Difficult-to-sequence genes in rare hereditary disorders – resolving unmet clinical needs using customized solutions

The Genetic Horizon
The Genetic Horizon

Leaps in DNA technology, and in our ability to understand and interpret genomic sequences, have prompted a disruption in healthcare. The promise of tailored treatments for individual patients based on their genetic makeup has started to materialize as technologies like next-generation sequencing and artificial intelligence. These new technologies enable us to accurately analyze the genomes of large patient populations for clinically actionable mutations.

In rare diseases especially, acceleration of progress in targeted treatments and gene therapies has been unmistakable. Clinical trials and drug development pipelines for rare disease drugs are growing fastest, and the first approved treatments have been successful. The field of precision medicine is still in its infancy, and more awareness is needed to drive the adoption of novel diagnostic and treatment modalities.

At Blueprint Genetics, we feel that transparency is the key to unlocking the mysteries of genetic testing and bringing powerful and novel tools to the rare disease community. Through both sharing of our experiences in problem-solving and crowdsourcing our upcoming challenges, we can truly take genetic diagnostics forward.

Accuracy at scale

Our ability to accurately detect actionable mutations in the human genome is improving. Single nucleotide variants, small insertions and deletions, and exon-level deletions and duplications can be reproducibly detected, almost throughout the whole genome, and applied in clinical care. However, we are still facing the challenges of testing clinically relevant, but highly homologous and repetitive, regions and genes.

There are disease-causing mutations residing in difficult-to-sequence genomic regions and complex sequence variations in the human genome that are not detectable at clinical scale with current technologies (Table 1). Altogether, 12% of the human genome is masked in gold standard reference data sets due to uncertain or ambiguous variant calls (GIAB references). We are committed to progress genetic testing beyond its current horizon by developing novel algorithms to analyze complex regions, and custom assays for difficult to detect variants.

Actionability for the rare

Rare diseases comprise a heterogeneous group of thousands of genetically and clinically distinct disorders. Molecular diagnostics enables optimization of a patient’s treatment. By sharing knowledge and working collaboratively, we can truly understand the depth of the challenge, make room for critical thinking, and, ultimately, reach solutions for improved patient care. Recent advances in gene therapy show great promise for the cure of these devastating diseases.

As an example, retinal gene therapy has the potential to cure different forms of blindness. The first FDA-approved gene therapy is a one-time treatment for individuals with retinal disease due to homozygous RPE65 gene mutations, such as Leber congenital amaurosis and retinitis pigmentosa. Both diseases are inherited forms of vision loss that may result in blindness. In the treatment a functional copy of the RPE65 gene is delivered directly to retinal cells (www.luxturna.com).

Similarly, targeted treatments for Spinal Muscular Atrophy (SMA) have entered clinical trials recently. SMA is a severe neuromuscular disease caused by a genetic defect in the SMN1 gene, leading to the loss of motor neurons and resulting in progressive muscle weakness and paralysis. Phase 1 clinical trials have been initiated to investigate the gene therapy treatment of SMA Type 2. In the treatment a functional copy of the SMN1 gene is delivered as a one-time intravenous treatment (www.avexis.com).

The power of targeted treatments and gene therapies is in their specificity. Identification of disease-causing mutations is prerequisite for targeted treatments and gene therapy, thus making genetic testing an integral part of rare disease management.
**Awareness and transparency**

Full transparency in genetic diagnostics is essential for clinicians to be able to understand the quality and suitability of the test for their patient. We have committed to providing a full disclosure of analytic validation of testing, technologies and datasets used in the diagnostic process, and critical assessment of performance metrics.

As the next step of our commitment to transparency, we set out to share our advances in regions that are, by genomic architecture, difficult-to-sequence. Even though the industry’s ability to accurately detect actionable mutations is increasing, there are still areas that current next generations sequencing (NGS) strategies and standard Sanger sequencing do not adequately cover. This leads to poor sensitivity and decreased diagnostic yield. We have had enough of talk about 100 percent quality without actionable proof that one can really, consistently, deliver at that level.

We are trying to fill the gaps in difficult-to-sequence regions, which are by nature hard to interpret and validate, by creating custom solutions. In this document, we share our methods and what is next in the pipeline.

*Samuel Myllykangas*

*Chief Operations Officer, PhD, Founder*

*Blueprint Genetics*

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<th>%</th>
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<tr>
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<td>Genes with long repeat expansions</td>
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<td>1.9%</td>
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**Table 1** Clinically actionable variation in the genetic horizon. The table depicts the proportions of difficult-to-sequence regions in the human genome.
Opening the black box of difficult-to-sequence genes

The way of working

Establishing a specialized team to provide custom solutions for challenging genetic regions was the first step in providing tailored clinical service for individual patient cases. Our Clinical R&D team consists of genetics and molecular biology professionals. The central part of the team’s work is focused on the difficult-to-analyze regions, too complex for standard NGS analysis. The team’s main focus is developing new methods to analyze challenging yet clinically important genes.

The difficult-to-analyze genetic regions can include clinically important genes that have pseudogenes or other highly homologous regions elsewhere in the genome, or they may consist of longer stretches of repetitive sequences. Additionally, inversions, translocations, and other complex genetic rearrangements usually require custom methods for sequence data analysis as well as confirmation analysis.

Our work is driven by the excitement of tackling the most challenging parts of our genome, revealing novel disease-causing mechanisms, and by the passion of finding genetic diagnoses for patients.
Clinical service work: going the extra mile to confirm the result

Innovative customized solutions for difficult-to-sequence genes

Developing new methods to analyze challenging and clinically important genes involves both innovations in bioinformatic data analysis as well as laboratory protocols optimized for a particular genetic region.

So far, our key examples of these methods include sequencing the repetitive ORF15 region of the *RPGR* gene, the major gene underlying X-linked retinitis pigmentosa, and copy number analysis of the highly homologous *SMN1* and *SMN2* genes associated with spinal muscular atrophy. At the end of this paper, you can find a roadmap of what we are working on next.

In addition to method development, Clinical R&D provides custom solutions to confirm variants in individual patient cases. A geneticist can refer a patient case to the Clinical R&D team when a detected variant requires a customized confirmation analysis. Sometimes even a low-quality variant call, when supported by the patient’s clinical information, can turn out to be the key factor in reporting the genetic diagnosis.

When standard Sanger sequencing cannot be applied in confirmation of a variant, our team sets up custom laboratory methods that are usually based on either long-range PCR-based sequencing or quantitative PCR. These methods involve specialized primer and probe designs as well as protocols optimized for the specific region of interest. Examples of our customized methods include analyses which confirm both variants and *Alu* element insertions in the polycystic kidney disease associated *PKD1* gene, which harbors six highly homologous genetic regions.

Results of a confirmation analysis tailored for an individual patient case are usually provided within 4–6 weeks, depending on the scale of development work needed.
Going beyond what is standard: Providing sufficient clinical information

Clinical information about the patient can make or break the case in difficult-to-sequence regions

When sufficient clinical information is available, the reporting geneticist can refer the patient case to Clinical R&D to work on customized solutions.

The need for custom solutions in sequencing may arise when:

- a low-quality variant is detected at a difficult-to-sequence or duplicated region
- strange single nucleotide polymorphism (SNP) clusters are observed
- other quality control steps, such as coverage analysis, detect any events deviating from normal.

Did you know?

- At the exome level, you can see about 20,000–35,000 variations in any patient, most of them unlikely to be related to the phenotype in question
- Information on whether the phenotype is syndromic or non-syndromic, can give a clue on the genetic origin of the disease
- Too little clinical information may result in more variants of uncertain significance (VUS) being reported

A quick roadmap to providing sufficient clinical information about your patient

1. A clear description of the phenotype – list your patient’s signs, symptoms, and also include what is normal about your patient. Be thorough. Sometimes it is the most unusual feature that is key.

2. Does the phenotype appear syndromic or non-syndromic in your patient?

3. Describe when and how your patient’s symptoms began.

4. List what kind of testing has already been done and describe the results, including those that have been normal.

5. Describe relevant family medical history.

6. Don’t hesitate to share your thoughts and clinical suspicions about what the diagnosis could be.

List provided by Helena Kääriäinen (MD, PhD) and Eveliina Salminen (MD, PhD).
The importance of clinical information in genetic diagnostics

From 20,000–35,000 possible variants explaining the phenotype...

Insufficient clinical information

Patient

Sufficient clinical information

Clinician

Clinical Laboratory

Information exchange between the clinician and the clinical laboratory is a part of best practices.¹

Our online ordering and networking platform

provides guidance for filling in clinical information correctly.

Custom analysis methods for difficult-to-sequence genes.

...to 1–2 pathogenic variants that explain patient's phenotype

Difficult to sequence genes at a glance – key examples

**RPGR**

*Mutations in RPGR are primarily associated with X-linked retinitis pigmentosa*

*RPGR* gene (OMIM *312610) encodes a protein with a series of six RCC1-like domains (RLDs), characteristic of the highly conserved guanine nucleotide exchange factors. This protein localizes to the outer segment of rod photoreceptors and is essential for their viability.

Mutations occurring in *RPGR* are mainly associated with X-linked retinitis pigmentosa (XLRP; OMIM #300029); and over 70% of the patients with XLRP have mutation(s) in *RPGR*. *RPGR* mutations have also been described in patients with other retinal dystrophies, including cone-rod dystrophy, atrophic macular degeneration, and syndromic retinal dystrophy with ciliary dyskinesia and hearing loss.

XLRP accounts for 10–20% of families with RP and is the most severe form of RP. In XLRP, affected males are symptomatic from early childhood and most patients are blind by the end of their third decade. Female carriers show a broad spectrum of fundus appearances, ranging from normal to extensive retinal degeneration. Typically, retinal disease in females with XLRP is less severe than that seen in males. In a study by Rozet et al., age at disease onset in affected females was delayed compared to affected males with similar truncating variants (20–40 years vs. 10–20 years; PMID: 11950860).

The ORF15 exon of RPGR has been identified as a mutational hotspot. ORF15 encodes 567 amino acids and has a repetitive domain with high glutamic acid and glycine content (PMID: 10932196, 12657579). The RPGR isoform which includes ORF15 is encoded by exons 1–15 and part of intron 15 (1152 amino acids, transcript id NM_001034853). The other major isoform of RPGR has 815 amino acids and is encoded by exons 1–19 (NM_000328). Both isoforms share exons 1–15 (residues 1–635). Disease-causing mutations have been identified in exons 1–15 and in ORF15, but not in exons 16–19 (PMID: 17195164). Currently, HGMD lists 203 different *RPGR* mutations in NM_000328.2 and 231 in NM_001034853.1 (ORF15) (HGMD Professional 2018.1). The majority of these variants produce nonsense and frameshift mutations leading to loss of function.

There is notable inter- and intrafamilial phenotypic variability in XLRP caused by *RPGR* mutations. In particular, patients with mutations in exons 1–14 have been shown to demonstrate smaller visual fields than patients with mutations in ORF15 (PMID: 14564670). Truncating variants in the C-terminal part of ORF15 have been associated with XL cone-rod dystrophy (i.e., c.2965G>T p.Glu989*, c.3197_3198delAG, c.3300_3301delTA) (HGMD; PMID: 23150612). Only one high-quality heterozygous truncating *RPGR* variant affecting major transcripts is present in the ExAC reference population (60,000 individuals), which is much less than expected (22) by gene size. The majority of these variants produce nonsense and frameshift mutations leading to loss of function.
SMN1/SMN2

Mutations in SMN1 / SMN2 are primarily associated with spinal muscular atrophies

The survival of motor neuron 1 (SMN1) gene (OMIM *600354) shares more than 99% nucleotide identity with the SMN2 gene (OMIM *601627), both genes encode a 294-amino acid RNA-binding protein, SMN, that is required for efficient assembly of small nuclear ribonucleoprotein (snRNP) complexes. These two genes, both containing nine exons, can be distinguished only by eight nucleotides (5 intronic, 3 exonic, 1 each located in exons 6, 7, and 8) (PMID: 9950358). SMN1 produces a full-length transcript, whereas SMN2 predominantly produces an alternatively spliced transcript lacking exon 7, which results in a less stable SMN protein (10339583, 10607836).

SMN1 and SMN2 are located close to each other in a region known as the SMN complex on chromosome 5q12.2-q13.3 where repetitive sequences, pseudogenes, transposable elements, deletions and inverted duplications are not unusual (PMID: 9950358). Homozygous loss of SMN1, caused by deletion or point mutation, causes spinal muscular atrophy (SMA; OMIM #253300); absence of SMN1 exon 7 has been identified in about 95% of patients with SMA (PMID: 9950358). Absence of SMN1 is partially compensated for by SMN2, which produces enough SMN protein to allow for relatively normal development in cell types other than motor neurons (OMIM *600354). However, SMN2 cannot fully compensate for loss of SMN1 because a majority of SMN2 transcripts are truncated and less stable than those of SMN1 transcripts (PMID: 7813012, 17307868).

Spinal muscular atrophies are autosomal recessive disorders characterized by degeneration of the anterior horn cells of the spinal cord, leading to symmetrical muscle weakness and atrophy (OMIM #253300). Five types of SMA are recognized based on the age of onset, the maximum muscular activity achieved, and survivorship (GeneReviews): type 0 (SMA0), congenital SMA; type I (SMA1, OMIM #253300), severe infantile acute SMA/Werdnig-Hoffman disease; type II (SMA2, OMIM #253550), or infantile chronic SMA; type III (SMA3, OMIM #253400), juvenile SMA, or Wohlfart-Kugelberg-Welander disease; and type IV (SMA4, OMIM #271150), or adult-onset SMA. All SMA types are caused by recessive mutations in SMN1. SMA type 1 has age of onset under 6 months and the life span of the patients is most often under 2 years. Milder SMA phenotypes are usually associated with a gene conversion of SMN1 sequences into SMN2 sequences, or more than 2 copies of SMN2 (PMID: 14705979, 16508748, 11839954).

SMA disease incidence per 100,000 live births is estimated 4–10 in Europe and USA, and the carrier frequency is estimated 1/50-90 (GeneReviews). There have been no approved drug treatments for SMA until recently when the novel drug nusinersen became available (PMID: 27939059).
**PKD1**

**Mutations in PKD1 are primarily associated with autosomal dominant polycystic kidney disease**

The *PKD1* gene encodes polycystin-1 protein. The encoded glycoprotein contains a large N-terminal extracellular region, multiple transmembrane domains, and a cytoplasmic C-tail. It is an integral membrane protein that functions as a regulator of calcium permeable cation channels and intracellular calcium homeostasis. Polycystin-1 forms a complex with polycystin-2 that regulates multiple signaling pathways to maintain normal renal tubular structure such as cillum length and function. It is involved in fluid-flow mechanosensation by the primary cillum in renal epithelium.

Mutations in *PKD1* cause autosomal dominant polycystic kidney disease type 1 (ADPKD1; OMIM *601313*). The genomic region encompassing exons 1-33 of the *PKD1* (chr16:2147418-2187265) shows 97.7% sequence homology with six known pseudogenes in chromosome 16. There are altogether 1,273 *PKD1* variants classified as definitely pathogenic, highly likely pathogenic or likely pathogenic in the PKD1 Mutation Database (Feb 2018); frameshifts 35.3%, missense 24.6%, nonsense 20.7%, splice site 9.7%, in-frame deletions/insertions 8.1% and gross deletions/duplications 1.6%.

Autosomal dominant polycystic kidney disease (ADPKD) is generally a late-onset multisystem disorder characterized by bilateral renal cysts; cysts in other organs including the liver, seminal vesicles, pancreas, and arachnoid membrane; and vascular abnormalities including intracranial aneurysms, aortic dilatation and dissection and abdominal wall hernias. Renal manifestations include hypertension and renal insufficiency. Approximately 50% of individuals with ADPKD have end-stage renal disease (ESRD) by the age of 60 years. The prevalence of intracranial aneurysms is higher in those with a positive family history of aneurysms or subarachnoid hemorrhage (22%) than in those without such a family history (6%). Substantial variability in severity of renal disease and extrarenal manifestations occurs even within the same family. Blood pressure monitoring, follow up of renal function and ultrasound as well as MRI angiography for screening of intracranial aneurysms in patients at high risk is recommended. Also, echocardiography is indicated in patients with a heart murmur and those with a family history of a first-degree relative with a thoracic aortic dissection.

Prevalence of ADPKD is between 1:400 and 1:1,000. It is estimated that *PKD1* and *PKD2* explain 85% and 15% of ADPKD cases, respectively. Approximately 10% of persons receiving renal transplants have ADPKD. Penetrance is very high: practically all older adults with a *PKD1* or *PKD2* pathogenic variant develop multiple bilateral cysts. Penetrance is reduced for ESRD although a majority of individuals with truncating *PKD1* variants experience ESRD during their lifetimes. (ADPKD1 - GeneReviews).
Case reports

**Retinitis pigmentosa**

**Patient information**

Patient is a 15-year-old male with retinitis pigmentosa. His brother and maternal great-uncle are also affected.

**Clinical question**

Is this patient’s disease X-linked retinitis pigmentosa (XLRP, OMIM#300029)?

**Genetic testing**

A comprehensive Blueprint Genetics Retinal Dystrophy Panel was requested which tests 266 genes, including assessment of non-coding variants. The Retinal Dystrophy panel is ideal for patients with clinical suspicion or diagnosis of isolated retinitis pigmentosa or isolated or syndromic retinal dystrophy.

**Diagnostic summary**

Sequence analysis identified a hemizygous variant c.2601_2602del, p.(Glu868Glyfs*210) in the **RPGR** ORF15 region leading to the diagnosis of X-linked retinitis pigmentosa (XLRP, OMIM#300029). The variant was confirmed with a custom Sanger sequencing method optimized for the ORF15 region consisting of GA-rich repetitive sequence.

This variant is absent in the Genome Aggregation Database (gnomAD) (n>120,000 exomes and >15,000 genomes) and it results in a frameshift transcript with a premature stop codon at the new position 1,077 instead of codon 1,153 as in the wild-type transcript. Such changes are predicted to cause loss of normal protein function through protein truncation. The variant was initially reported by Bader et al. who identified it in one family in a RP2 and **RPGR** mutation screening of 58 index patients from families with X-linked retinitis pigmentosa (described as g.ORF15 848_849delGG in the publication PMID: 12657579). Subsequently, the variant has been reported in an additional male patient with X-linked RP (PMID: 28322733). In addition, we have detected the variant in two patients with X-linked retinitis pigmentosa (unpublished observations).

**Diagnostic implications**

Considering the current literature and the well-established role of **RPGR** c.2601_2602del, p.(Glu868Glyfs*210) as a disease-causing variant, it was classified as pathogenic. Genetic counseling and family member testing were recommended. Disease caused by **RPGR** variants is inherited in an X-linked manner. Carrier testing of the mother was recommended. If the mother is a carrier, each offspring has a 50% chance of inheriting the variant. Each daughter of an affected male will inherit the variant, while sons will remain unaffected.

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**Figure 1**

Sanger confirmation of patient’s variant c.2601_2602del, p.(Glu868Glyfs*210). Confirmation of variants found in **RPGR** ORF15 is made possible with a customized sequencing method, optimized for highly repetitive GA-rich sequence.
Spinal muscular atrophy

Patient information

Patient is a 60-year-old male with spinal muscular atrophy type III diagnosed at the age of 27 years based on results from electromyoneurography (EMG) and muscle biopsy. The patient manifested symptoms throughout childhood and adolescence: clumsiness while running, and difficulties in climbing stairs. He suffers from impaired physical condition, inability to transition independently, and overall weakened control of body and cervical spine movement. There is no known family history of similar disease.

Clinical question

Is this patient’s disease spinal muscular atrophy type III (OMIM #253400)?

Genetic testing

A Blueprint Genetics Spinal Muscular Atrophy Panel was requested which tests 30 genes, including assessment of non-coding variants. The Spinal Muscular Atrophy Panel is ideal for patients with a clinical suspicion of distal hereditary motor neuropathy or spinal muscular atrophy.

Diagnostic summary

Bioinformatic analysis developed specifically for copy number determination of the SMN1 and SMN2 genes identified a homozygous deletion including at least exon 7 of the SMN1 gene, which is considered comparable to whole gene deletion. In addition, at least three copies of SMN2 were detected. These findings were confirmed using a RNase H2-dependent PCR (rhPCR) developed specifically for SMN copy number analysis.

Diagnostic implications

Considering the current literature and well-established role of SMN1 deletion as a disease-causing variant, it was classified as pathogenic. Disease caused by SMN1 variants is inherited in an autosomal recessive manner. The patient is homozygous for the variant, which is in line with autosomal recessive inheritance. The recurrence risks deviate slightly from the norm for autosomal recessive inheritance because about 2% of affected individuals have a de novo SMN1 variant on one allele; in these instances, only one parent is a carrier of an SMN1 variant, and thus the siblings are not at increased risk for SMA. If both parents are found to be carriers of this mutation, each sibling of an affected individual has a 25% chance of being a homozygous carrier of the mutation and thus being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Genetic counseling and family member testing were recommended.

Figure 2

Our SMN copy number confirmation method takes advantage of RNA-blocked primers, which are activated by an RNase H2 enzyme only when stable primer annealing takes place. This allows us to differentiate the copy numbers for highly homologous SMN1 and SMN2 genes.
Polycystic kidney disease

Patient information

Patient is a 25-year-old female diagnosed with polycystic kidney disease at 4 years of age. There is a family history of autosomal dominant polycystic kidney disease (ADPKD) in multiple generations.

Clinical question

Is this patient’s disease polycystic kidney disease (OMIM #173900)?

Genetic testing

A Blueprint Genetics Cystic Kidney Disease Panel was requested which tests 40 genes, including assessment of non-coding variants. The Cystic Kidney Disease Panel is ideal for patients with multicystic dysplastic kidneys with or without additional congenital anomalies.

Diagnostic summary

The patient was identified with a heterozygous nonsense variant c.4957C>T, p.(Gln1653*) in exon 15 of PKD1. This variant was confirmed with Sanger sequencing utilizing primers that were manually designed to maximize their PKD1 specificity over several highly homologous pseudogenes. The variant is absent in the Genome Aggregation Database (gnomAD) (n>120,000 exomes and >15,000 genomes). The variant causes a premature stop codon and is thus predicted to cause loss of normal protein function either through protein truncation (1653 out of 4303 aa) or nonsense-mediated mRNA decay. The variant has been listed as pathogenic in the PKD1 Mutation Database, where it has been reported in four families with autosomal dominant polycystic kidney disease (ADPKD).

Diagnostic implications

Considering the current literature and the established role of PKD1 c.4957C>T, p.(Gln1653*) as a disease-causing variant, it was classified as pathogenic. Genetic counseling and family member testing were recommended. Disease caused by PKD1 variants is inherited in an autosomal dominant manner, and thus each child of an affected individual has a 50% chance of inheriting the variant. An index patient with autosomal dominant disease may have the disorder as a result of a de novo event.

Figure 3

PKD1 has multiple highly homologous pseudogenes in the genome. Patient’s variant c.4957C>T, p.(Gln1653*) is clearly visible in forward and reverse Sanger sequences, while no contaminating signal from the pseudogenes is observed in positions that are unique for PKD1 (marked in red).
In the pipeline

We are constantly striving to expand our tests to cover more difficult-to-analyze genetic regions and variants. This means improving our NGS protocols and sequence data analysis algorithms as well as developing new ancillary assays when required.

Our future projects include:

**New genes to be added to our test selection when high-quality sequencing data is available:**
- **OPN1MW** (Blue cone monochromacy, cone dystrophy)
- **OPN1LW** (Blue cone monochromacy, cone dystrophy)

**On-going validations for structural variants in the following genes:**
- **CYP21A2** (Congenital adrenal hyperplasia)
- **HBA1** (Hemoglobinopathy)
- **HBA2** (Hemoglobinopathy)
- **MSH2** (Lynch syndrome)
Our commitment to the genetic community

We urge researches, genetic testing laboratories, healthcare professionals, patients and other organizations to share their thoughts on what clinically relevant, challenging genes should be looked at next. Where we focus our R&D efforts arise from the feedback we receive from the healthcare community and unmet clinical needs in rare inherited disorders.

As part of our commitment to the clinical community, we will continue to share our advancements in the area of difficult-to-sequence genes.

Also available online at blueprintgenetics.com

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At Blueprint Genetics, we feel that transparency is the key to unlocking the mysteries of genetic testing and providing powerful and novel tools to the rare disease community.