA) is necessary for an accurate diagnosis. In summary, sensitivity to detect pathogenic variants, if they result from complex gene conversion/gene rearrangements events, may be reduced. For the HEXB gene, the common 16 kb deletion that causes disease in 30% of affected patients is not included in CGT analysis. Furthermore, this test does not evaluate the HFE gene.

Then, a negative CGT result significantly reduces but does not completely exclude the possibility of being a carrier of a variant associated with single gene disorders (see residual risk table). The presence of pseudogenes and/or rare polymorphisms and/or homopolymers may lead to false negative or false positive results. In addition, a negative result for the CGT variants does not exclude the possibility of a de novo variant occurring in the offspring. Germline mosaicism or low-level somatic mosaicism cannot be detected. As with any laboratory test, there is a small chance that this result may be inaccurate for a procedural reason such as an error during sample collection, labelling, processing, data collection or interpretation. Please note that the clinical classification of variants can change over time. To check whether there have been any changes to the classification of reported variants, please contact IGENOMIX.

LEGAL/QUALITY

IGENOMIX ARGENTINA S.A will only release the report once a completed test requisition form is received. The clinic/clinician/certified health professional requesting the test is responsible for obtaining and taking custody of "Informed Consent" from the patient as depicted by national guidelines and/or legislation. This test was developed, and its performance characteristics determined by IGENOMIX SPAIN LAB, SLU. It has not been cleared or approved by the US Food and Drug Administration. The test is used as a laboratory developed test for clinical purposes.

Part of this test has been outsourced to a reference laboratory whose Quality Management System is based on high Quality Standards, periodically monitored by Igenomix SPAIN* and audited by independent external groups.

*IGENOMIX SPAIN holds CLIA Certificate of Compliance: #99D2146167.

EXEMPTION CLAUSE OF DIAGNOSTIC LIABILITY

The genetic diagnosis services carried out by IGENOMIX ARGENTINA S.A are exclusively intended to be interpreted by qualified/certified health professionals.

The result obtained by this test and the information that could be derived from it, cannot be considered in any case as substitute of genetic counselling or medical treatment by a trained professional neither represent itself a medical enquiry. We recommend that you consult your physician for genetic testing & counselling upon reception of your results.

Any result should be interpreted in the context of all available clinical findings, within the general context of a medical investigation, which must be conducted by clinically trained professionals. IGENOMIX ARGENTINA S.A is not responsible for any decisions made or actions undertaken by the contracting party based on the results provided by IGENOMIX ARGENTINA S.A or otherwise., nor the harmful temporary consequences diverted by its use, making specific discretion of taking appropriate legal measures assuming an improper use of those mentioned studies and analysis.

SIGNED	**COUNTERSIGNED**
Martina Di Bastiano	**Arantxa Hervas PhD**
	3025-CV
Laboratory Leader	Biotechnologist

This test or part of this test has been outsourced to a referral Laboratory. Lab CLIA No.: 99D2146167

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency

What is Congenital adrenal hyperplasia due to 21-hydroxylase deficiency?

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) follows an autosomal recessive pattern of inheritance and is caused by pathogenic variants in the CYP21A2 gene. This condition is associated with impaired hormone production by the adrenal glands, leading to excess androgen (or male sex hormones). The symptoms of 21-OHD CAH range in severity. There are two forms of 21-OHD: classic CAH and non-classic CAH. The combination of CYP21A2 variants may help to predict clinical presentation, with the inheritance of one or two mild variants in the CYP21A2 gene most often leading to non-classic CAH.

Classic 21-OHD CAH presents in infancy and is further divided into salt-wasting and simple virilizing types. With the salt-wasting form, affected males and females are unable to retain proper sodium (salt) levels, which can be life-threating if left untreated. Infants with the simple virilizing form of 21-OHD CAH do not experience salt-wasting. In both types of classic 21-OHD CAH, female infants may be born with ambiguous genitalia. Males and females with classic 21-OHD CAH may shows signs of precocious puberty, advanced bone age, and decreased fertility, and benefit from ongoing management.

Non-classic 21-OHD CAH is milder and more common; salt-wasting and ambiguous genitalia are not seen in individuals with the non-classic form of CAH. The onset of non-classic 21-OHD CAH symptoms is typically in adolescence, with variable degrees of postnatal androgen excess, leading to acne, excess hair growth, frontal balding, shorter stature in adulthood, and decreased fertility. Females with non-classic 21-OHD CAH may have menstrual irregularity and symptoms that could mimic polycystic ovary syndrome. Some individuals with non-classic 21-OHD CAH remain asymptomatic.

What is the next step if I am a carrier of Congenital adrenal hyperplasia due to 21-hydroxylase deficiency?

If you are a carrier of Congenital adrenal hyperplasia due to 21-hydroxylase deficiency it is important that your partner (or gamete donor) is tested to determine if she/he is also a carrier of this condition.

What if my partner isn't a carrier?

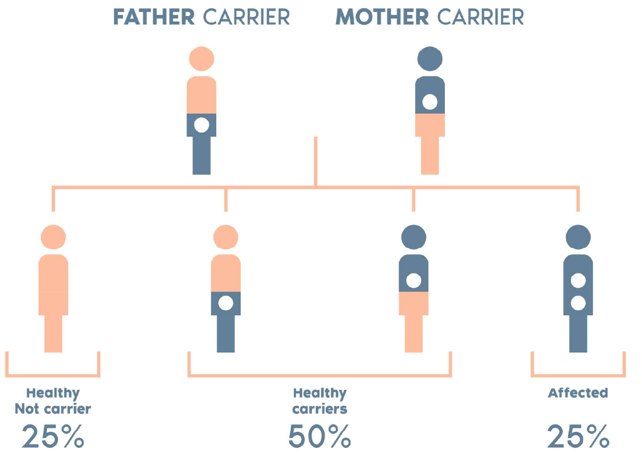
If your partner tests negative for Congenital adrenal hyperplasia due to 21-hydroxylase deficiency, the possibility of having an affected child is very low, significantly lower than the incidence of disease in the general population. However, there is not a test capable of detecting all existing pathogenic variants. Therefore, a residual risk remains of having unknown or undetectable pathogenic variants using current technology.

What if both parents are carriers of Congenital adrenal hyperplasia due to 21-hydroxylase deficiency?

When both parents are carriers of Congenital adrenal hyperplasia due to 21-hydroxylase deficiency, the probability of having a child with the disease is 25% in each pregnancy. (See graph)

What if I am going to use gamete donation?

In this case it is advisable to use the same assay (CGT) to test candidate donors and choose one that is negative for the same condition.



If both are carriers of the disease contact your doctor or genetic counselor for information on genetic options for family planning.

LIST OF ANALYZED GENES

Gene mean coverage >100x GJB2, HBA1, HBA2, HBB, ATP7A, ATRX, DKC1, ARSL, IL1RAPL1, HSD17B10, UPF3B, BTK, CUL4B, DMD, EMD, CD40LG, WAS, THOC2, MTM1, OTC, PQBP1, CYBB, SH2D1A, PDHA1, OCRL, FGD1, BRWD3, PHF8, GLA, F9, RP2, GPR143, F8, COL4A5, G6PD, HPRT1, IL2RG, L1CAM, FMR1, PRPS1, RPGR, SYN1, KDM5C, ZNF711, CFTR, CYP21A2

Gene mean coverage 50x-100x HCFC1, SLC6A8, SLC16A2, OPHN1, DLG3, ABCD1, ARX, CHM, PLP1, NR0B1, FTSJ1, MID1, ZDHHC9, NDP, RS1, GJB1, PGK1

Gene mean coverage < 50x MECP2, POU3F4, DCX, PAK3, EDA, AP1S2, IDS, AR, SMN1

GLOSSARY

TYPES OF INHERITANCE:

- AR: Autosomal recessive

  Inherited conditions that require two pathogenic variants (one from each parent) in a given gene to display symptoms.
- XR: X-linked recessive

  The gene is located on the X chromosome. Men with a pathogenic variant have the disease. Women with a pathogenic variant are carriers and generally asymptomatic or may mild symptoms.
- Digenic inheritance

  In some diseases, the symptoms could be explained by the coexistence of pathogenic variants in two different genes related with the disease instead of two pathogenic variants in the same gene.

ALLELES:

Pathogenic variants present in the two copies of a gene.

- Homozygous pathogenic variant (Hom.):

  Each copy of the gene has the same pathogenic variant. Generally, this is associated with clinical symptoms.
- Compound heterozygous (Het.):

  Each copy of the gene has a different pathogenic variant. Generally, this is associated with clinical symptoms. This situation is referred as having variants "in trans".

Pathogenic variant present in one copy of a gene.

- Heterozygous pathogenic variant (Het.):

  Only one copy of a gene has a pathogenic variant. There is another normal gene copy.

Note: Sometimes an individual has two pathogenic variants in the same gene copy. This situation is referred as having variants in cis and it is considered as a single pathogenic variant.

CNV:

Refers to copy number variation (deletion or duplication), i.e., the number of copies of a particular gene (or gene region) is different from the usual two copies.

LARGE GENE CONVERSION:

Refers to pathogenic variants caused by gene sequence exchange or replacement between a normal functional gene and a quasi-identical non-functional gene (pseudogene).

X-linked conditions

Chrom	Gene	Disease/Condition	Carrier Rate	Residual Risk
X	ABCD1	Adrenoleukodystrophy	1 in 3750	1 in 37500
X	AP1S2	Mental retardation, X-linked, syndromic, type 5 (Pettigrew syndrome)	< 1 in 100 000	Reduced
X	AR	Androgen insensitivity syndrome	1 in 6250	1 in 10417
X	ARSL	Chondrodysplasia punctata, brachytelephalangic	< 1 in 100 000	Reduced
X	ARX	Epileptic encephalopathy, early infantile, type 1; ARX-related developmental disorders	1 in 25 000	1 in 100000
X	ATP7A	Menkes disease; Occipital horn syndrome	1 in 25000	1 in 100000
X	ATRX	Mental retardation-hypotonic facies syndrome, X-linked; Alpha-thalassemia/mental retardation syndrome	< 1 in 100 000	Reduced
X	BRWD3	Mental retardation, X-linked, type 93	1 in 10000	1 in 50000
X	BTK	Agammaglobulinemia X-linked, type 1	1 in 50,000	1 in 333333
X	CD40LG	Hyper-IgM syndrome, type 1 (immunodeficiency, X-linked, with hyper-IgM, type 1)	< 1 in 100 000	Reduced
X	CHM	Choroideremia	1 in 18750	1 in 66964
X	COL4A5	Alport syndrome, X-linked	1 in 10000	1 in 50000
X	CUL4B	Mental retardation, X-linked, syndromic, type 15 (Cabezas type)	< 1 in 100 000	Reduced
X	CYBB	Chronic granulomatous disease, X-linked	1 in 300	1 in 1500
X	DCX	Lissencephaly, X-linked, type 1	1 in 2500	1 in 50000
X	DKC1	Dyskeratosis congenita, X-linked	1 in 62500	1 in 1250000
X	DLG3	Mental retardation, X-linked, type 90	1 in 45000	1 in 300000
X	DMD	DMD-related conditions	1 in 2625	1 in 131250
X	EDA	Ectodermal dysplasia, type 1, hypohidrotic, X-linked	1 in 2500	1 in 16667
X	EMD	Emery-Dreifuss muscular dystrophy, type 1, X-linked	< 1 in 100 000	Reduced
X	F8	Hemophilia A	1 in 3500	1 in 89285
X	F9	Hemophilia B	1 in 6250	1 in 62500
X	FGD1	Aarskog-Scott syndrome; Mental retardation, X-linked syndromic, type 16	1 in 10000	1 in 125000
X	FMR1	FMR1-related conditions	1 in 400	1 in 40000
X	FTSJ1	Mental retardation, X-linked 44	1 in 45000	1 in 300000
X	G6PD	G6PD deficiency	1 in 25	1 in 250
X	GJB1	Charcot-Marie-Tooth neuropathy, X-linked dominant, type 1	1 in 9803	1 in 196060
X	GLA	Fabry disease	1 in 18750	1 in 187500
X	GPR143	Ocular albinism, type 1 (Nettleship-Falls type)	1 in 15000	1 in 18750
X	HCFC1	Mental retardation, X-linked 3 (methylmalonic acidemia and homocysteinemia, cblX type)	< 1 in 100 000	Reduced
X	HPRT1	Lesch-Nyhan syndrome	1 in 95000	1 in 380000
X	HSD17B10	HSD10 mitochondrial disease	< 1 in 100 000	Reduced
X	IDS	Mucopolysaccharidosis, type 2	1 in 25000	1 in 125000
X	IL1RAPL1	Mental retardation, X-linked, type 21/34	1 in 25000	1 in 357143
X	IL2RG	Severe combined immunodeficiency, X-linked	1 in 25000	1 in 500000
X	KDM5C	Mental retardation, X-linked, syndromic, Claes-Jensen type	1 in 4000	1 in 57143
X	L1CAM	L1 Syndrome	1 in 7500	1 in 150000
X	MECP2	Encephalopathy, neonatal severe; Rett syndrome	1 in 37500	1 in 250000
X	MID1	Opitz GBBB syndrome, type 1	1 in 18750	1 in 125000
X	MTM1	Myotubular myopathy, X-linked	1 in 12500	1 in 83333
X	NDP	Norrie disease	1 in 50,000	<1 in 1,000,000
X	NR0B1	Adrenal hypoplasia, congenital	1 in 17500	1 in 58333
X	OCRL	Lowe Syndrome; Dent disease type 2	< 1 in 100 000	Reduced
X	OPHN1	Mental retardation, X-linked, with cerebellar hypoplasia and distinctive facial appearance	< 1 in 500	Reduced
X	OTC	Ornithine transcarbamylase deficiency	1 in 50000	1 in 166667
X	PAK3	Mental retardation, X-linked, type 30	1 in 40000	1 in 800000
X	PDHA1	Pyruvate dehydrogenase E1-alpha deficiency	< 1 in 100 000	Reduced
X	PGK1	Phosphoglycerate kinase 1 deficiency	< 1 in 100 000	Reduced
X	PHF8	Mental retardation syndrome, X-linked, Siderius type	< 1 in 100 000	Reduced
X	PLP1	Pelizaeus-Merzbacher disease	1 in 353	1 in 441
X	POU3F4	Deafness, X-linked, type 2	1 in 556,112	<1 in 1,000,000
X	PQBP1	Renpenning syndrome	< 1 in 100 000	Reduced
X	PRPS1	PRPS1-related disoders	< 1 in 100 000	Reduced
X	RP2	Retinitis pigmentosa, type 2, X-linked	1 in 5000	1 in 62500
X	RPGR	Retinitis pigmentosa, type 3, X-linked; Cone-rod dystrophy, X-linked, 1	1 in 20000	1 in 28571
X	RS1	Retinoschisis	1 in 15000	1 in 100000
X	SH2D1A	Lymphoproliferative syndrome, X-linked, type 1	< 1 in 100 000	Reduced
X	SLC16A2	Allan-Herndon-Dudley syndrome	< 1 in 100 000	Reduced
X	SLC6A8	Cerebral creatine deficiency syndrome, type 1	< 1 in 100 000	Reduced
X	SYN1	Epilepsy, X-linked, with variable learning disabilities and behavior disorders	1 in 30000	1 in 150000
X	THOC2	Mental retardation, X-linked 12	< 1 in 100 000	Reduced
X	UPF3B	Mental retardation, X-linked, syndromic, type 14	1 in 15000	1 in 75000
X	WAS	Wiskott-Aldrich syndrome; Thrombocytopenia, X-linked	< 1 in 100 000	Reduced
X	ZDHHC9	Intellectual developmental disorder, X-linked syndromic, Raymond type	1 in 45000	1 in 450000
X	ZNF711	Mental retardation, X-linked, type 97	1 in 45000	1 in 225000

Autosomal recessive conditions

Chrom	Gene	Disease/Condition	Carrier Rate	Residual Risk
7	CFTR	Cystic fibrosis	1 in 25	1 in 833
6	CYP21A2	Congenital adrenal hyperplasia due to 21-hydroxylase deficiency	1 in 62	1 in 1240
13	GJB2	Deafness, autosomal recessive, type 1A; Deafness, digenic, GJB2/GJB6	1 in 40	1 in 500
16	HBA1	Alpha thalassemia	1 in 30	1 in 200
16	HBA2	Alpha thalassemia	1 in 30	1 in 200
11	HBB	HBB-related hemoglobinopathies	1 in 67	1 in 6700
5	SMN1	Spinal muscular atrophy	1 in 50	1 in 588

N/A: no data prevalence unknown