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Il contributo di Heal Italia alla costruzione dei nuovi approcci del prendersi cura

Finanziato dall'Unione europea NextGenerationEU
Ministero dell'Università e della Ricerca
Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA
HEAL ITALIA

Sequenziamento personalizzato

nature Vol 452|17 April 2008|doi:10.1038/nature06884

LETTERS

The complete genome of an individual by massively parallel DNA sequencing

HUMAN GENETICS

Dr Watson's base pairs

Maynard V. Olson

The application of new technology to sequence the genome of an individual yields few biological insights. Nonetheless, the feat heralds an era of 'personal genomics' based on cheap sequencing.

This issue of *Nature* contains a paper that is, in a curious way, a sequel to one published 55 years ago — the description by James Watson and Francis Crick[1] of the double-helical structure of DNA. At the information-carrying core of this beautiful structure, with its far-reaching implications for biology and medicine, are the base pairs that Watson discovered by fitting together cardboard cut-outs of the bases adenine, thymine, guanine and cytosine. Now, on page 872, Wheeler *et al.*[2] describe the use of massively parallel DNA sequencing to determine the order of the base pairs in Watson's own genome. This achievement is a technical *tour de force* that points towards routine use of whole-genome sequencing as a research tool in human genetics. Given the choice of James Watson as an identified research subject, the paper is also a conspicuous effort to publicize the arrival of the era of personal genomics and the willingness of a famous geneticist to put his genome sequence in the public domain.

Technically, the paper's interest stems from its reliance on a DNA-sequencing platform that differs greatly from the one used during the first great era of genome sequencing, which culminated in the Human Genome Project (HGP). In the HGP platform, each kilobase-pair fragment of genomic DNA was captured

James Watson decoded.

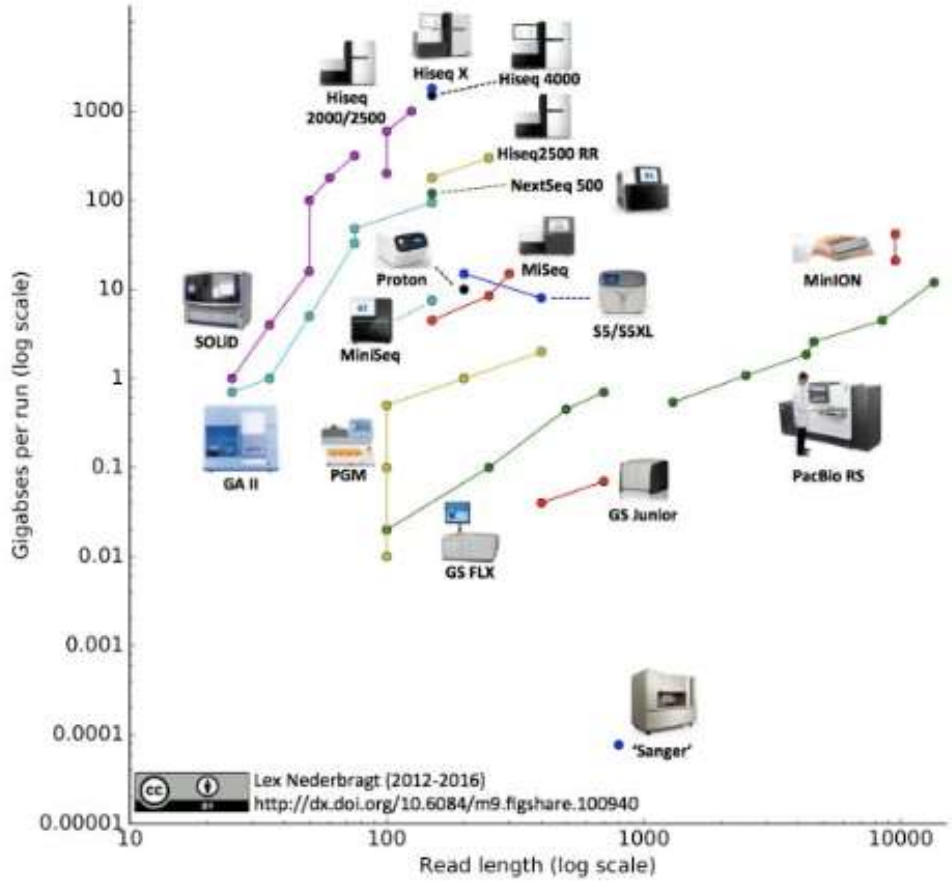
PHOTO: BETTMANN/CORBIS

efficiency of the new methods lies in massive parallelization of the biochemical and measurement steps. The instruments used by Wheeler *et al.* are marketed by 454 Life Sciences, a component of Roche Diagnostics, which joined forces with the Human Genome Sequencing Center at Baylor College of Medicine in Houston, Texas, to sequence Watson's genome.

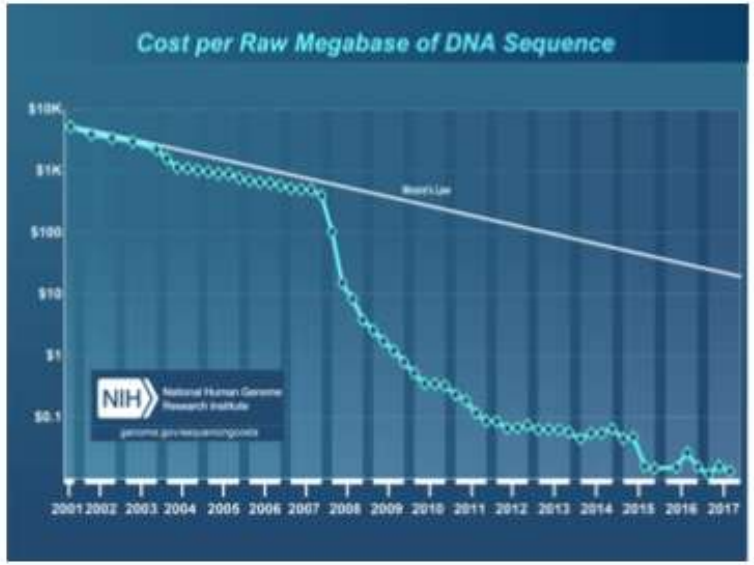
The 454 instruments achieve massive parallelization in two different ways[5]. In an initial step, single DNA molecules are attached to synthetic beads and then amplified enzymatically. During amplification, the beads are trapped in tiny water droplets within a water–oil emulsion; hence, more than 100,000 samples can be processed in parallel in a single test tube. In a later step, during which optical measurements are used to collect the actual sequencing data, each bead is confined to a picolitre-scale well etched into the end of a glass fibre within a fibre-optic bundle. Although costs have not yet dropped to the much-ballyhooed target of US$1,000 per genome[6], they are now low enough to make the era of personal genomics a reality rather than a distant dream.

What can we expect to learn from the sequences of individual genomes? The main lesson from the analyses by Wheeler *et al.* is that it will be extremely difficult to extract medically, or even

The explosion of DNA sequencing capacity



10M-fold increase in the sequencing capacity (Gigabases per run) from Sanger to today DNA sequencers



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The international journal of science / 11 May 2023

nature

HUMAN PANGENOME

Data from 47 individuals combine to create reference resource that reflects human diversity

Considered position
The debate over priorities for autism research

Predictive power
Four steps to fashion a science of human–algorithm behaviour

Screen test
MicroLEDs induced to self-assemble into next-generation display

Article

A draft human pangenome reference

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Check for updates

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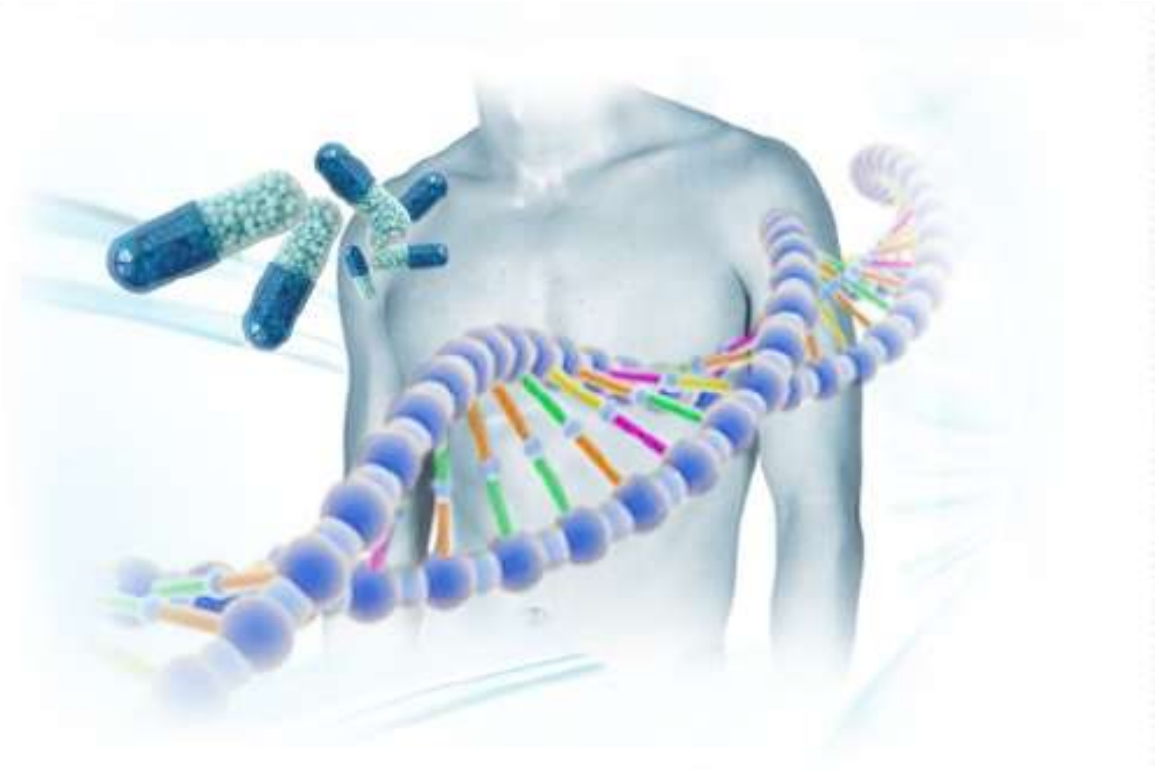
Sequenziamento genomico esteso all’intera popolazione



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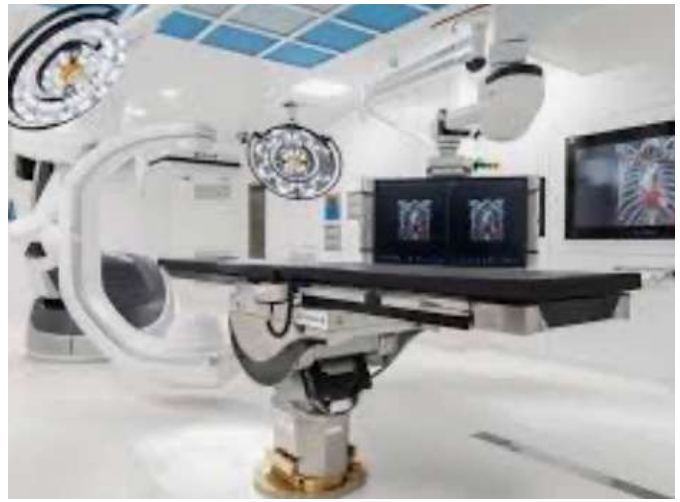
Il sequenziamento genomico esteso all'intera popolazione potrebbe portare a una innovazione nell'ambito dello studio e della cura delle malattie

Nuovo concetto di Ospedale Tecnologico



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Heal-Italia può affrontare questa sfida complessa che pone il paziente al centro dei percorsi di cura e che cerca di restituirgli un approccio terapeutico il più possibile individualizzato

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Heal-Italia può contribuire con la sua ricerca a dimostrare la sostenibilità per il Sistema Sanitario Nazionale

- Costi legati alla produzione
- Costi per la conservazione del dato

- Riduzione dei costi legati a terapie non appropriate
- Riduzione dei costi inerenti percorsi diagnostici
- Risparmi per ricoveri e cure continue nel tempo di quei pazienti affetti da patologie complesse e/o croniche che potevano essere prevenute.

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Passaporto farmacogenetico

Istituzione di un passaporto farmacogenetico: consente di determinare la risposta individuale ai farmaci sulla base di varianti genetiche.

- The fluoropyrimidines 5-fluorouracil and capecitabine are widely used in the treatment of solid tumors including colorectal and breast cancer, and cancers of the aerodigestive tract.
- Approximately 10–40% of fluoropyrimidine-treated patients develop severe and some- times life-threatening toxicity (neutropenia, nausea, vomiting, severe diarrhea, stomatitis, mucositis, hand-foot syndrome)
- 5-Fluorouracil has a narrow therapeutic window, resulting in a small difference between minimum efficacious and maximum tol- erable dose.
- Dihydropyrimidine Dehydrogenase (DPD) is the first and rate-limiting step in the catabolic pathway converting 5-fluorouracil to dihydrofluorouracil (DHFU)
- DPD levels show high inter- and intraindividual variation, which influences 5-fluorouracil exposure
- Reduced activity of DPD results in reduced clearance and increased half-life of 5-fluorouracil, and can cause profound dose-related toxicities.
- Capecitabine is a prodrug of 5-fluorouracil, being converted to 5-fluorouracil and also metabolized by DPD. Therefore, toxic effects are similar in patients with decreased/no function DPYD variants

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Table 1 Assignment of likely DPD phenotypes based on *DPYD* genotypes

Likely phenotype	Activity score[a]	Genotypes[b]	Examples of genotypes[c]
DPYD normal metabolizer	2	An individual carrying two normal function alleles.	c.[=];[=], c.[85T>C];[=], c.[1627A>G];[=]
DPYD intermediate metabolizer	1 or 1.5	An individual carrying one normal function allele plus one no function allele or one decreased function allele, or an individual carrying two decreased function alleles.	c.[1905+1G>A];[=], c.[1679T>G];[=], c.[2846A>T];[=]; c.[1129–5923C>G];[=][d]; c.[1129–5923C>G];[1129–5923C>G][d]; c.[2846A>T];[2846A>T]
DPYD poor metabolizer	0 or 0.5	An individual carrying two no function alleles or an individual carrying one no function plus one decreased function allele.	c.[1905+1G>A];[1905+1G>A], c.[1679T>G];[1679T>G], c.[1905+1G>A];[2846A>T] c.[1905+1G>A]; [1129-5923C>G]

[a]Calculated as the sum of the two lowest individual variant activity scores. See text for further information. [b]Allele definitions, assignment of allele function and references can be found on the CPIC website (*DPYD* Allele Functionality Table available at [ref 4]) [c]HGVS nomenclature using the reference sequence NM_000110.3 [d]Likely HapB3 causal variant. See *DPYD* Allele Functionality Table available at [ref 4] for other HapB3 proxy SNPs.

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Table 2 Recommended dosing of fluoropyrimidines[a] by DPD phenotype

Phenotype	Implications for phenotypic measures	Dosing recommendations	Classification of recommendations[b]
DPYD normal metabolizer	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity.	Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.	Strong
DPYD intermediate metabolizer	Decreased DPD activity (leukocyte DPD activity at 30% to 70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	Reduce starting dose based on activity score followed by titration of dose based on toxicity[c] or therapeutic drug monitoring (if available). **Activity score 1:** Reduce dose by 50% **Activity score 1.5:** Reduce dose by 25% to 50%	**Activity score 1:** Strong **Activity score 1.5:** Moderate
DPYD poor metabolizer	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	**Activity score 0.5:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose[d] with early therapeutic drug monitoring.[e] **Activity score 0:** Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	Strong

[a]5-fluorouracil or capecitabine. [b]Rating scheme described in Supplement. [c]Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities. [d]If available, a phenotyping test (see main text for further details) should be considered to estimate the starting dose. In the absence of phenotyping data, a dose of <25% of the normal starting dose is estimated assuming additive effects of alleles on 5-FU clearance. [e]Therapeutic drug monitoring should be done at the earliest timepoint possible (e.g., minimum timepoint in steady state) in order to immediately discontinue therapy if the drug level is too high.

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nucleotide_change	protein_change	ref	alt	het	hom	Phenotype
c.1627A>G	p.I543V	T	C	230	30	DPYD normal metabolizer
c.85T>C	p.C29R	A	G	254	33	DPYD normal metabolizer
c.2846A>T	p.D949V	T	A	6	0	DPYD Intermediate metabolizer
c.1905+1G>A	splicing defect	C	T	6	0	DPYD Intermediate metabolizer
c.1129-5923C>G		G	C	30	0	DPYD Intermediate metabolizer

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Genome Sequencing in the clinic

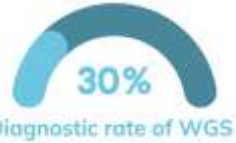
GS increasingly suggested as first-tier clinical test to replace ES for diagnosis of genetic disorders

➢ In recent years, studies and meta-analyses were published on the topic

European Journal of Human Genetics

The performance of genome sequencing as a first-tier test for neurodevelopmental disorders

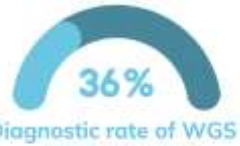
Bart P. G. H. van der Sanden, Gaby Schobers, Jordi Corominas Galbany, David A. Koolen, Margje Sinnema, Jeroen van Reeuwijk, Connie T. R. M. Stumpel, Tjitske Kleefstra, Bert B. A. de Vries, Martina Rutterkamp-Versteeg, Nico Lelsten, Michael Kwint, Ronny Derks, Hilde Swinkels, Amber den Ouden, Rolph Pfundt, Tuula Rinne, Nicole de Leeuw, Alexander P. Stegmann, Servi J. Stevens, Arthur van den Wijngaard, Han G. Brunner, Helger G. Yntema, Christian Gilissen, ... Lisenka E. L. M. Vissers



CellPress

Genome sequencing and comprehensive rare-variant analysis of 465 families with neurodevelopmental disorders

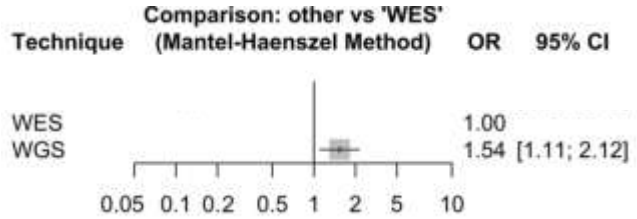
Alba Sanchis-Juan, Karyn Megy, Jonathan Stephens, Camila Armirola Ricaurte, Eleanor Dewhurst, Kayyi Low, Courtney E. French, Detelina Grozeva, Kathleen Stirrups, Marie Erwood, Amy McTague, Christopher J. Penkett, Olga Shamardina, Salih Tuna, Louise C. Daugherty, Nicholas Gleadall, Sofia T. Duarte, Antonio Hedrera-Fernández, Julie Vogt, Gautam Ambegaonkar, Manali Chitre, Dragana Josifova, Manju A. Kurian, Alasdair Parker, Julia Rankin, Evan Reid, Emma Wakeling, Evangeline Wassmer, C. Geoffrey Woods, NIHR BioResource, F. Lucy Raymond, and Keren J. Carss



Archives of Public Health

Whole genome sequencing diagnostic yield for paediatric patients with suspected genetic disorders: systematic review, meta-analysis, and GRADE assessment

Mario Cesare Nurchis, Gerardo Altamura, Maria Teresa Riccardi, Francesca Clementina Radio, Giovanni Chillemi, Enrico Silvio Bertini, Jacopo Garlasco, Marco Tartaglia, Bruno Dallapiccola & Gianfranco Damiani



- uniform coverage (including coding)
- comprehensive variant calling
- coding + non-coding

- higher computational and human workload
- more interpretation challenges
- more demanding infrastructure

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ES/GS in >50 NeuroDevelopmental Disease (NDD) families

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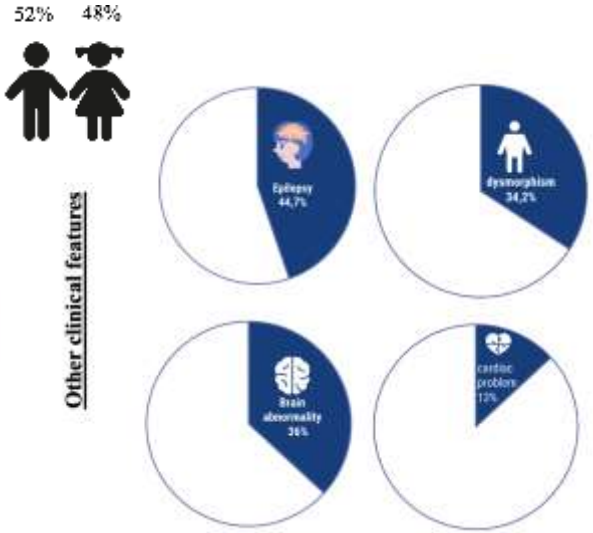
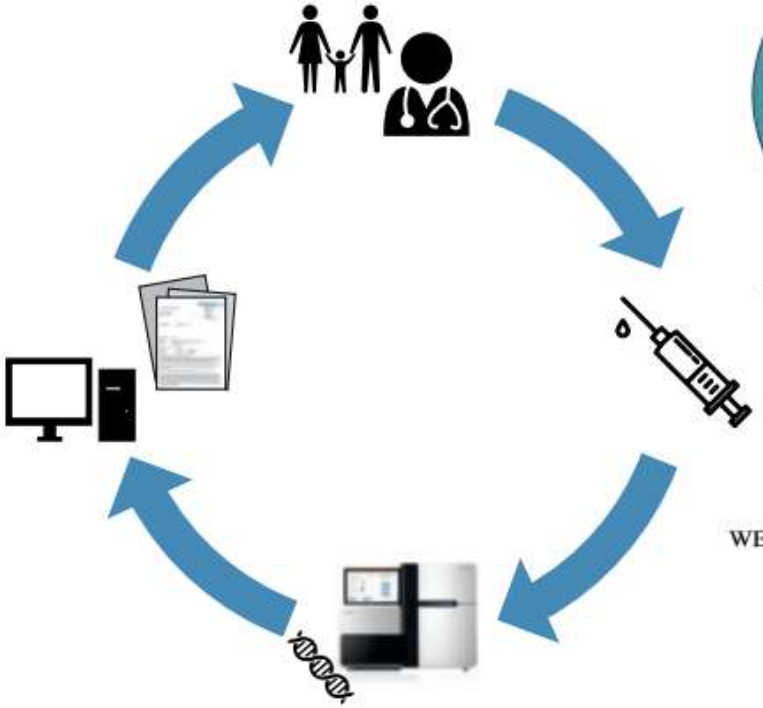
Patients and Samples

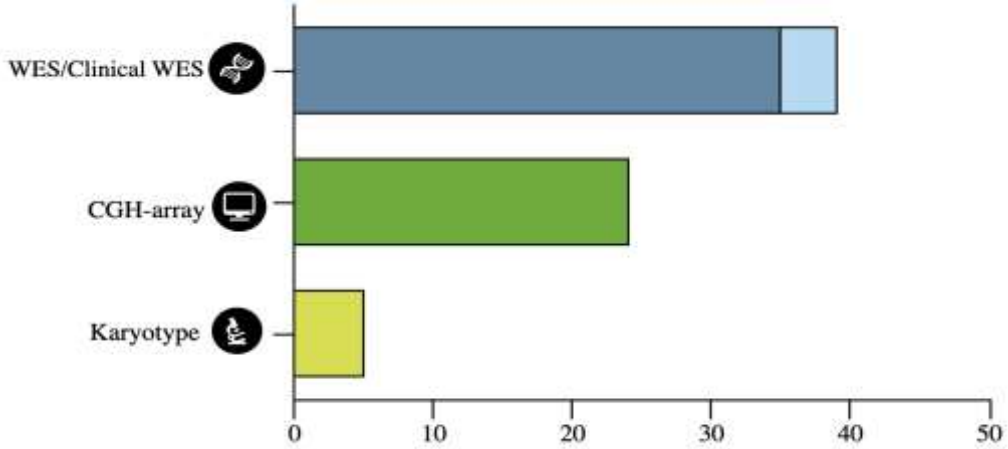
Analysis of 55 families completed
52 trios and 3 quartets



GS data were processed through a DRAGEN/GATK pipeline



Collect of DNA from blood samples and HPO-standardized clinical information



All family members had GS at mean coverage 50x

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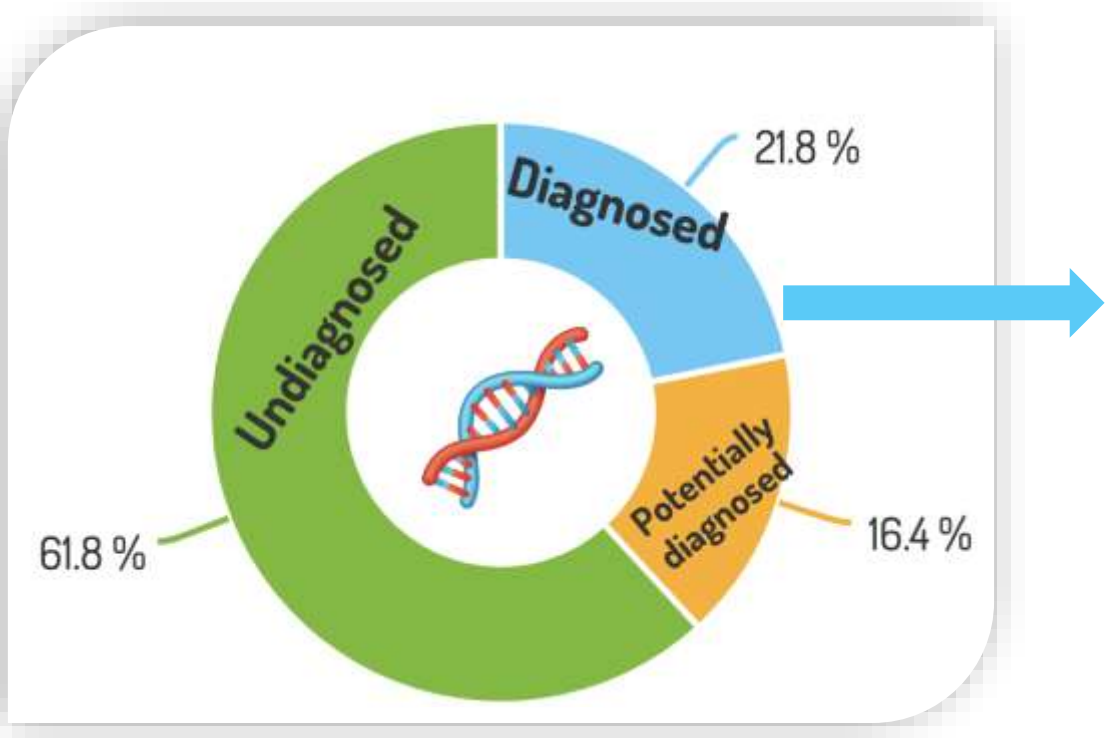
Diagnostic rate

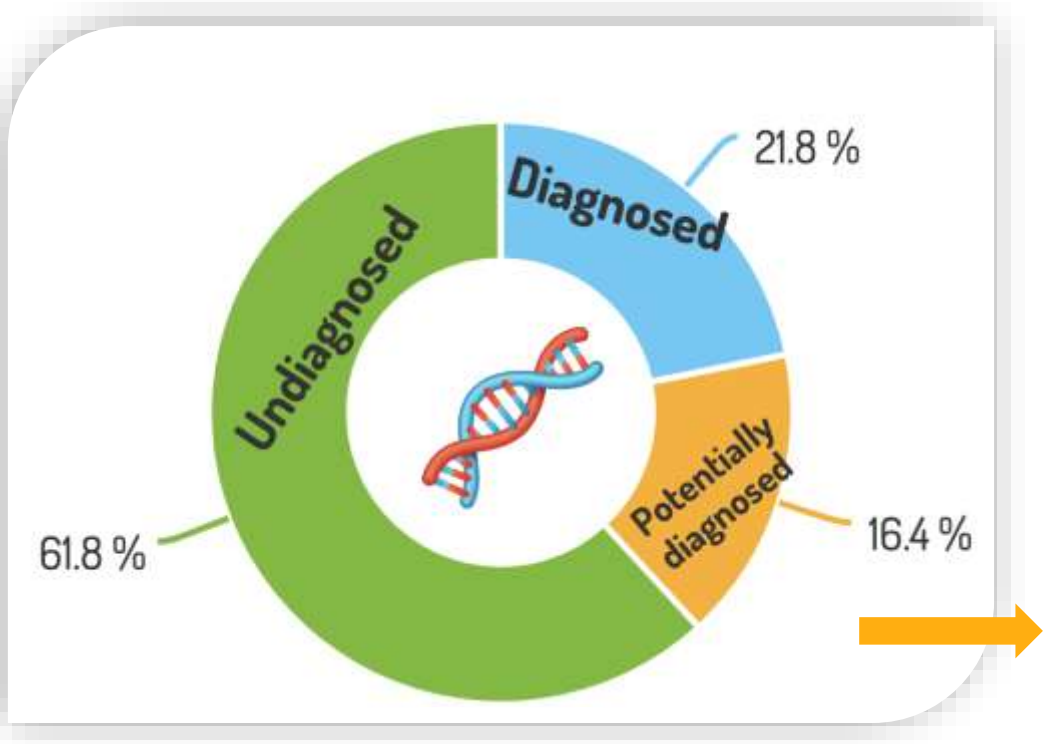
The GS-exclusive variants are highlighted in bold (25%)



Case	Gene	Transcript	Variant	Inheritance	type od variant	Potentially detectable with WES
FID_1	CREBBP	NM_004380.3	p.Arg1868Trp	DN	SNV	Y
FID_2	**MT-ATP8**	**ENST00000361851.1**	**p.Lys57***	**MT**	**SNV**	N
FID_3	**RIF1**	**NM_018151.5**	**2-151426560-6821_del**	**DN**	**SV**	**N**
FID_4	**MED12**	**NM_005120.3**	**c.4477_4527+56dup**	**DN**	**SV**	**N**
FID_7	HECW2	NM_001348768.2	p.Arg1330Trp	DN	SNV	Y
FID_8	AFF4	NM_014423.4	p.Arg258Trp	DN	SNV	Y
FID_22	CYFIP2	NM_001037333.3	p.Asp877GlufsTer57	DN	SNV	Y
FID_10	TRIT1	NR_132405.1	p.Trp228Arg, p.Arg150Ter	AR	SNV	Y
FID_38	SCAMP5	NM_138967.4	p.Gly180Trp	AD	SNV	Y
FID_31	RAC1	NM_006908.5	p.Tyr64His	DN	SNV	Y
FID_45	ZNF865	NM_001195605.2	p.(Ser800PhefsTer163)	DN	SNV	Y
FID_47	DDX1	NM_004939.3	p.(Glu371Lys)	DN	SNV	Y

The overall diagnostic yield is consistent with studies reported in the literature on cohorts of patients with NDDs (PMID: 36114283, PMID:37541188, PMID37541188)

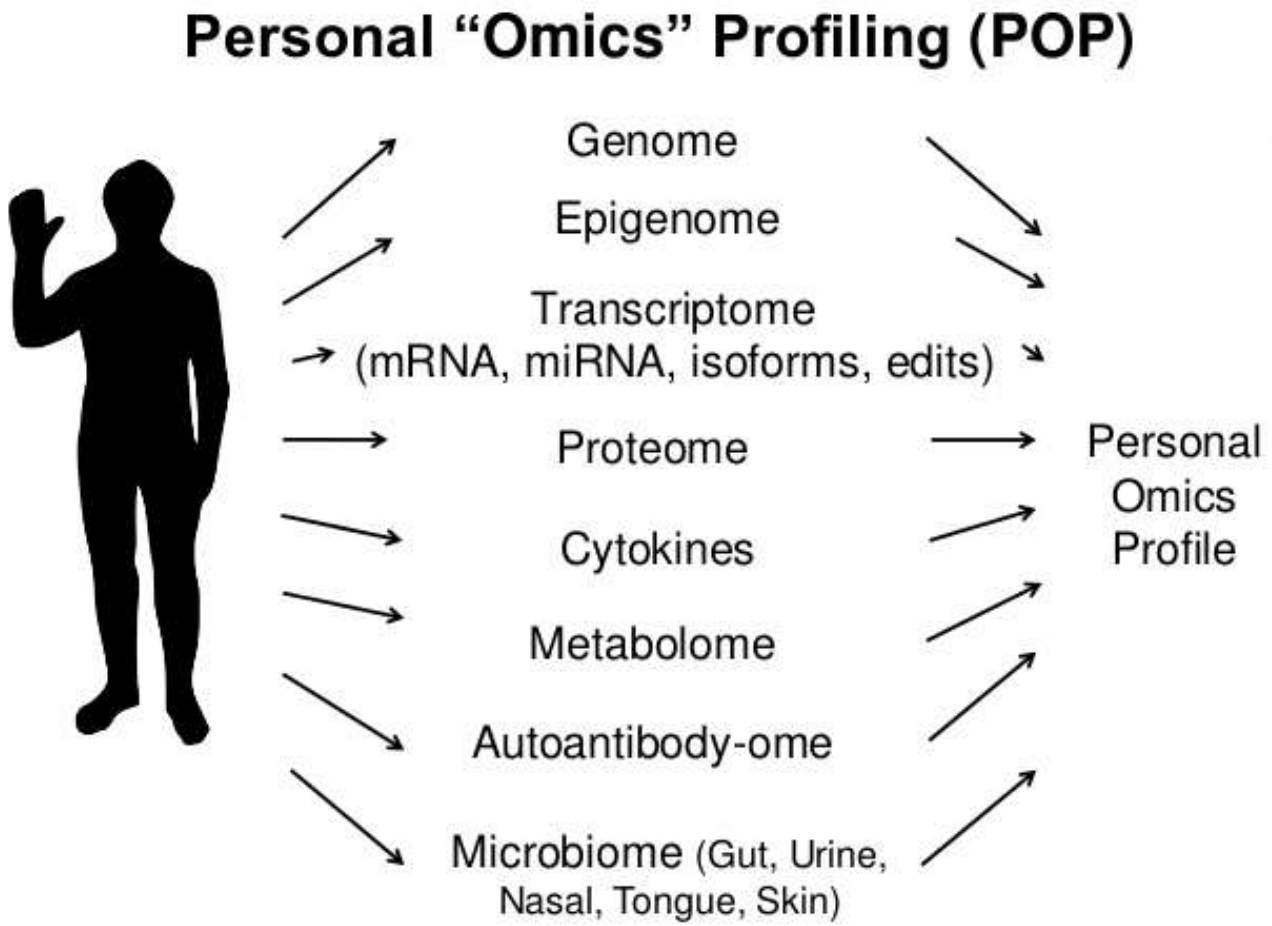
Diagnostic rate



Case	Gene	Transcript	Variant	Inheritance	type od variant	genomic region	Potentially detectable with WES
FID_29	HDLBP	NM_005336.5	p.Arg839His	DN	SNV new gene	Coding	Y
FID_18	CHRDL1	NM_001143981.2	p.Lys300Ter	XLR	SNV	coding	Y
	FGF13	**NM_004114.5**	**c.-25A>C**	**XLR**		**non-coding**	**N**
FID_19	**MT-RNR2**	**ENST00000387347**	**M-3251-A-G**	**MT**	**SNV**		**N**
	NLGN4X	**ENST00000381095.8**	**X:5863700+300_ins**	**XLR**	**SV**	**non-coding**	**N**
FID_11			**inv(X)(p22.13q28)**	**DN**	**SV**	**non-coding**	**N**
	GCH1	NM_001024024.1	p.Thr94Met	DN	SNV	Coding	Y
FID_39	**FGF14/TLX1NB**		**t(10,13);**	**DN**	**SV**	**Coding**	**N**
	SYNJ1	**ENST00000674351.1**	**p.Pro1255Leu c.*2436A>G**	**AR**	**SNV**	**Coding**	**N**
FID_50	PIK3R2	NM_005027.4	(Glu338Gly)	M	SNV	Coding	Y
	GPC3	**NM_004484.4**	**c.175+4751A>**	**XLR**	**SNV**	**non-coding**	**N**
	OGT	**NM_181672.3**	**c.218+56A>G**	**XLR**	**SNV**	**non-coding**	**N**
FID_54	SRCAP	NM_006662.3	p.(Arg945Leu)	AD	SNV	Coding	Y
FID_42	COL23A1	NM_173465.4	p.Arg495Cys	AR	SNV/ROH gene nuovo ma paziale phen	Coding	Y
FID_25	TENM2	ENST00000518659.6		AD	SNV gene nuovo in un CRE	non-coding	N

E dall’esoma in poi…

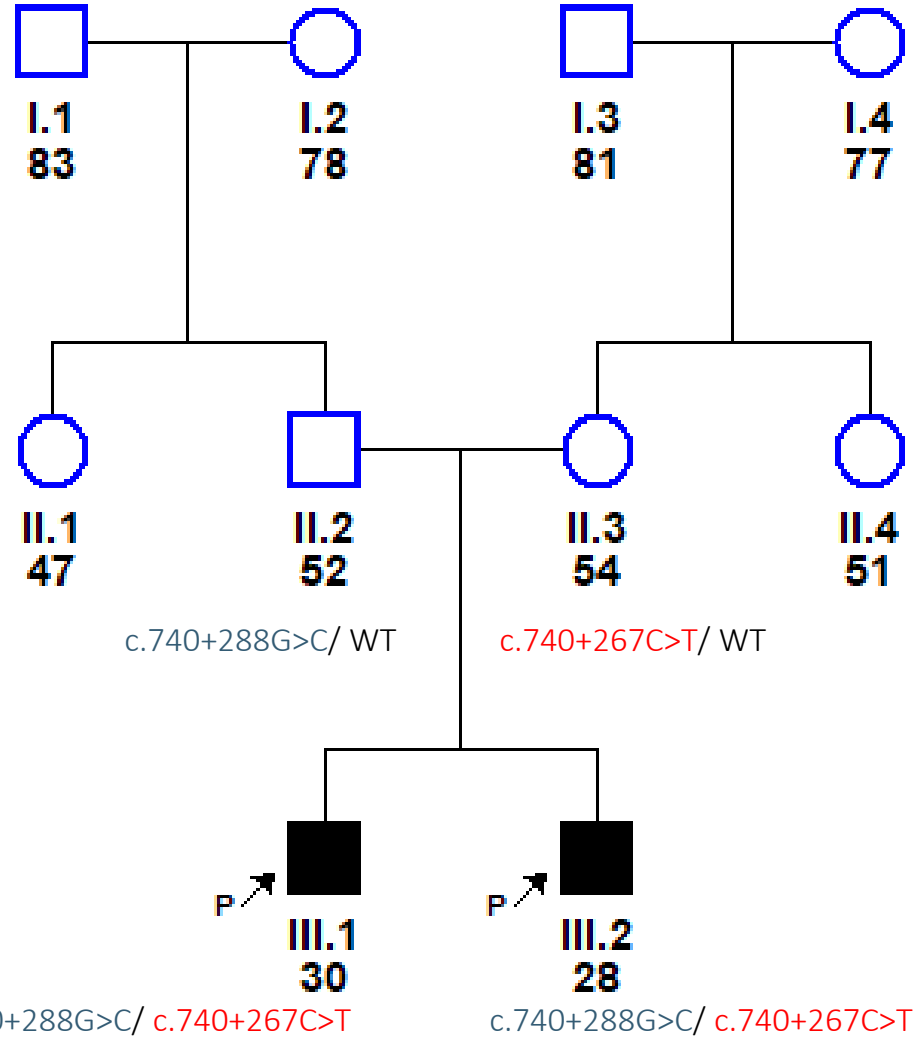
- Pazienti negativi all’analisi dell’esoma>>>> **analisi del genoma** (costi/analisi dei dati ancora complessa)



Family history

III.1
- Hemeralopia: onset at 20 yo
- Nicturia and hypertension at 27 yo: ESRD diagnosis
- Kidney biopsy suggestive of Nephronophthisis
- Kidney transplantation at 29 yo

Eye examination (2021):
- Fundus: attenuated retinal vessels, waxy optic nerve pallor, salt and pepper peripheral retinopathy
- OCT: extrafoveal photoreceptors atrophy
- Rod – cone dystrophy



III.2
- Hemeralopia: onset at 20 yo
- Hypertension
- Mild renal failure

Eye examination (2021):
- Fundus: bone spicule pigment deposits and salt and pepper peripheral retinopathy
- OCT: extrafoveal photoreceptors atrophy
- Rod – cone dystrophy

WES result (probands + parents)
SDCCAG8 (NM_006642): c.740+267C>T / SDCCAG8 (NM_00642): c.740+288G>C

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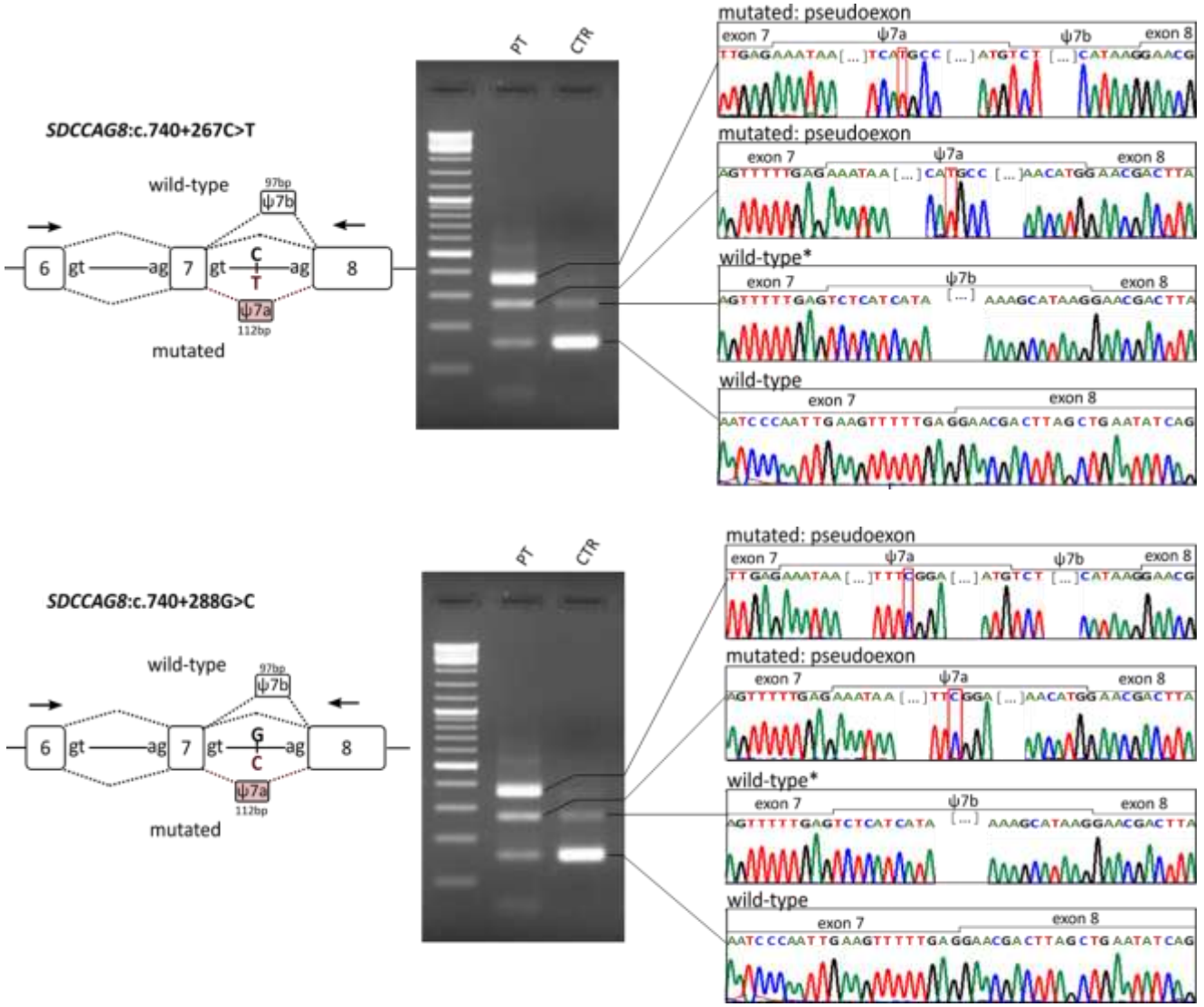
In vitro validation of cryptic variants



By RT-PCR experiments on cDNA derived from patients' fibroblasts, we characterized the splicing anomalies associated with the c.740+267C>T and the c.740+288G>C deep intronic variants in the *SDCCAG8* gene. Both variants alter an ESE/ESS motif, causing the creation of a 112bp pseudoexon (Ψ7a). Interestingly, two wild-type splicing isoforms have been detected (7-8 and 7- Ψ7b-8).

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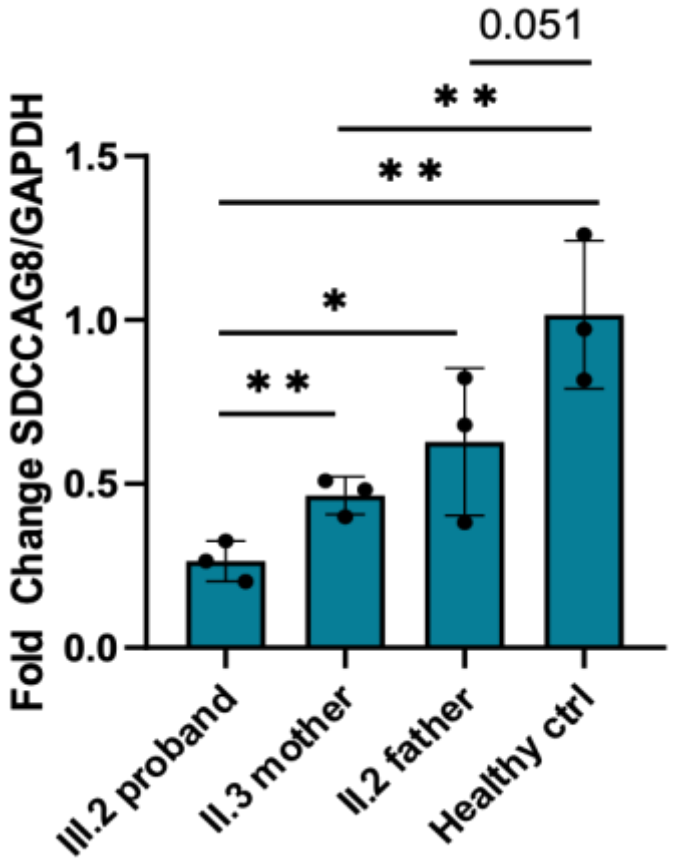
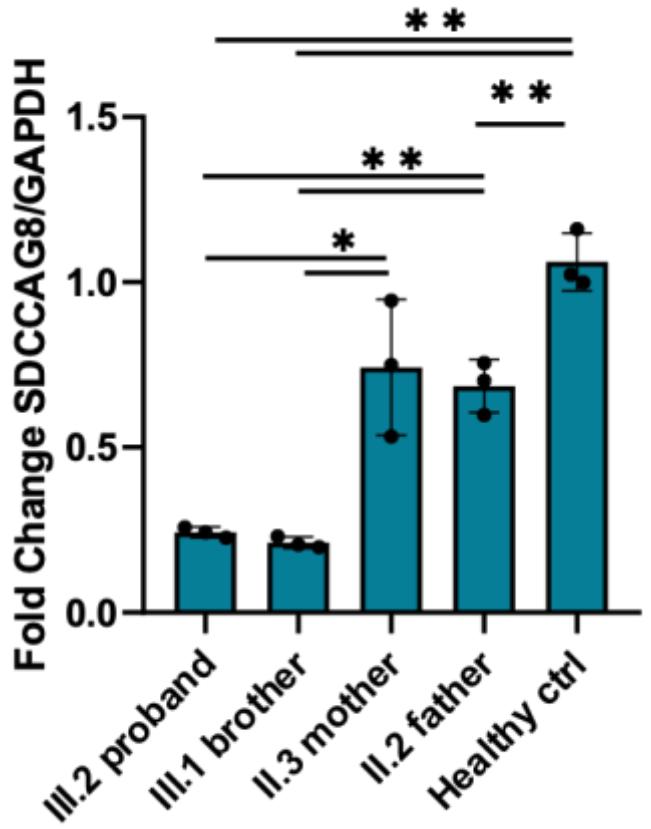
Testing the effect of our *SDCCAG8* variants on splicing

RNA SOURCE: URINARY STEM CELLS



RNA SOURCE: SKIN FIBROBLASTS



qRT-PCR experiments show significant reduction of the WT transcript in affected patients vs their parents and the healthy control on t-test (* $p < 0.05$; ** $p < 0.01$), in skin fibroblast and urinary stem cells

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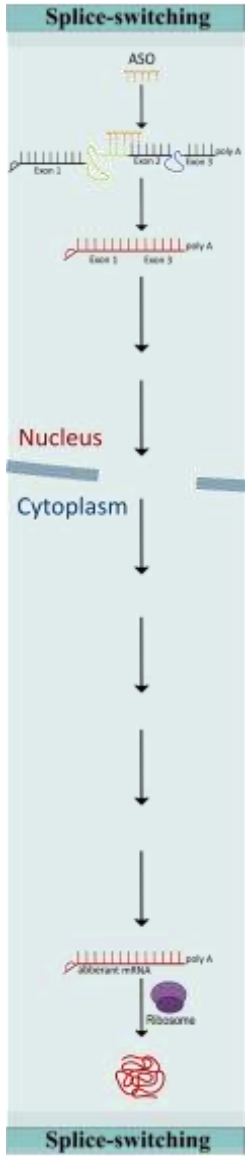
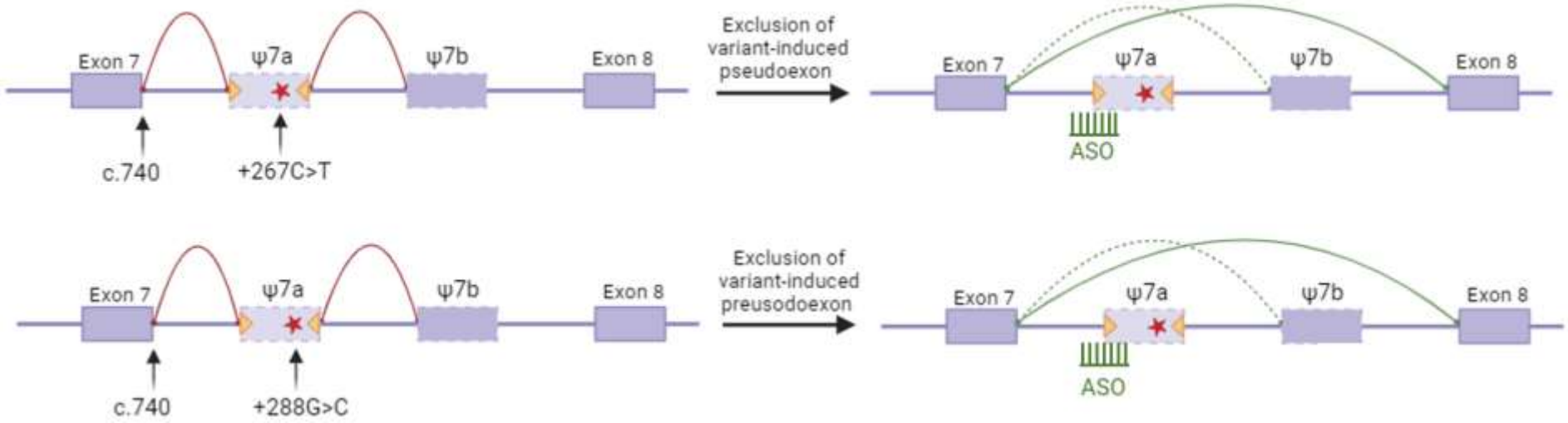
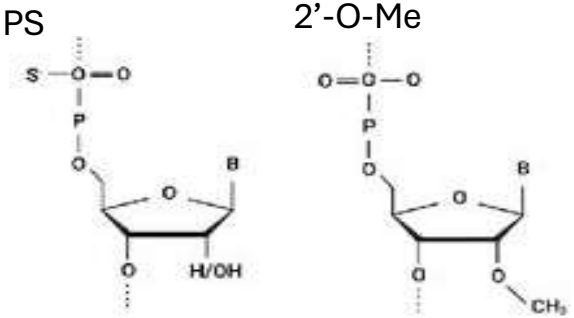


Our ASO strategy to target *SDCCAG8* cryptic variants.



We designed and synthetized four splice-switching ASO to restore normal *SDCCAG8* splicing at the pre-mRNA level.

To the molecules we have added a 2'-O-methyl RNA phosphorothioate (2OMePS) **chemical modification** in order to increase stability and improves the affinity for the target sequence.



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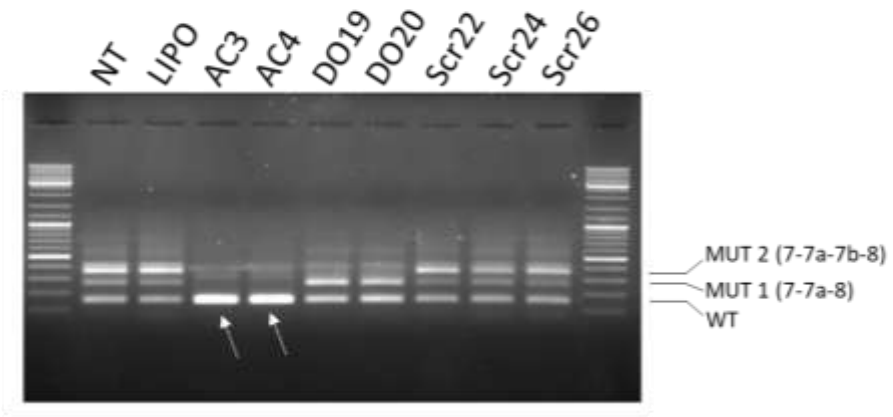
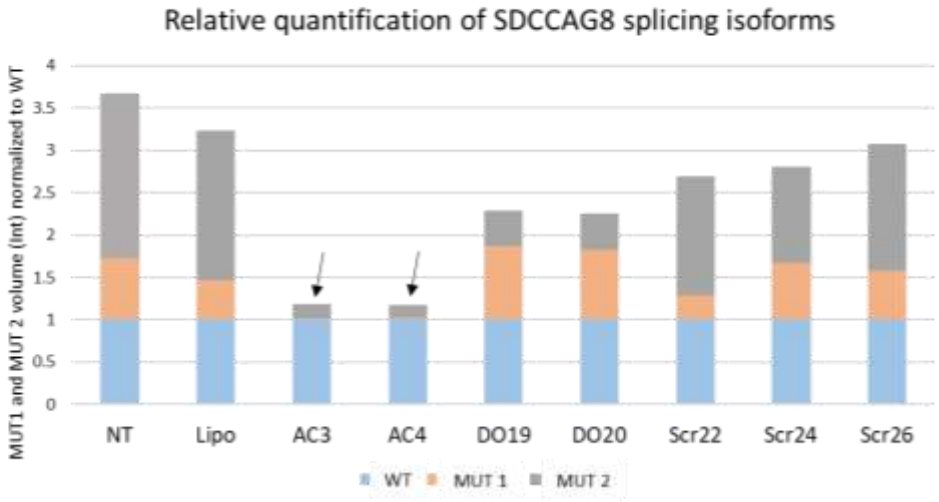
In vitro evaluation of ASOs therapeutic potential

Patient fibroblasts were treated with 20, 35, 50 and 65 nM concentrations of ASOs for 48h. Total RNA was isolated and RT-PCR was performed to evaluate the therapeutic potential of our molecules.





Our preliminary experiments show the efficacy of AC3 and AC4 ASOs in restoring the physiological splicing pattern (arrows) at all concentration tested. The treatments dramatically improved *SDCCAG8* splicing correction of pre-mRNA.

The relative quantification of MUT 1 and MUT 2 splicing isoforms *vs* the WT one clearly states the therapeutic potential of our molecules, indeed mutant bands had almost disappeared, suggesting a complete abrogation of the aberrant splicing.

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Portales-Casamar *et al. Epigenetics & Chromatin (2016) 9:25*
DOI 10.1186/s13072-016-0074-4

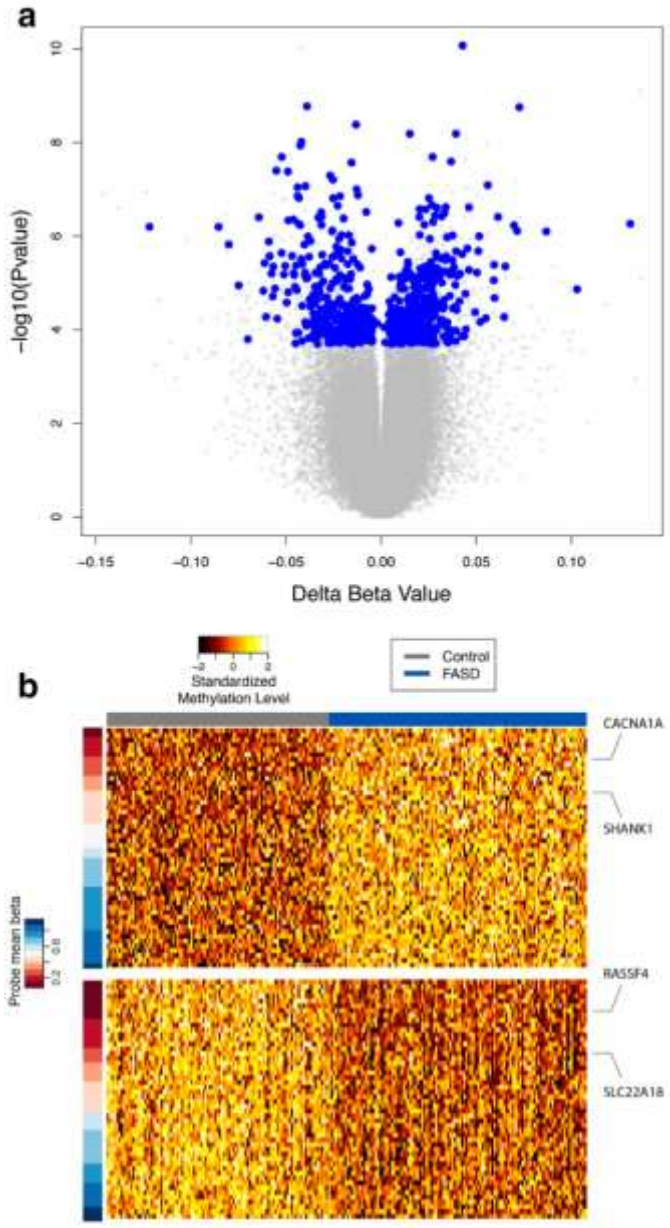
Epigenetics & Chromatin

RESEARCH Open Access

DNA methylation signature of human fetal alcohol spectrum disorder

Elodie Portales-Casamar[1†], Alexandre A. Lussier[2†], Meaghan J. Jones[2], Julia L. MacIsaac[2], Rachel D. Edgar[2], Sarah M. Mah[2], Amina Barhdadi[3], Sylvie Provost[3], Louis-Philippe Lemieux-Perreault[3], Max S. Cynader[4], Albert E. Chudley[5,6], Marie-Pierre Dubé[3,7], James N. Reynolds[8], Paul Pavlidis[1] and Michael S. Kobor[2,9*]

Conclusions: These findings suggested that prenatal alcohol exposure is associated with distinct DNA methylation patterns in children and adolescents, raising the possibility of an epigenetic biomarker of FASD.



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Other challenging scenarios

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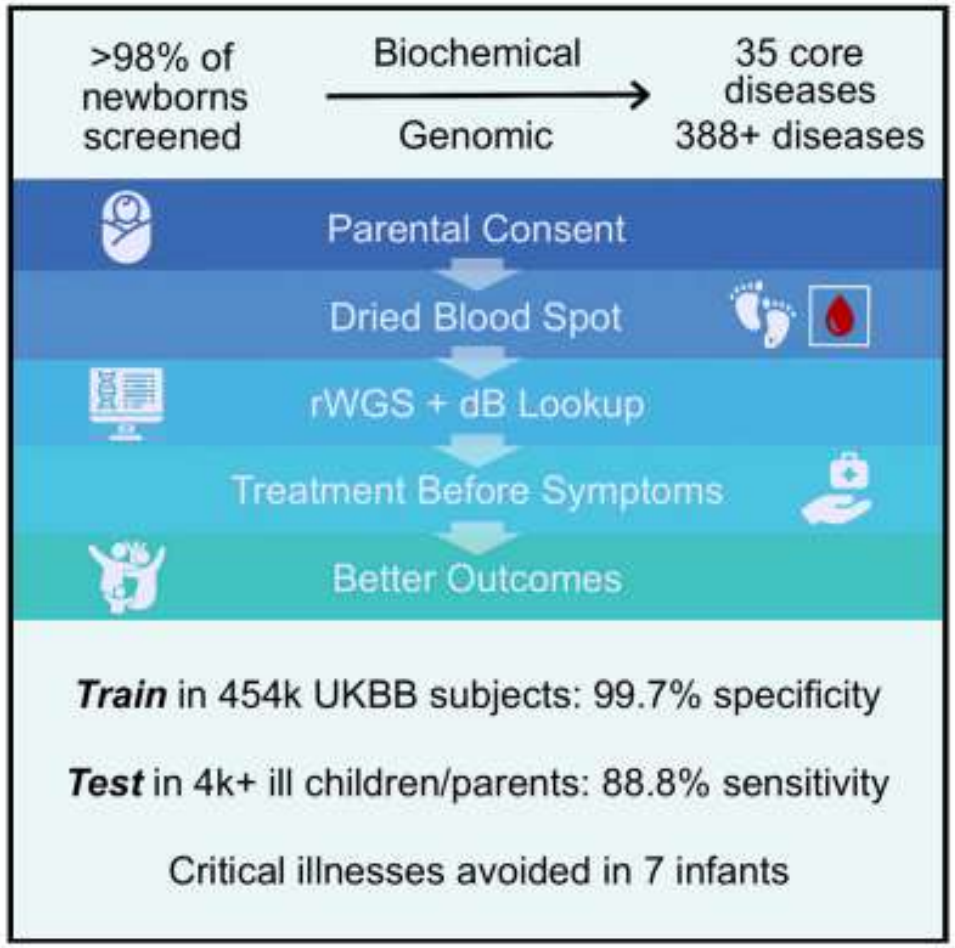
ARTICLE

A genome sequencing system for universal newborn screening, diagnosis, and precision medicine for severe genetic diseases

Stephen F. Kingsmore,[1,2,3,*] Laurie D. Smith,[1] Chris M. Kunard,[4] Matthew Bainbridge,[1,2] Sergey Batalov,[1,2] Wendy Benson,[1,2] Eric Blincow,[1,2] Sara Caylor,[1,2] Christina Chambers,[6] Guillermo Del Angel,[5] David P. Dimmock,[1,2] Yan Ding,[1,2] Katarzyna Ellsworth,[1,2] Annette Feigenbaum,[1,2,6] Erwin Frise,[7] Robert C. Green,[8] Lucia Guidugli,[1,2] Kevin P. Hall,[4] Christian Hansen,[1,2] Charlotte A. Hobbs,[1,2] Scott D. Kahn,[11] Mark Kiel,[9] Lucita Van Der Kraan,[1,2] Chad Krilow,[10] Yong H. Kwon,[1,2] Lakshminarasimha Madhavrao,[1,2] Jennie Le,[1,2] Sebastien Lefebvre,[5] Rebecca Mardach,[1,2,6] William R. Mowrey,[5] Danny Oh,[1,2] Mallory J. Owen,[1,2] George Powley,[10] Gunter Scharer,[1] Seth Shelnutt,[10] Mari Tokita,[1,2] Shyamal S. Mehtalia,[4] Albert Oriol,[1,2] Stavros Papadopoulos,[10] James Perry,[2,6] Edwin Rosales,[1,2] Erica Sanford,[1] Steve Schwartz,[9] Duke Tran,[4] Martin G. Reese,[7] Meredith Wright,[1,2] Narayanan Veeraraghavan,[1,2] Kristen Wigby,[1,2,6] Mary J. Willis,[1] Aaron R. Wolen,[10] and Thomas Defay.[5]

Summary

Newborn screening (NBS) dramatically improves outcomes in severe childhood disorders by treatment before symptom onset. In many genetic diseases, however, outcomes remain poor because NBS has lagged behind drug development. Rapid whole-genome sequencing (rWGS) is attractive for comprehensive NBS because it concomitantly examines almost all genetic diseases and is gaining acceptance for genetic disease diagnosis in ill newborns. We describe prototypic methods for scalable, parentally consented, feedback-informed NBS and diagnosis of genetic diseases by rWGS and virtual, acute management guidance (NBS-rWGS). Using established criteria and the Delphi method, we reviewed 457 genetic diseases for NBS-rWGS, retaining 388 (85%) with effective treatments. Simulated NBS-rWGS in 454,707 UK Biobank subjects with 29,865 pathogenic or likely pathogenic variants associated with 388 disorders had a true negative rate (specificity) of 99.7% following root cause analysis. In 2,208 critically ill children with suspected genetic disorders and 2,168 of their parents, simulated NBS-rWGS for 388 disorders identified 104 (87%) of 119 diagnoses previously made by rWGS and 15 findings not previously reported (NBS-rWGS negative predictive value 99.6%, true positive rate [sensitivity] 88.8%). Retrospective NBS-rWGS diagnosed 15 children with disorders that had been undetected by conventional NBS. In 43 of the 104 children, had NBS-rWGS-based interventions been started on day of life 5, the Delphi consensus was that symptoms could have been avoided completely in seven critically ill children, mostly in 21, and partially in 13. We invite groups worldwide to refine these NBS-rWGS conditions and join us to prospectively examine clinical utility and cost effectiveness.



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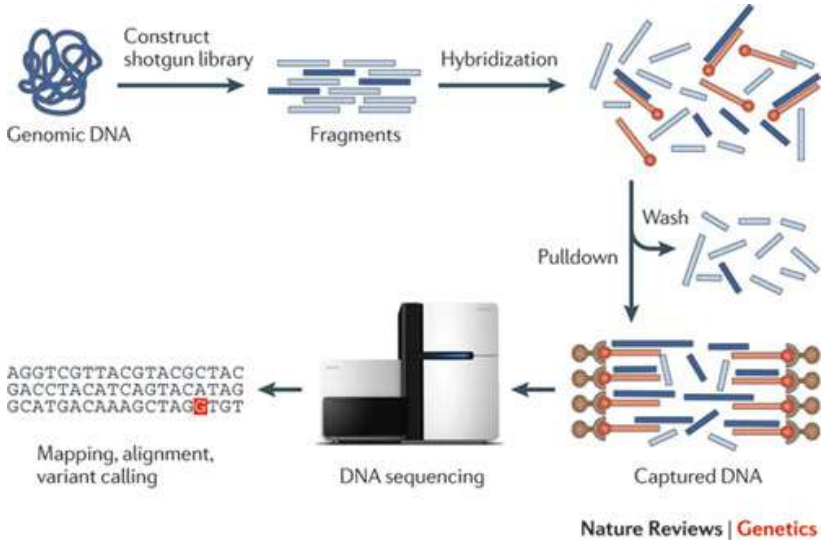
Gene theraphies approved

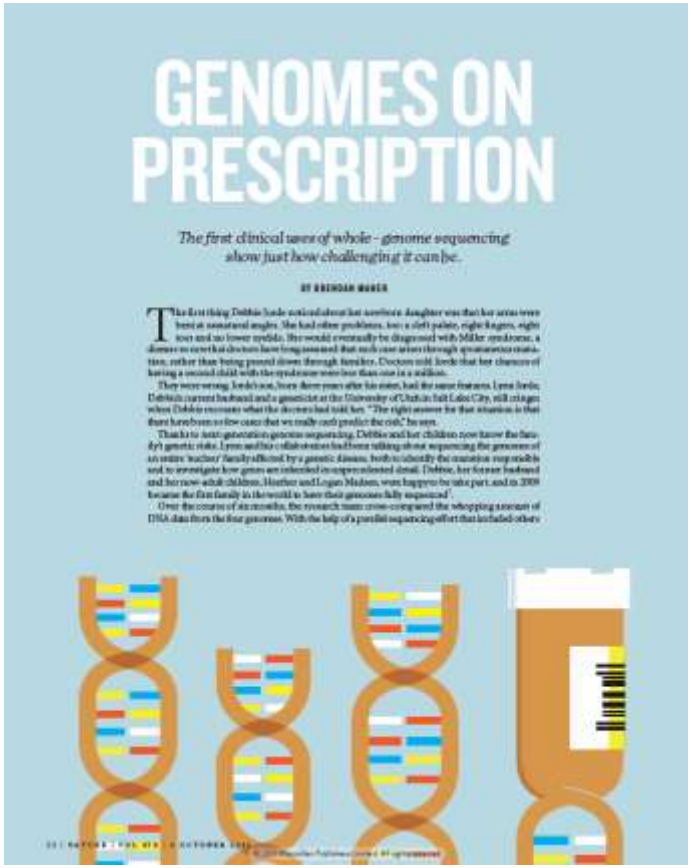
INN*	INDICAZIONE	SOMMINISTRAZIONE E VETTORE
alipogene tiparvovec	**deficit familiare di lipasi lipoproteica** con gravi o ripetuti attacchi di pancreatite	**in vivo** virus adeno-associato
talimogene laherparepvec	**melanoma inoperabile** con metastasi regionali o a distanza (Stadio IIIB, IIIC e IVM1a)	**in vivo** virus herpes simplex
frazione cellulare arricchita di cellule autologhe CD34+ contenente cellule CD34+ geneticamente modificate contenente la sequenza di cDNA che codifica per l'ADA umana	**ADA-SCID** nei casi di assenza di donatore consanguineo	**ex vivo** retrovirus
voretigene neparvovec	**distrofia retinica ereditaria**	**in vivo** virus adeno-associato
betibeglogene autotemcel	**beta talassemia trasfusione dipendente** senza genotipo β0/β0 (sopra ai 12 anni)	**ex vivo** lentivirus

INN*	INDICAZIONE	SOMMINISTRAZIONE E VETTORE
onasemnogene abeparvovec	**atrofia muscolare spinale** (SMA) di tipo 1; oppure di pazienti con SMA che hanno fino a tre copie del gene SMN2	**in vivo** virus adeno-associato
cellule autologhe CD34+ che codificano il gene ARSA	**leucodistrofia metacromatica**	**ex vivo** lentivirus
elivaldogene autotemcel (Lenti-D™)	**adrenoleucodistrofia cerebrale** precoce con una mutazione nel gene ABCD1	**ex vivo** lentivirus
eladocagene exuparvovec	**deficit della decarbossilasi degli L aminoacidi aromatici**	**in vivo** virus adeno-associato
valoctocogene roxaparvovec	**emofilia A grave** (carenza congenita di Fattore VIII)	**in vivo** virus adeno-associato

INN*	INDICAZIONE	SOMMINISTRAZIONE E VETTORE
etranacogene dezaparvovec	**emofilia B** grave e moderatamente grave (carenza congenita di Fattore IX)	**in vivo** virus adeno-associato

New diagnostic and therapeutic perspectives




GENOMES ON PRESCRIPTION

The first clinical uses of whole-genome sequencing show just how challenging it can be.