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Genetics of the patent ductus arteriosus (PDA) and pharmacogenetics of PDA treatment

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SUMMARY

Patent ductus arteriosus (PDA) is a frequent, complex, and difficult to treat clinical syndrome among preterm infants in the neonatal intensive care unit. In addition to known clinical risk factors, there are emerging data about genetic predisposition to PDA in both animal and human models. Clinical response and toxicity from drugs used to treat PDA are highly variable. Developmental and genetic aspects of pharmacokinetics and pharmacodynamics influence exposure and response to pharmacologic therapies. Given the variable efficacy and toxicity of known drug therapies, novel therapeutic targets for PDA treatment offer the promise of precision medicine. This review addresses the known genetic contributions to prolonged ductal patency, variability in response to drug therapy for PDA, and potential novel drug targets for future PDA treatment discovery.

Keywords

Infant; Newborn; Ductus arteriosus; Genetic predisposition

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Conflict of interest statement

None declared.

1. Introduction

Preterm infants experience high rates of patent ductus arteriosus (PDA), but the correlation between gestational age at birth and PDA is not absolute. There are known clinical risk factors outside of gestational age which predispose infants to PDA including sepsis, respiratory distress syndrome, intrauterine growth restriction, and others [1]. Genetic variability is a potentially highly relevant and understudied influence on PDA incidence and treatment. The goal of this review is to discuss current knowledge on the genetic predisposition to PDA, the genetic determinants of drug exposure and drug response, and potential clinical and research implications of these data.

2. Genetic predisposition to prolonged DA patency

Although generally considered a sporadic defect with strong environmental factors, several lines of evidence support a genetic predisposition to PDA. Recurrence risk in siblings is 5% [2] and PDA correlation among monozygotic twins exceeds that for dizygotic twins [3]. One twin study determined that 76% of the variance in liability for PDA was accounted for by genetic factors or the shared environment [4]. Several animal models have been developed to investigate genetic contributions to PDA and recent human studies identified both rare and frequent genetic variants associated with PDA [5,6].

2.1. Mouse models of PDA

The prostaglandin pathway has many logical candidates for generating PDA mouse models. Prostaglandin synthesis is dependent on two bi-functional cyclooxygenase (COX) enzymes, COX-1 (Ptgs1) and COX-2 (Ptgs2). Mice deficient in *Ptgs1* have normal growth, survival, and DA closure [7]. However, 35% of mice deficient in *Ptgs2* die shortly after birth with PDA [7]. Mice lacking both *Ptgs1* and *Ptgs2* have large PDAs and nearly 100% mortality on the first day of life [8]. Prostaglandin E₂ (PGE₂) mediates DA relaxation through the EP₄ receptor (*ptger4*), and *EP4*^{-/-} mice have a high rate of PDA resulting in neonatal death [9,10]. Selective breeding can reduce PDA and allow survival in 5–21%, suggesting that other alleles provide an alternate mechanism for ductus closure [9]. Similarly, mice deficient in the prostaglandin transporter gene, *Slco2a1*, succumb to a PDA by postnatal day 2 [11]. Finally, deletion of the primary gene responsible for PGE₂ metabolism, hydroxyprostaglandin dehydrogenase (*Hpgd*), caused elevated PGE levels resulting in a lethal PDA phenotype [12].

Other mouse models of PDA emerged after disruption of genes regulating or comprising the smooth muscle contractile apparatus. Mice lacking the neural crest-specific transcription factor, *Tfap2b*, have a PDA and die within the first day of life. The DAs of these mice have significantly reduced expression of calponin and Hif2 α , markers of differentiated smooth muscle cells [13]. In addition, mice with selective myocardin (*Myocd*) ablation in cardiac neural-crest-derived vascular smooth muscle cells (SMCs) exhibit PDA [14]. Myocardin regulates expression of genes required for the contractile phenotype in neural-crest-derived SMCs and these mice have sharply reduced expression of SMC contractile proteins. Similarly, mice lacking smooth muscle myosin heavy chain (*Myh11*) have delayed DA closure [15].

Several PDA mouse models invoke a multiple-hit hypothesis, where knockout of a single gene results in PDA (or an increased incidence of PDA) only after an additional gene is eliminated. For instance, bone morphogenic protein 9 (*Bmp9*) knockout mice treated with a neutralizing anti-Bmp10 antibody at postnatal days 1 and 3 experienced a re-opening of the DA at day 4 [16]. Similarly, smooth-muscle-specific deletion of *Notch2* resulted in PDA in ~40% of mice, but when combined with heterozygous loss of *Notch3*, PDA was observed in 100% [17]. A further implication of the Notch pathway in PDA pathogenesis comes via smooth-muscle-specific deletion of the Notch ligand, *Jag1*. *Jag1*^{-/-} mice have a lethal PDA and succumb by postnatal day 2 [18]. Other PDA mouse models include mice with defects in platelet biogenesis (*Nfe2*^{-/-}) or adhesion (*Itga2b*^{-/-}) who completed initial DA constriction, but were unable to seal the vessel lumen and achieve permanent fibroblastic transformation, suggesting platelets are required for complete occlusion and remodeling of the postnatal DA [19]. Finally, mice lacking smooth muscle expression of the chromatin remodeling gene, Brahma-related gene 1 (*Brg1*) die due to cardiovascular anomalies including PDA [20].

2.2. Genetic variants in humans associated with PDA

In humans, there are several single-gene dysmorphic syndromes associated with PDA including Mowat–Wilson (SMADIP1), Loeys–Dietz (TGFB1/2), Noonan (PTPN11), Holt–Oram (TBX5), Rubinstein–Taybi (CREBBP), DiGeorge (TBX1), periventricular heterotopia (FLNA), Cantu (ABCC9/KCNJ8), and Char (TFAP2B) [5,6,21,22]. PDA is also associated with syndromes resulting in aortic aneurysms caused by mutations in smooth muscle genes (MYH11 [23], ACTA2 [24]). Studies have also identified single nucleotide polymorphisms (SNPs) associated with non-syndromic cases of PDA. A frequent polymorphism in *TFAP2β* (rs987237) was associated with PDA in premature infants from a single-center study which included a replication cohort [25]. The same study also identified a significant association with SNPs in TNF receptor-associated factor-1 *TRAF1* (rs1056567). Similarly, a variant (rs5186) in the angiotensin II type 1 receptor gene, *AGTR1*, was also associated with PDA [26]. By contrast, variants (rs493694, rs693649) in the prostaglandin I₂ synthase gene, *PTGIS*, were associated with decreased incidence of PDA [25]. Similarly, male infants heterozygous for SNP in the estrogen receptor-α gene *ESR1* (rs2234693) had a decreased risk for PDA [27]. Low-birth-weight infants with SNP in the interferon-γ gene *IFN-γ* (rs2430561) also had a decreased risk for both PDA and bronchopulmonary dysplasia [28]. Consanguineous marriage and family pedigrees with excess PDA have also provided insights into specific chromosome regions that confer susceptibility to PDA [2].

3. Pharmacogenetics of PDA treatment

In order to fully understand the effects of a drug on PDA, one must begin with an acknowledgement that a given drug dose may result in variable drug exposure, and that a given drug exposure may result in variable clinical response. This paradigm, referred to as ‘dose–exposure–response’, is an important concept when researching variability in drug response [29]. For each drug used to treat PDA, there are specific genetic implications to the dose–exposure–response paradigm. Developmental trajectory (ontogeny) and genetic variability of drug-metabolizing enzymes (DMEs) may contribute to unpredictable drug

exposures given the same weight-based dose of a drug. These same variables can affect the responsiveness of the drug target to a known drug exposure (Fig. 1). In addition to individual genetic variability, ethnicity plays a substantial role in the distribution of functionally significant pharmacogenetic differences, so population-level differences may also play an important role.

In relation to PDA treatment, the redundant pathways which contribute to normal prostaglandin homeostasis further complicate the therapeutic effects of drugs. The evolutionarily necessary maintenance of DA patency required for in-utero survival has made sufficient inhibition of prostaglandin signaling required for DA closure very challenging, and this is a barrier faced during attempts to pharmacologically close the PDA. There are alternate pathways modulating DA patency, including nitric oxide (NO) signaling [30], which our current therapies do not address.

Lastly, there is a complex interplay of drug factors (pharmacokinetics (PK), pharmacodynamics (PD) and pharmacogenetics), patient factors, and environmental factors which all contribute to DA patency (Fig. 1). Despite complex interactions between these contributors, developing a thorough understanding of the factors which affect the drug dose–exposure–response paradigm is an important first step in optimizing therapies.

3.1. Pharmacogenetics of dose–exposure relationship in drugs used to treat PDA

3.1.1. Indomethacin—It has been known since 1975 that indomethacin and other non-steroidal anti-inflammatory drugs (NSAIDs) decrease systemic prostaglandins and promote PDA closure [31–33]. Soon thereafter, the treatment response to indomethacin in preterm infants was studied in multiple trials [34,35]. There have been more than 40 studies enrolling >3000 infants in NSAID treatment trials since that time [36,37], including multiple studies on the pharmacokinetics of NSAIDs in preterm infants [38–41]. Although weight and age are consistent predictors of clearance and exposure, nearly every study shows high levels of variability in plasma concentrations given the same weight-based dosing.

Genetic variability in indomethacin metabolism may explain the variability observed in drug exposure. Indomethacin is primarily metabolized by the cytochrome P450 enzyme, CYP2C9, and the serine esterase, carboxylesterase (CES1). CYP2C9 is a polymorphic enzyme with evidence in the adult literature of varying efficacy [42] and toxicity [43] of multiple drugs by genotype. Recently, CYP2C9 genotype has been associated with response to indomethacin in preterm infants with PDA [44]. CES1 is a complex locus [45] that offers the potential for personalized drug-treatment strategies [46]. In preterm infants, the effect of genotypic variation cannot be appreciated until the enzyme is sufficiently expressed and functional. Infants do have evidence of significant CYP2C9 and CES1 expression in fetal and early neonatal life [47,48] and that expression matures rapidly during infancy. Using microsomal and cytosolic fractions from pediatric livers, it has recently been reported that infants aged <3 weeks have significantly less CES1 and CES2 than older infants and children [48].

3.1.2. Ibuprofen—In addition to indomethacin, ibuprofen has been proven safe and efficacious for PDA closure [36]. Ibuprofen is dosed as a racemic mixture of (R) and (S)

enantiomers. Both enantiomers are metabolized by Phase I hepatic enzymes, but the metabolic pathways differ, making ibuprofen clearance more complex than indomethacin. CYP2C8 and CYP2C9 contribute to the oxidative metabolism of ibuprofen. In adults, carriers of variant *CYP2C8* alleles (*3*3 and *1*3) have a 37–40% lower clearance of (R)-ibuprofen as compared to individuals with the reference genotype [49]. The majority of participants who carried the *CYP2C8* variant allele also carried *CYP2C9**2, so it is difficult to establish which genetic variant has the largest effect on ibuprofen metabolism.

An additional study has shown that *CYP2C8**3 homozygotes have one-ninth the clearance of (R)- and (S)-ibuprofen as compared to wild-type patients [50]. Carriers of *CYP2C9**3 variants have a gene-dose-dependent effect on PGE₂ levels, reflecting varying PGE₂ inhibition based on genotype [51]. Infants who carry the variant allele would have decreased clearance of ibuprofen, higher parent drug exposure, and potentially greater clinical effect. Durmeyer et al. [52] investigated CYP genetics and PDA closure in infants aged <5 days, and found that infants who carried variant 2C8 and 2C9 alleles were less likely to respond to ibuprofen, although this effect was no longer significant after multivariate analysis, likely due to very young age and lack of enzyme functional significance. Of note, non-Caucasian ethnicity was a significant predictor, and this may be a marker of genetic variation not captured in traditional SNP analysis.

3.1.3. Acetaminophen—Both intravenous [53,54] and enteral [55,56] acetaminophen can be used to treat symptomatic PDA in preterm infants. Doses studied include 60 mg/kg/day divided in four doses, and loading doses of 20 mg/kg throughout 24 h followed by 7.5 mg/kg/dose every 6 h. For acetaminophen, the optimal drug concentration for PDA closure is poorly understood. Variability in acetaminophen pharmacokinetics, pharmacodynamics, and efficacy have been published for many populations [57].

Acetaminophen is metabolized in the liver by UGT1A1 and UGT1A6 [58], and additionally SULT1A1 and SULT 1A3 [59]. The developmental ontogeny of UGT1A1 and UGT1A6 were studied by Strassburg et al. [60]. Although these glucuronyl transferases are not present in fetal liver, they are highly expressed by postnatal age of six months. By contrast, SULT1A1 is expressed at similar levels between fetal and postnatal human livers [61]. The relative contribution of different metabolism pathways and how these change with time manifest as increasing glucuronide:sulfate ratios from premature infants to adult ages [62]. Genetic variability in these DMEs must be viewed in light of these developmental changes.

SNPs in the 3'UTR which control expression of all UGT DMEs have been identified in human liver samples [63]. Rs8330 is the SNP most significantly related to acetaminophen metabolism and demonstrates a reduced risk of hepatic toxicity due to more extensive acetaminophen glucuronidation, shunting the parent drug away from the toxic metabolic pathway. The rs8330 minor allelic frequency (MAF), or rate at which this SNP is observed within different patient populations, varies by race. African-American patients have a MAF of 0.39 whereas White and Asian populations have a MAF of 0.16 and 0.13 respectively [63]. Three coding region SNPs in *UGT1A6* have been studied in relation to acetaminophen metabolism. Compared to wild-type enzyme, the *UGT1A6**2 shows a doubling of intrinsic clearance of acetaminophen. In addition to SNPs, splicing variants may affect drug

metabolism. Co-expression of reference *UGT1A6* allele and the splicing variant *UGT1A6_i2* inhibits acetaminophen glucuronidation by 90% [63]. Although not studied specifically for acetaminophen metabolism, it is known that SNPs in *SULT1A1* may lead to variable hepatic enzymatic activity [64], thus affecting metabolism and parent drug exposure. Copy number variants in *SULT1A1* with a potential functional significance have also been identified [65]. Given the known genetic variability in acetaminophen metabolism, it is possible that therapeutic failures in neonates may be related to decreased drug exposure.

3.2. Pharmacogenetics of the drug exposure–response relationship in PDA treatment

In addition to variability in the drug–exposure relationship, variability in drug exposure–response relationship due to drug target ontogeny and genetics may influence outcomes. Early studies of persistent PDA after NSAID treatment pointed to potential risk factors. An early report based on data from 36 infants with prophylactic treatment with indomethacin found that male sex and White race, but not serum indomethacin levels, were associated with persistent PDA [66]. Subsequently, in a cohort of 446 indomethacin-treated infants, Chorne et al. also found that Caucasian race, but not indomethacin concentrations, was associated with degree of ductus patency, even after adjusting for gestational age, antenatal betamethasone, and severity of respiratory distress [67]. Caucasian race and earlier gestational age have also been identified as risk factors for non-response to ibuprofen [52].

The replicated finding of non-response to medical therapy in Caucasian/white infants with PDA led to a search for differences in gene expression in DA tissue across ancestry groups; of 48 candidate genes quantified in 273 fetal samples, two had consistently different expression by ancestry: *SLCO2A1* (encoding solute carrier organic anion transporter family member 2A1, also known as the prostaglandin transporter, PGT) and *NOS3* (encoding nitric oxide synthase-3 or endothelial NOS) [68]. These are compelling candidates to modulate the exposure–response relationship as they are major stimuli for DA patency, prostaglandin and NO signaling. The authors posit that the balance of signaling from prostaglandins versus NO is population specific, and this balance affects response to COX inhibition.

Additional candidate genes for modifying the exposure–response relationship come from clinical studies. In healthy adolescents and adults, the rs20417 SNP in the promoter for *PTGS2*, encoding COX-2, has been associated with differential changes in COX expression and analgesic response to ibuprofen, endpoints that may or may not be relevant to PDA closure [69]. The rs5186 variant in the angiotensin II type I receptor (encoded by *AGTR1*) was associated with increased responsiveness to prophylactic indomethacin in 159 preterm infants [26]. This association was not confirmed in a larger, stepwise study of 204 and 162 infants, in which novel associations of indomethacin response with variants rs987237 in *TFAP2B* and rs1867785 in *EPAS1* (encoding transcription factor AP-2 beta and endothelial PAS domain protein 1, respectively) were observed [25]. Finally, Waleh et al. found that the rs2817399 SNP in *TFAP2B* was associated with indomethacin resistance as well as decreased expression of calcium and potassium channel genes (*Cav3.1*, *Cavβ2*, *Kv1.2*) [70].

The mechanism(s) by which variants in these and other genes alter NSAID response have not been established, but may be related to the complex molecular network regulating DA patency before and after birth. All of these potential gene–drug–response interactions require

replication prior to any clinical implementation of pharmacogenomic-guided therapy for NSAID treatment in infants with PDA.

4. Potential new ductus arteriosus drug targets

PDA that persists into adulthood has been associated with subacute bacterial endocarditis and irreversible pulmonary hypertension, and has been shown to contribute to shorter lifespans in animals and humans [7,71,72]. Current therapeutic use of non-selective COX inhibitors in neonates is not ideal as they can result in generalized constriction of renal, cerebral, and mesenteric vascular beds [73]. In addition, treatment with indomethacin and ibuprofen has been associated with adverse effects including spontaneous intestinal perforation, necrotizing enterocolitis, renal failure, and hyperbilirubinemia [74]. Furthermore, despite pharmacological treatment, the DA fails to close in approximately 30% of infants and surgical ligation is required, a procedure accompanied by concerning risks including vocal cord paralysis, chylothorax, scoliosis, and infection [75,76]. Although catheter-based closure is also an option, its usefulness is limited by the technical challenges of implanting devices in very preterm infants [77,78]. Conversely, certain congenital heart defects require that the DA remain patent via prostaglandin infusion or stent implantation in order to maintain life-saving pulmonary or systemic circulation prior to corrective surgery [79,80]. However, adverse effects including peripheral vasodilation and apnea have been associated with infusion of PGE₁ [81]. Given the importance of appropriate DA function and the inadequate pharmacological modifiers currently available, it is necessary to develop more efficient DA-specific therapeutic options.

To this end, transcriptome analysis has been used to identify the DA's unique gene expression profile. Animal and human studies [68] found that the DA is enriched in several subsets of genes including transcription factors, genes required for smooth muscle contraction, members of the prostaglandin signaling cascade, and various classes of ion channels (Fig. 2). These groups represent a rich source of functionally relevant targets that could be pharmacologically modified.

One critical consideration when identifying new therapeutic targets is whether or not that target falls within the "druggable genome". Compiled in 2002, the druggable genome represents a subset of ~4500 genes that encode proteins likely to bind drug-like molecules [82]. Several factors deem a protein druggable. First, the protein would share sequence or structural similarities to many targets of existing drugs, thus conferring a likelihood of drug binding [82]. The majority of currently approved drugs target enzymes, receptors, ion channels, or transporters. Next, the target should be disease-modifying or have a proven function in the disease pathology [83]. The current success rate of drug development programs is staggeringly low. Only 4% of prospective compounds that enter clinical trials yield licensed drugs. However, recent reports suggest that targeting specific genes known to contribute to the risk of a disease significantly increases the success rate of developing disease-modifying drugs [83].

When trying to uncover novel targets in the DA, it is reasonable to assume that candidates with the highest likelihood of clinical success would be enriched in the DA, have a strong

association with PDA, and meet the criteria for inclusion in the druggable genome. PTGS1 and PTGS2 are proofs of this concept as they are the targets of the only currently available DA therapeutics and fulfill all three of the above criteria. Other potential targets also meet these standards (central region, Fig. 2). PTGIS (also known as CYP8A1) is an ideal choice because it is enriched in the DA and is currently used as a therapeutic target in various types of lung cancer [84]. DA drugs targeting PTGIS may be effective since variants in the gene have been associated with reducing the risk of PDA in humans [25]. Another CYP enzyme with DA drug potential is CYP1B1. Interestingly, naturally occurring polyphenols including Kaempferol and Resveratrol inhibit CYP1 and a recent report suggests that pregnant women should avoid polyphenol-rich foods in order to protect against fetal ductus constriction [85]. Another strong DA drug candidate is PTGER4. Unlike in other vessels, this G-protein-coupled receptor is the most predominant prostaglandin receptor in the DA [86–88], thereby conferring a layer of tissue specificity to any drugs targeting this protein.

Other potential DA therapeutics include pathways already being targeted by drugs frequently administered in the neonatal intensive care unit. Phosphodiesterase (PDE) genes inhibit cAMP and/or cGMP, key second messengers in the prostaglandin signaling cascade. PDE inhibitors used to combat pulmonary hypertension are known to cause off-target DA dilation [1]. Conversely, novel PDE1B, PDE3B, or PDE5A activators may encourage DA closure. Similarly, loop-diuretics targeting chloride channels and cotransporters inadvertently relax the DA [89]. Novel drugs targeting GABRA1, a ligand-gated chloride channel, or NKCC1, a Na–K–Cl cotransporter, may have beneficial vasoactive effects on the DA.

Other candidates to consider include the oxygen-sensitive voltage-gated potassium channels, Kv1.5, Kv2.1, Kv1.2, and Kv9.3. Support for their use as therapeutic agents comes from in-vitro gene transfer studies showing that transferring Kv1.5 or Kv2.1 into DA rings or isolated smooth muscle cells increased oxygen responsiveness [90]. Similarly, ROCK1 is a downstream mediator of the Rho-kinase signaling cascade necessary for sustained oxygen-induced constriction of the DA [91]. Fausudil, a pan-ROCK inhibitor, is currently used to treat cerebral vasospasm and hypertension [92]. ROCK1-specific drugs have not been used in a clinical setting but may be useful to modulate DA tone in a vessel-specific manner. Finally, the Notch ligand, JAG1, represents an interesting candidate given its high level of DA expression and lethal PDA phenotype in mice [18,86]. Most Notch-related drugs are γ -secretase inhibitors that prevent cleavage of the Notch intracellular domain. Targeting specific Jag ligand isoforms, such as JAG1, would be a more tissue-specific approach that may avoid the gastrointestinal toxicity issues that may occur with current pan-Notch inhibitors [93].

5. Summary

Taken together, the lack of specific and efficient drugs that are currently used to close a PDA or maintain patency for DA-dependent lesions necessitates the development of novel therapeutic options. Conventional drug targets including a variety of ion channels, enzymes, and G-protein-coupled receptors remain untapped and have the potential to modify DA tone. Whereas most gene candidates are not exclusively expressed in the DA, any candidate that is highly enriched in the ductus compared to other tissues suggests that it may be possible to

exploit a “Goldilocks effect,” whereby a seemingly low dose of drug will be just right to have a potent effect on the DA, but will be insufficient in other tissues given relatively lower expression or affinity of the target protein. Moreover, as larger-scale genome-wide association studies become increasingly available, new PDA-associated genes will likely be identified, increasing the success rate of DA drug development programs. Finally, the pharmaceutical industry itself will play a critical role in developing novel DA therapeutics by continuing to expand their repertoire of strategies used to target moieties once thought to be undruggable (such as protein–protein interactions and nucleic acids). As this occurs, ligands such as JAG1 and heretofore unidentified micro-RNAs or other modifiers of the ductus may become viable targets for DA-specific drugs.

Practice points

- Persistence of the ductus arteriosus is multi-factorial, with prenatal, environmental, demographic and genetic risk factors.
- Variability in drug response for PDA closure is complex and could be related to sub-optimal drug exposure due to genetic variation in drug metabolism, or to genetic variation in the drug targets.

Research directions

- Drug studies for PDA treatment should account for genetic variability in drug exposure and response.
- The most promising novel drug targets for PDA closure need to be translated into human studies, with the collaboration of academia, regulatory bodies and drug companies.
- Development of DA-specific pharmacological therapies should be prioritized.
- Focus on implementation of large-scale genomic studies to identify new PDA-associated genes.
- Neonatologists should be honest with families about the unknowns of PDA treatment and adopt a culture of research that will support development and labeling of new precision therapeutics for PDA.

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Fig. 1.

Dose–exposure–response paradigm for patent ductus arteriosus pharmacogenetics. Adapted, with permission, from Lewis [29]. PK, pharmacokinetics; PD, pharmacodynamics; DMEs, drug-metabolizing enzymes.

Fig. 2.

Potential ductus arteriosus (DA) drug targets. Diagram of select genes known to be enriched in the DA (blue), genes linked to DA function or patent ductus arteriosus (PDA) (red), and genes contained in the druggable genome (white). DA drug targets with the highest likelihood of clinical success meet all three criteria (overlapping central region). TF, transcription factor.