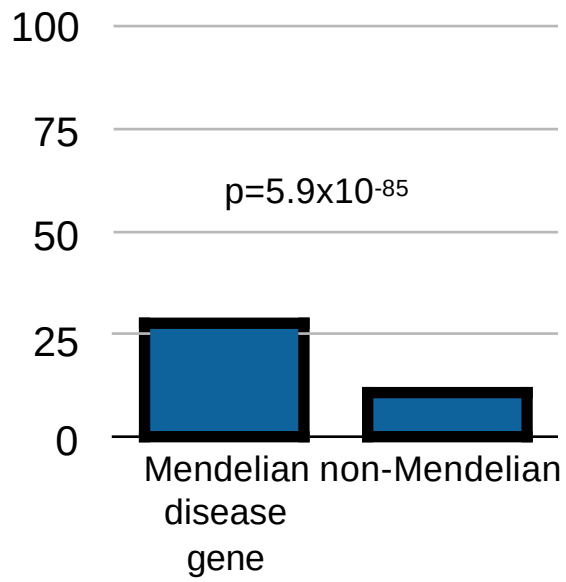
Drug devopment for rare diseases requires significant industry effort

Genetics guides drug development. But what kind of genetics?

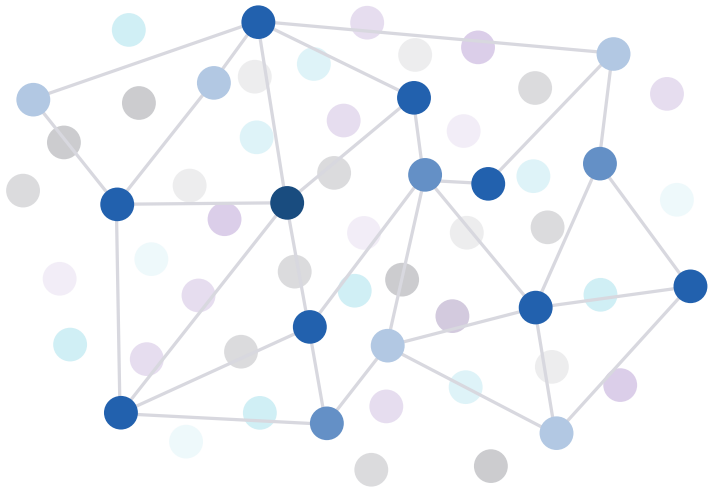
Rare to common pivot

Mendelian disorder genes 2.6X more likely to be a drug target



See also King et al. 2019, Plenge et al. 2013

Common Disease: Heterogenous Population



A Major Drug Discovery Problem:

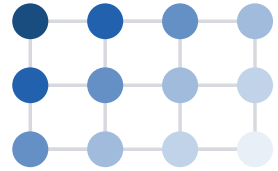
Defining a high impact drug target for a common disease with a mixed population has very low probability of success

Rare Disease

Actio's Rare Disease First Approach:

Start with a defined population (one gene, one disease) and enhance the understanding and clinical value of drug and target

Common Disease: Defined Population



Leverage Rare Disease Paradigm to Inform Drug Development for Common Diseases:

Rare disease genes regulate biological pathways relevant to more common diseases

Mendelian disease genes are enriched drug targets

Epilepsy genes and common indications

Advanced three drug candidates to clinical trials

PRAXIS

Praxis Precision Medicines Announces Closing of Initial Public Offering and Exercise in Full of the Underwriters' Option to Purchase Additional Shares

October 20, 2020 16:05 ET | Source: Praxis Precision Medicines, Inc

CAMBRIDGE, Mass., Oct. 20, 2020 (GLOBE NEWSWIRE) -- Praxis Precision Medicines, Inc. (NASDAQ: PRAX), a clinical-stage biopharmaceutical company translating genetic insights into the development of therapies for central nervous system disorders characterized by neuronal imbalance, today announced the closing of its upsized initial public offering of 11,500,000 shares of common stock, including the exercise in full by the underwriters of their option to purchase up to 1,500,000 additional shares of common stock, at a public offering price of $19.00 per share.

Approved drug targets are enriched for rare disease genes

TNFR1 Inhibition for RA HUMIRA adalimumab	PDE3A Inhibition for PVD Cilostazol Tablets IP 50 mg Pletoz-50
GUCY2C activation for Idiopathic Constipation Linzess (linaclotide) capsules	PCSK9 Inhibition for High LDL-C Repatha (evolocumab) injection 140 mg/mL

- Drugs that target rare disease genes are approved three times more often common diseases

Cancer teaches us we can target Gain of Function mutations

Cancer

Validated paradigm with multiple approved therapeutics to inhibit GoF mutations in cancer

ALK Mutation

ALECENSA alectinib
ALUNBRIG BRIGATINIB
XALKORI CRIZOTINIB
ZYKADIA ceritinib 150 mg tablets

BRAF Mutation

BRAFTOVI (encorafenib)
Tafinlar (dabrafenib)
ZELBORAF (vemurafenib) tablets

EGFR Mutation

IRESSA gefitinib
TAGRISSO osimertinib
Tarceva erlotinib

KRAS Mutation

LUMAKRAS (sotorasib)

Rare Diseases

Therapies targeting GoF mutations are lacking in rare diseases

actio BIOSCIENCES

- Large opportunity for successful drugs targeting GoF mutations in rare diseases
- Proven approach in cancer, greater efficacy expected in rare diseases (lack resistance mechanisms)
- Actio is the first company to focus, and do this systematically for rare diseases

Leveraging Human Genetics for New Target Discovery

Recent expansion of disease genetics & population genetics databases empowers new opportunities to identify drug targets

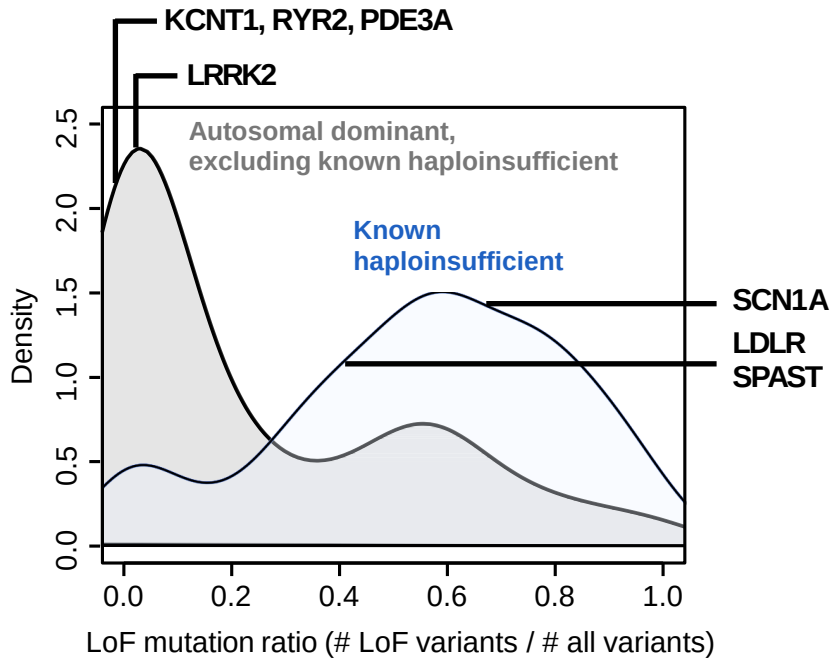
High proportion of:

Pathogenic missense variants: target for **inhibition**

- **KCNT1** - 15 missense, 0 LoF, targeted by Praxis Precision Medicine for epilepsy
- **LRRK2** - 10 missense, 1 LoF, targeted by Denali Therapeutics for Parkinson's disease
- **RYR2** - 28 missense, 0 LoF, targeted by flecainide for ventricular tachycardia
- **PDE3A** - 7 missense, 0 LoF, targeted by milrinone for pulmonary hypertension, heart failure

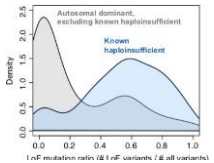
Pathogenic loss-of-function mutations: target for **transcriptional restoration**

- **SCN1A** - 203 missense, 132 LoF, causal for Dravet syndrome
- **LDLR** - 902 missense, 598 LoF, causal for familial hypercholesterolemia
- **SPAST** - 76 missense, 48 LoF, causal for spastic paraplegia



Human Genetics-Driven Discovery Engine For Rare Disease Treatments

Mendelian Disease Genes
Dominant Inheritance Pattern



- Distribution of disease mutations
- Literature review
- Allele functional studies
- Loss-of-function intolerance
- Mouse knockout phenotypes
- GWAS datasets
- eQTL / pQTL datasets
- Mendelian randomization
- Statistical co-localization
- Biobank information (PheWAS)

Gain-of-function diseases

Druggable

Direct inhibition

Existing examples:

- PCSK9 - Cholesterol
- Nav1.7, Nav1.9 – Pain
- LRRK2 - Parkinson's disease
- KCNT1 – Epilepsy
- RYR2 - Ventricular Tachycardia, Flecainide
- PDE3A – Hypertension, Milrinone

Near-term opportunities:

- KCND3 - Spinocerebellar Ataxia, atrial fibrillation, Brugada syndrome
- TRPV4 - Motor neuropathies, Peripheral neuropathy

Not druggable

Transcriptional inhibition

Existing examples

- PXT3003 (PMP22) - Charcot-Marie-Tooth

Near-term opportunities

- EEF1A2 – Epilepsy
- MYL2 - Hypertrophic cardiomyopathy

Longer-term opportunities

- SPTAN1 - Epilepsy
- GNAO1 - Epilepsy

Loss-of-function diseases

Transcriptional restoration
Allied examples (paralog rescue by up-regulation)

- Spinraza (SMN1/2)- Spinal muscular atrophy
- Hydroxyurea (HbF) - Sickle cell anemia

Near-term opportunities

- BAG3 - Dilated cardiomyopathy
- SLC2A1 - GLUT1 deficiency
- JAG1 - Alagille syndrome

Longer-term opportunities

- DSG2 - Arrhythmogenic right ventricular cardiomyopathy
- PPP3CA - Epilepsy

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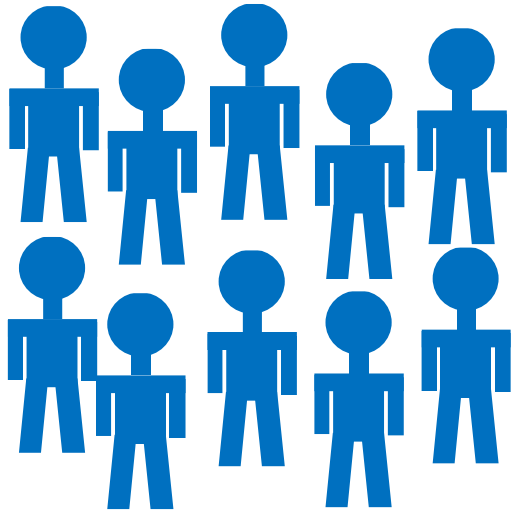
Challenges to Precision Medicine Paradigm

- Limited application?
- Clinical trials
- Economics

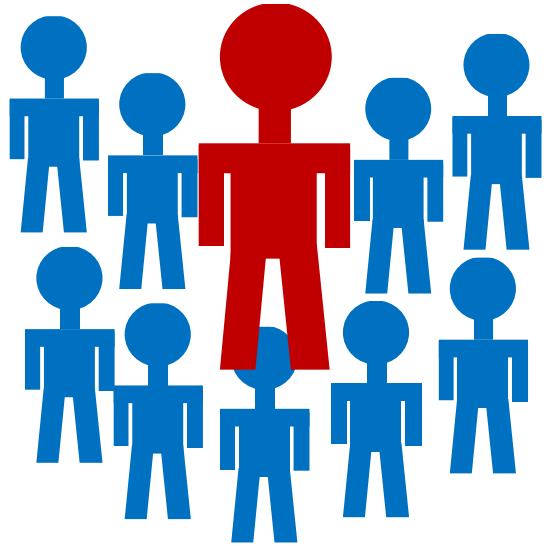
Diagnostic Utility of Exome Sequencing For Kidney Disease

ES of 3,315 individuals with all-cause CKD



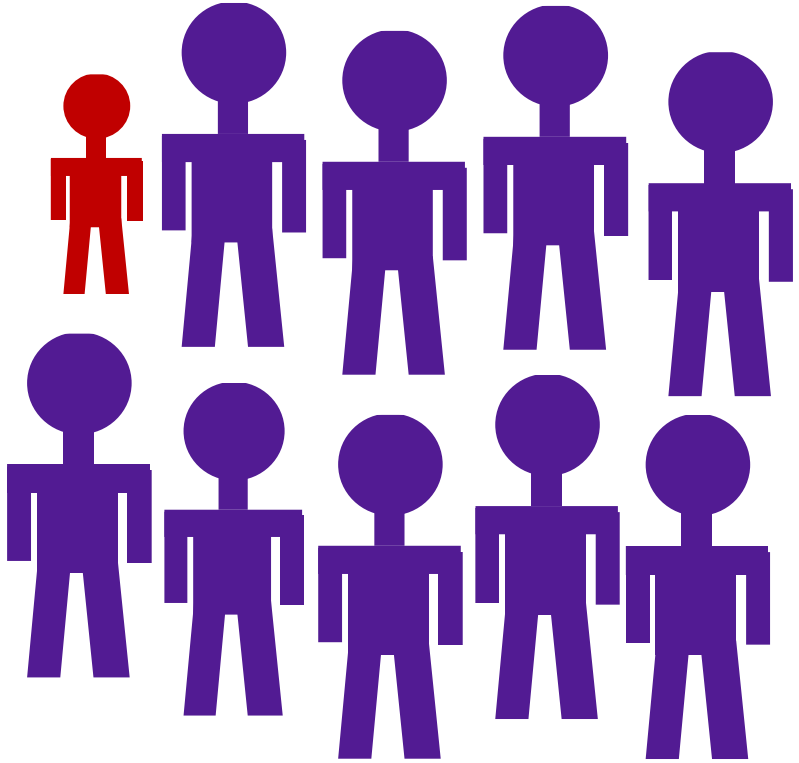
91.6% adults
35.6% non-white
European ethnicity

~1 in 10 (9.3%) have diagnostic findings



66 different single-gene etiologies
59% unique cases

In 89% of cases genetic findings inform clinical care



Groopman et al., *NEJM* 2019

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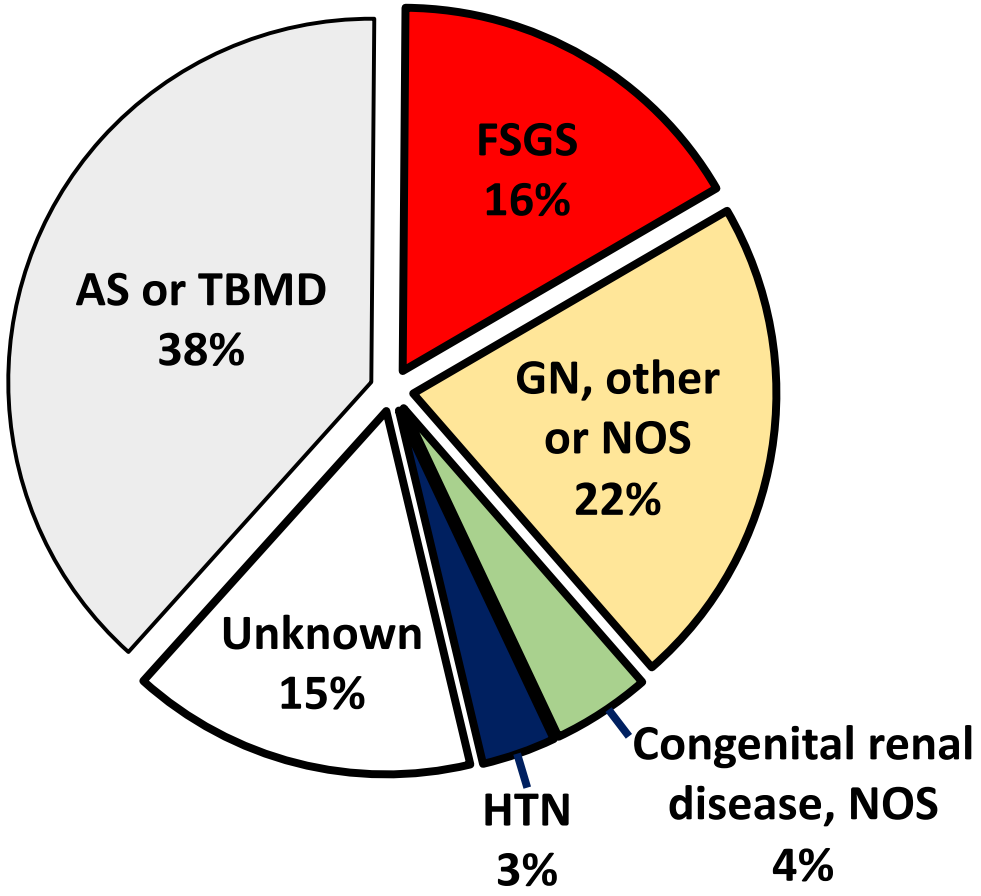
Most Common Genetic Diagnoses

Diagnosis Gene	Proband Count	Cohort
COL4A5	35	CKD
COL4A3	17	CKD
COL4A4	14	CKD
SCN1A	12	Epilepsy, ID/DD/ASD
NF1	10	CKD, Epilepsy, ID/DD/ASD
PKD1	10	CKD
SCN2A	10	Fetal Anomaly, Epilepsy, ID/DD/ASD
NF1	9	Epilepsy, ID/DD/ASD
TRPC6	8	CKD
NSD1	7	Epilepsy, ID/DD/ASD
UMOD	7	CKD
CACNA1A	6	Epilepsy, ID/DD/ASD, Ataxia
EYA1	6	CKD, Fetal
HNF1A	6	CKD
NPHS2	6	CKD
COL4A1	5	Fetal Anomaly, Epilepsy, Congenital Anomaly
PAX2	5	CKD
PTPN11	5	CKD, ID/DD/ASD

- Identified a primary result in 568/4890 probands that fully or partially explains phenotype
- Genetic diagnoses were identified across multiple cohorts

Clinical Diagnostic Spectrum of Individuals with Diagnostic *COL4A3/4/5* Variants



Clinical Utility

- Clarify inheritance mode → **family counseling, renal transplant donor selection**
- **Inform disease prognosis** (variant type ~ disease severity)
  -Workup for **extra-renal features**
- **Targeted treatment**
  → Early initiation of ACE-I
  → **Avoid immunosuppression**
  → Referral for clinical trials

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Multiple Hit Genes

No.	Gene	Cohort
10	**SCN1A**	Neuro + DiagSeq
7	**SCN2A**	Neuro + DiagSeq
6	**NSD1**	Neuro + DiagSeq
5	**CACNA1A**	Neuro + DiagSeq
4	**CSNK2B**	Neuro + DiagSeq
4	**GNB1**	Diagseq
4	KMT2A	Diagseq
4	NF1	Diagseq

No.	Gene	Cohort
3	**COL4A1**	Neuro + DiagSeq
3	**DEPDC5**	Neuro
3	GNAS	Neuro + DiagSeq
3	**KANSL1**	Neuro + DiagSeq
3	**KCNQ2**	Neuro
3	**KIF1A**	Neuro + DiagSeq
3	**SCN8A**	Neuro
3	TCF4	Diagseq
2	**KIAA2022**	Neuro + DiagSeq
2	**ANKRD11**	Neuro + DiagSeq

- 2 Cases: ANKRD11, ASXL3, ATM, BRAF, COL27A1, CREBBP, GNAO1, GRIN1, KCNQ3, KDM6A, KIAA2022, NHS, PAFAH1B1, PPP2R1A, PRRT2, SON, TAB2

Conclusion

Many Mendelian disease genes are tractable targets with broader application than assumed

A proportion of Mendelian disease genes represent key points for intervention for common diseases

Actio's first target causes a rare neuropathy that includes a key common disease symptom