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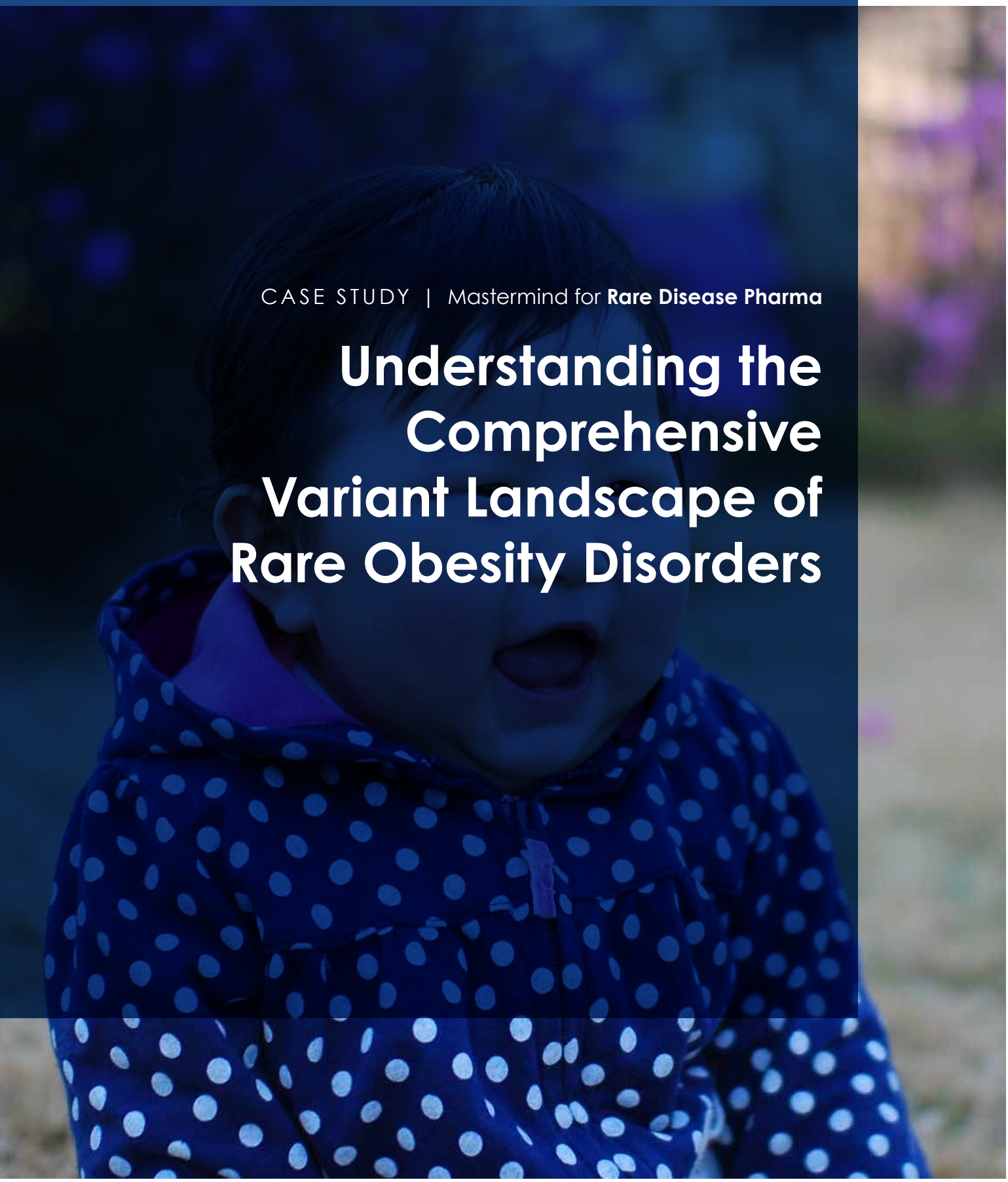

CASE STUDY | Mastermind for **Rare Disease Pharma**

Understanding the Comprehensive Variant Landscape of Rare Obesity Disorders

"Genomenon's comprehensive and organized collection of genomic evidence significantly accelerated our work in several key steps along our development process."

Vice President,
Translational Research & Development,
Rare Disease Pharmaceutical Company

EXECUTIVE SUMMARY

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RARE DISEASE PHARMACEUTICAL COMPANY'S GOALS

- Generate a compendium of genetic variants supported by the evidence in published literature associated with MC4R-pathway deficiency obesity
- Identify the pathogenicity of each variant according to ACMG/AMP guidelines and its potential contribution to obesity
- Identify a comprehensive set of genomic biomarkers that can be used to segregate patient selection for Phase III clinical trials
- Provide scientific evidence to support genomic biomarker selection for FDA submission

CHALLENGES

- Manual curation found only a small number of genomic drivers for monogenic obesity
- Keeping up with the latest published research and varied nomenclature was a constant struggle
- The limited number of pathogenic variants found though manual curation constrained the patient population for the Phase III clinical trials

APPROACH

- Genomenon's Mastermind database immediately identified over 10,000 relevant variants and 120 obesity-related genes
- The curated dataset from Mastermind provided a literature-backed ACMG pathogenicity classification for each variant
- The data can be updated regularly, allowing the company to add new variants for target selection as new scientific research is published

ACCOMPLISHMENTS

- Mastermind provided the replete list of genetic drivers of monogenic obesity that the company had been searching for for two years
- The Mastermind curated dataset provided a line of evidence from the medical literature that supported each variant and its pathogenic classification for use in FDA approval
- The company was able to significantly expand their list of genetic biomarkers used for clinical trial segregation, increasing the chances of success in their Phase III trials

CASE STUDY

Mastermind for **Rare Disease Pharma**

ABOUT THE RARE DISEASE PHARMA COMPANY

This U.S.-based biotech company is dedicated to understanding rare genetic disorders of obesity. Its approach takes a leaf from the world of oncology: What if obesity, like cancer, is a constellation of disorders that could be stratified based on germline genetics?

Following this theory, the company focused on the genes affecting one specific biological system: The melanocortin-4 receptor (MC4R) pathway, which affects feelings of hunger. But compared to genes that give rise to cancer, very little was known about the genetics of obesity. Despite substantial early research on MC4R, the information was difficult to find in the literature, didn't fully consider genetic variants, and sometimes used different terms to describe the same thing.

"When you're looking for very specific biological information, you want to make sure you're looking at every aspect. But that's a huge amount of information to glean! So once we had laid a good foundation, we knew we needed Genomenon to provide a comprehesive genomic landscape for us."

Vice President,
Translatiional Research & Development,
Rare Disease Pharmaceutical Company

MASTERMIND BROADENS UNDERSTANDING OF THE MC4R PATHWAY

As the company's Vice President of Translational Research & Development put it, "Aggregating data from the medical literature is painful. We all know what it's like as scientists to have to trawl through PubMed to identify papers that may be relevant, download them, and read them. Obviously that's painstaking and takes a very long time to achieve."

After two years of such traditional methods, the VP and his colleagues had focused on 3 genes and 12 variants known to be pathogenic related to the MC4R pathway. Then, as the VP puts it, "Our relationship with Genomenon started by recognizing that we needed a far quicker and more replete way of being able to review the published literature and make sure that we had captured all of the variants associated with our pathway."

Genomenon used a combination of machine learning (ML) and manual curation to quickly compile a comprehensive list of genomic biomarkers for the MC4R pathway using Mastermind, the world's most comprehensive database of genomic literature. The dataset delivered included literature citations and pathogenicity assessments according to ACMG/AMP guidelines. As the VP said, "You can just imagine how long that would take if I had to sit down and read every paper. But they came through in relatively short order -- certainly shorter by an order of magnitude than it would have taken my team."

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MASTERMIND CURATED DATASETS

Pharmaceutical companies use Mastermind's Curated Genomic Datasets to inform precision medicine development, deliver genomic biomarkers for clinical trial target selection, and support CDx regulatory submissions with empirical evidence.

FROM THE LAB TO CLINICAL TRIALS TO PATIENT CARE

With the initial research complete, the company turned to its next challenge: The upcoming Phase III clinical trial, where procedures are tested in a broad, real-world environment. Identifying the right patients for the trial is crucial -- and that means more research.

But in literature spanning decades, there are often terms and methods that have changed over the years. As the VP said, "The semantic nuances and inconsistencies of reporting on variants creates a lot of heartache: Researchers can report a variant by its genomic location, by a cDNA position, or by its protein consequence. And unless you're familiar with every gene, every variant, and every context, it's very easy to leave something behind." He credits Mastermind's patented Genomic Language Processing with helping to cut through the tangled mass of nomenclature. "That was one of the best things they helped us with," he said. "Genomenon was able to pull out the variants we were interested in, even if they had different names."

With the evidence provided by Genomenon, the company was able to expand their clinical trial targets significantly, enabling rolling trials with additional sets of biomarkers and increasing their chances of success.

Beyond the Phase III trial, the company will stay abreast of new developments through the updates Mastermind provides. "We can generate terabytes of genomic information when we sequence someone's genome," the VP said. "But our ability to understand what it means for the phenotype of that individual is a lot more challenging. Mastermind's ability to pull out relevant sentence fragments from the full text of the research gives us really important information to build an association between the genotype and phenotype."

Ultimately, it's the obese individual who benefits from the company's ability to get its research to the public. As the VP pointed out, "We know that body weight is the the second-most heritable trait in humans, and that 50-90% of an individual's body weight can be predicted by genetics. The more we understand about the genes, and the more we understand about the variants, the better we'll be able to improve the way in which this population is treated."

MASTERMIND FEATURES

- Exhaustive dataset of biomarkers for disease, gene, or pathway of interest
- Evidence from the most comprehensive collection of genomic literature
- Results are displayed in easy-to-use interface, available for download
- Each biomarker is pre-curated for pathogenicity according to ACMG/AMP
- Updated quarterly with the data from the latest research publications

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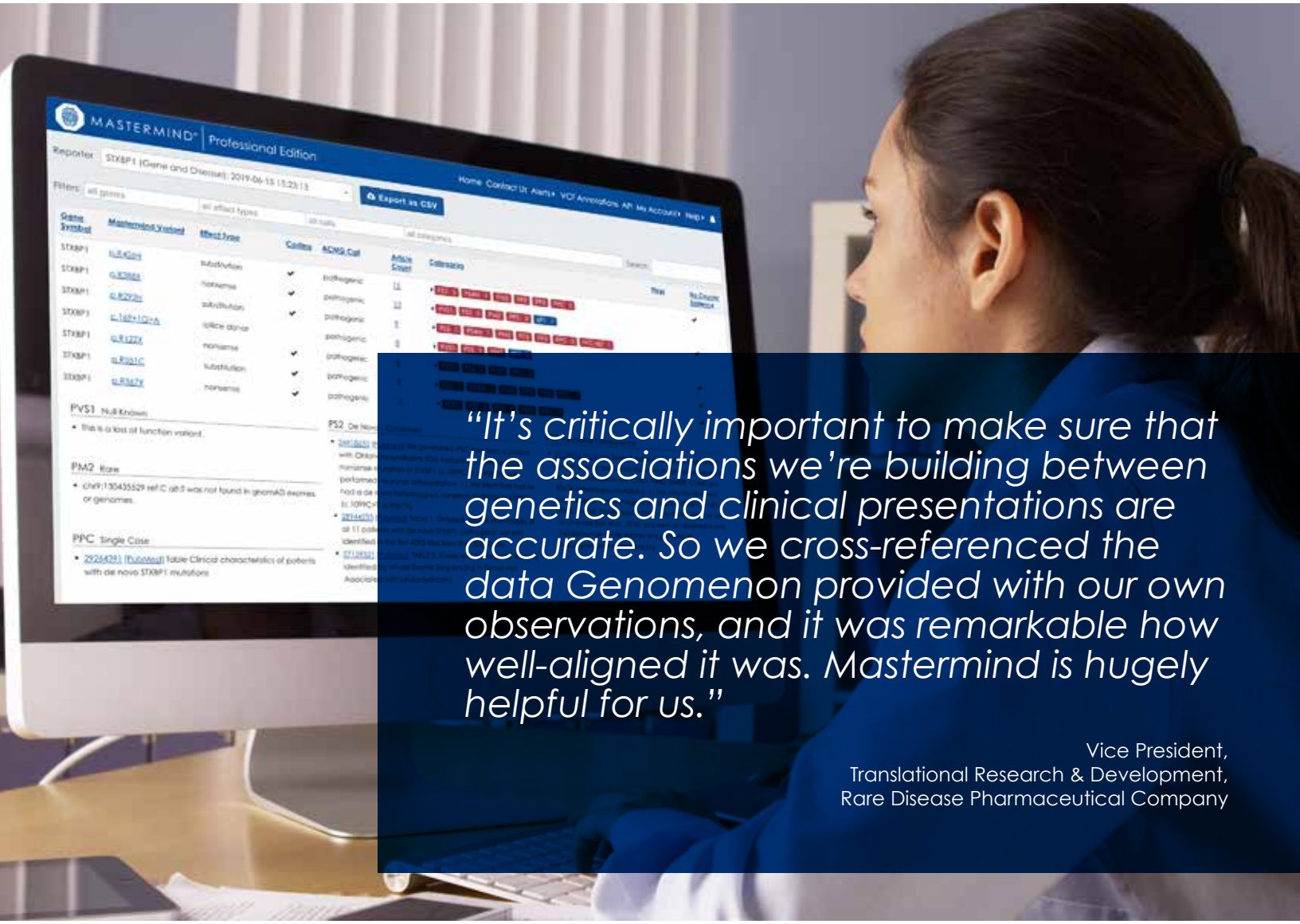

"It's critically important to make sure that the associations we're building between genetics and clinical presentations are accurate. So we cross-referenced the data Genomenon provided with our own observations, and it was remarkable how well-aligned it was. Mastermind is hugely helpful for us."

Vice President,
Translational Research & Development,
Rare Disease Pharmaceutical Company

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CONTACT US
3135 S. State Street
Suite 350 BR
Ann Arbor, MI 48108
E: hello@genomenon.com
P: +1-734-794-3075