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The Implementation of Clinical Genomics: Ethical, Societal and Regulatory Considerations

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ABSTRACT

As the cost of next-generation sequencing continues to decrease exponentially, it is becoming both affordable and relatively easy for laboratories outside of large-scale sequencing centers to perform exon capture and eventually whole genome sequencing in selected individuals. However, the current genomics system lacks a systematic way to deliver results to participants, even in matters of life and death, as we have discovered in some of our recent research[1,2]. There is substantial debate in the medical genetics and ethics communities concerning whether genomic data originating from research can or should be returned to participants or not, and, if so, under what conditions. The exponential increase in human genetic information is shining a spotlight on the problems with how researchers handle and process human genomic information. Specifically, researchers are largely unable to share the information that arises from their sequencing efforts with participants – without whom, the research wouldn't be possible. At the moment, human genetics researchers operate in a totally unregulated environment, following their own protocols to obtain, store, track, and analyze DNA – creating many opportunities for samples to be mixed up, or other errors. Researchers take shortcuts to save time and money, given that most never expect (as did I) that their results might actually directly impact the unique life of another human being. Here, I present two real-world scenarios from our own research highlighting the issues involved[1,2]. I am suggesting that we change the way we collect and process samples for human genetics research. I argue that we should create a formalized protocol akin to the rigorous process doctors and other healthcare workers go through during any clinical lab test, practically eliminating the chances of mistakes and mix-ups. An added benefit is that sharing the genomic data with research participants will allow them the opportunity to share their own data with other researchers and citizen-scientists, thus allowing for potentially faster and easier replication of published results. We cannot forget the wise words of the late Charles Epstein, from his 2001 William Allan award lecture: "the operative word in '*human genetics'* is '*human.'* Human genetics is about human beings—about humanity and humaneness."[3]

RESULTS

Last year, we characterized a unique, previously unrecognized syndrome, with an X-linked inheritance pattern in two unrelated families (**Table 1** and **Figure 1** and **2**)[1]. We used X-chromosome exon capture and sequencing to determine variants that might be responsible for the disorder. We then used a new probabilistic disease-gene discovery algorithm (VAAST) to determine the genetic basis of this illness. This variant was absent in ~6000 other exomes, and we performed biological studies to further bolster proof of causality[1]. We suggested calling this disease Ogden syndrome, in honor of the town in which the family lives. Last year, we also performed exome sequencing on another family and discovered an unrelated, secondary finding explaining the genetic basis of idiopathic hemolytic anemia in one family member (**Figure 3**) [2,5].

However, in both of these studies, this research was not conducted in a CLIA-certified laboratory, nor was the blood collected or processed in a clinical-grade manner. All Clinical Diagnostic Tests are regulated in America within Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories, and preferably also with College of American Pathology (CAP) certification. Delivering research-grade results back to research participants can lead to errors and confusion. Prior to the implementation of CLIA, several women were given false negative Pap smear results derived from faulty laboratory testing. These women subsequently developed cervical cancer and died. There have been other instances of faulty test results with breast cancer (BRCA-1) and HIV. The Hippocratic Oath includes the statement, "First, do no harm". From a physician perspective, this means that all laboratory testing should achieve a high standard of analytic validity.

Once a laboratory test meets this standard of high analytic validity, the next question is whether there is clinical validity (or utility) for this accurate test result. Unfortunately, much human genetic variation is currently locked away in various databases and siloes, not available broadly. There is therefore an enormous need for one broad database of human genotype-phenotype correlations, so that penetrance (or expressivity) of individual rare mutations can be best calculated. Otherwise, it is very difficult to calculate the penetrance of any one mutation. It is also incredibly important to calculate penetrance within "clans", so as to avoid confounding factors such as population stratification and environmental effects.

Figure 1.

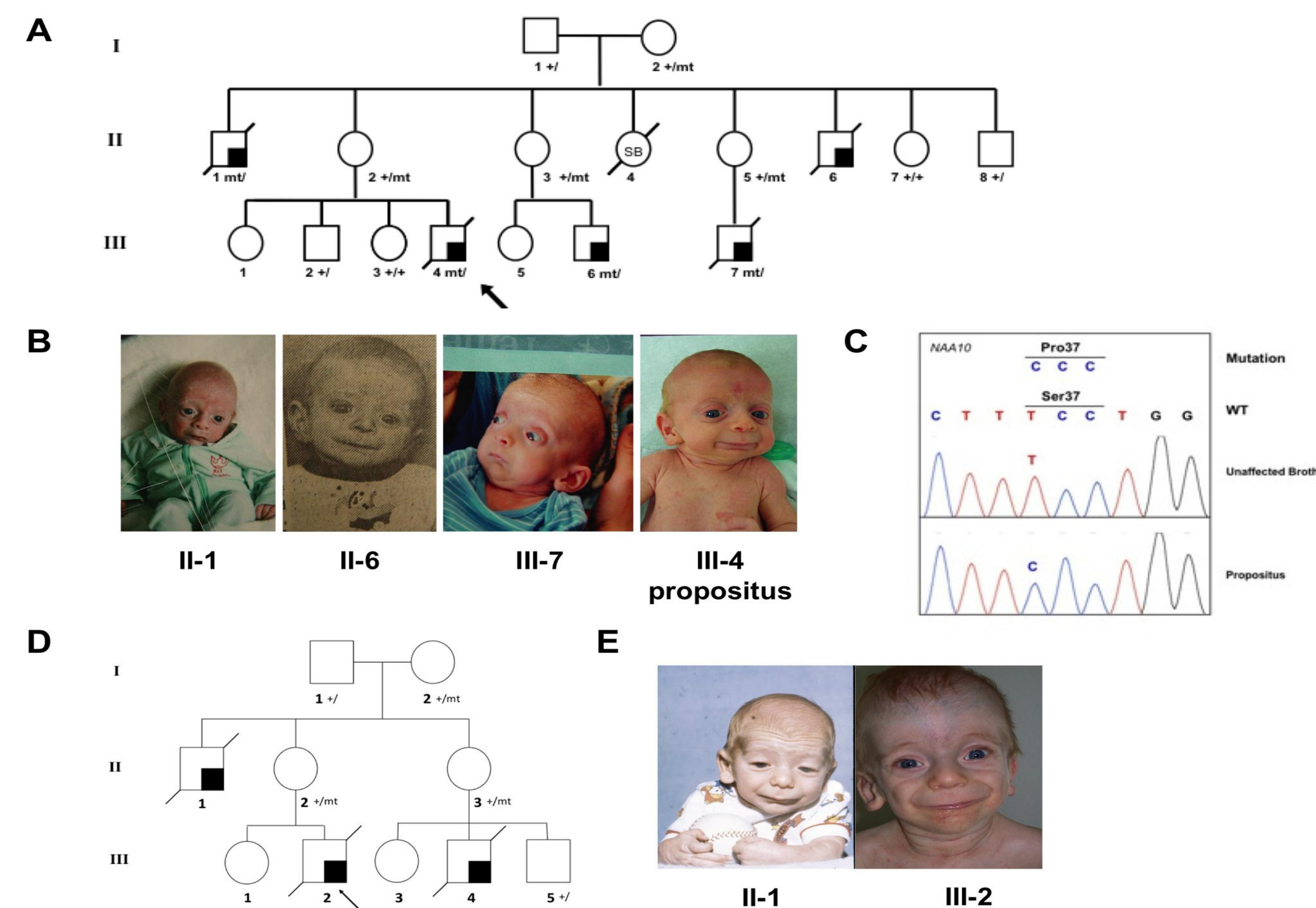

Figure 1. Pedigree drawing and Pictures of Families 1 and 2. A) Pedigree drawing for Family 1. The most recent deceased III-4 is indicated by an arrow. SB, stillborn. Genotypes are marked for those in which DNA was available and tested. + is normal variant, mt is rare mutant variant. **B)** Pictures of four affected/deceased boys in this family, showing the aged appearance. **C)** Sanger sequencing results of *NAA10* in III-4 from Family 1. **D)** Pedigree for Family 2 contributed by Les Biesecker at NIH. The most recent deceased III-2 is indicated by an arrow. **E)** Picture of II-I and III-2 at ~1 year of age in Family 2.

Figure 2.

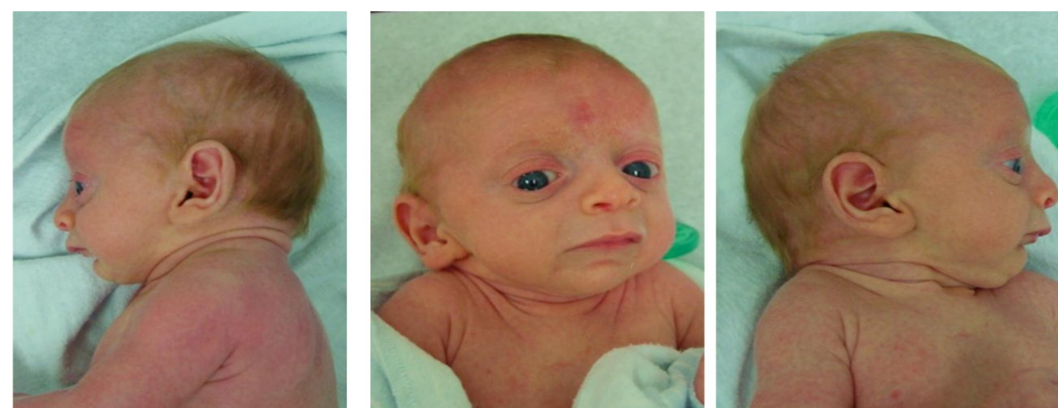

Figure 2. Triptych of III-4 from Family 1. These pictures demonstrate the prominence of eyes, down-sloping palpebral fissures, thickened lids, large ears, beaking of nose, flared nares, hypoplastic alae, short columella, protruding upper lip and micro-retrognathia.

Table 1. Features of the syndrome

Growth	post-natal growth failure
Development	global, severe delays
Facial	prominence of eyes, down-sloping palpebral fissures, thickened lids large ears beaking of nose, flared nares, hypoplastic alae, short columella protruding upper lip micro-retrognathia
Skeletal	delayed closure of fontanels broad great toes
Integument	redundancy / laxity of skin minimal subcutaneous fat cutaneous capillary malformations persistent lanugo of the face
Cardiac	ventricular septal and atrial level defects, pulmonary artery stenoses) arrhythmias (Torsade de points, PVCs, PACs, SVtach, Vtach) death usually associated with cardiogenic shock preceded by arrythmia.
Genital	inguinal hernia hypo- or cryptorchidism
Neurologic	hypotonia progressing to hypertonia cerebral atrophy neurogenic scoliosis

The shaded region includes features of the syndrome demonstrating variability. Though variable findings of the cardiac, genital and neurologic systems were observed, all affected individuals manifested some pathologic finding of each.

We are in the midst of a profound social revolution with the advent of digital technologies and companies and foundations such as Google, Amazon, Facebook, Twitter, 23andMe, PatientsLikeMe, Ancestry.com, and Sage Bionetworks. It is my opinion that centralized whole genome sequencing with high analytic validity could allow for deposition of whole genome data in a central repository of Human Genotype-Phenotype correlations. However, such a central database has not yet been fully created.

Figure 3.

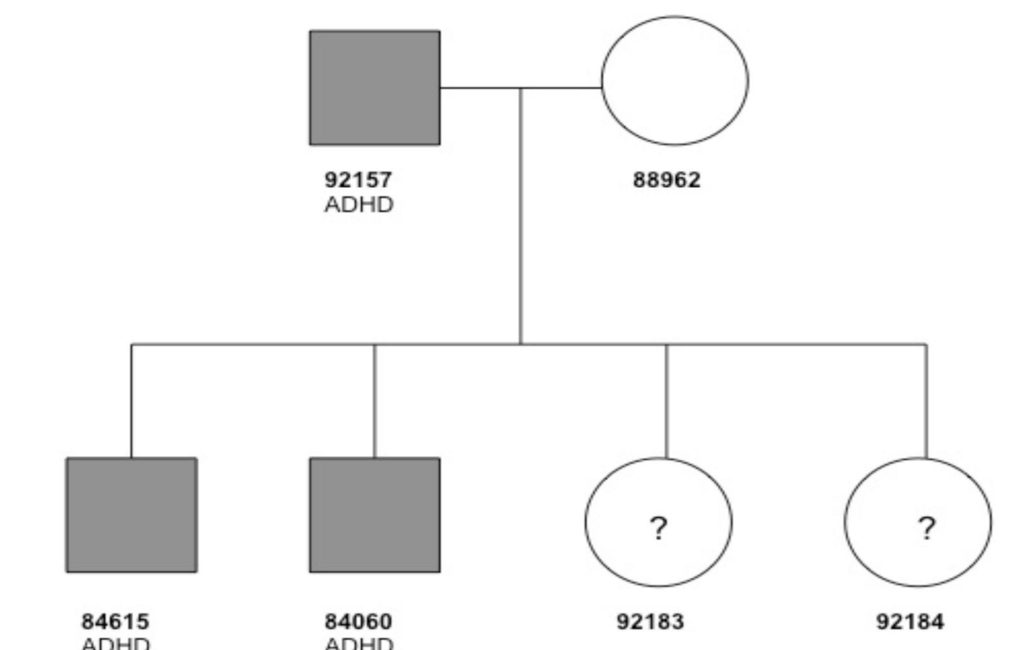

Figure 3. The pedigree structure is shown, with corresponding ID numbers. The three subjects in the pedigree affected with ADHD are shaded. Only 84060 has the idiopathic hemolytic anemia. The mother, father and two sons were sequenced. The two sisters in the family declined to participate in the study, thus their phenotype status is unknown and marked as "?".

Figure 4.

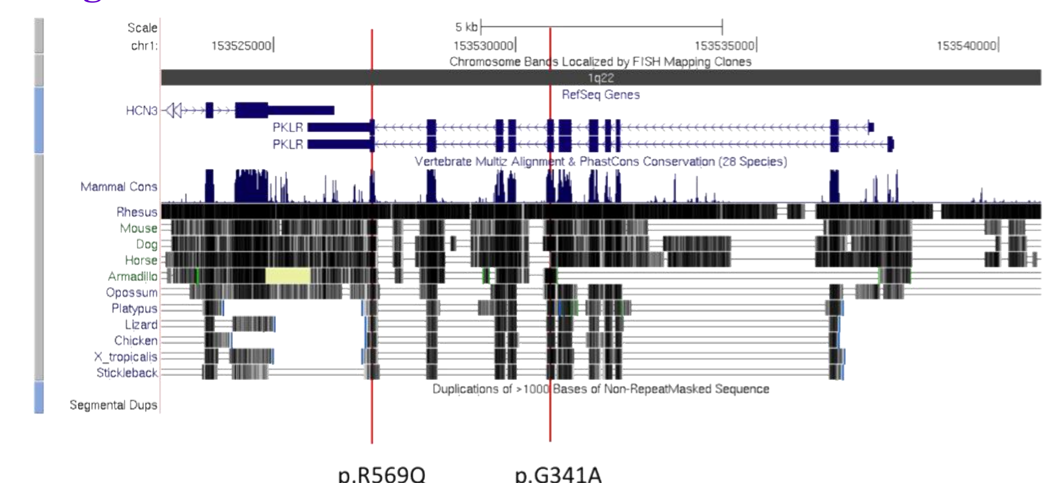

Figure 4. Genome browser shot of PKLR and the location of the two causal mutations for the hemolytic anemia. Each of the two mutations sits within an evolutionarily conserved region, and has been reported once in patients affected with PKLR deficiency.

CONCLUSIONS

◆Why not help the families and research participants directly now by deriving maximal value from every human we sequence? This could be enabled by engagement with social media (e.g. Facebook) and consumer-driven genomics (e.g. PatientsLikeMe and 23andMe).

◆The entire process of DNA collection and germline genome sequencing for humans could and should be performed from the outset in a proper clinical environment, so that at least physicians and genetic counselors can immediately return all relevant genomic information much more easily, and perhaps even link such information to medical records, so that it is available for re-analysis as our knowledge expands.

◆To make these changes possible, we must establish new clinically certified protocols for obtaining, processing, cataloging and returning human genomic data, including genetic findings perhaps unrelated (or secondary) to the original research goals[2,5].

REFERENCES

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